Colorectal Cancer Clinical Investigator Think Tank:
Proceedings from a CME Satellite Symposium at the Gastrointestinal Cancers Symposium in Orlando, Florida

EDITOR AND MODERATOR

Neil Love, MD

FACULTY

Richard M Goldberg, MD
Axel Grothey, MD
Daniel G Haller, MD
Howard S Hochster, MD
Neal J Meropol, MD
Alan P Venook, MD
Norman Wolmark, MD

from the publishers of Colorectal Cancer™ UPDATE

CME Certified

Download MP3s of this program at ColorectalCancerUpdate.com/GI_2007

Colorectal Cancer Clinical Investigator Think Tank:
Proceedings from a CME Satellite Symposium at the Gastrointestinal Cancers Symposium in Orlando, Florida
A Continuing Medical Education Audio Program

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. 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.

LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in gastrointestinal cancer treatment and incorporate these data into management strategies.
- Evaluate recent data and ongoing trials on various treatment approaches for localized colon cancer and explain the absolute risks and benefits of adjuvant chemotherapy to patients.
- Integrate emerging data on biologic therapies into the management of advanced colon and rectal cancers.
- Discuss neoadjuvant radiation therapy/chemotherapy approaches for patients with rectal cancer.

PURPOSE OF THIS ISSUE

The purpose of this enduring program is to offer the perspectives of Drs Goldberg, Grothey, Haller, Hochster, Meropol, Venook and Wolmark 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 4.25 *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, 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/GI_2007** 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**.

This program is supported by education grants from Genentech BioOncology and Sanofi-Aventis.

TABLE OF CONTENTS

Editor's Note: For this special Think Tank edition of *Colorectal Cancer Update*, we gathered seven clinical investigators for a panel discussion at a satellite meeting during the Fourth Annual Gastrointestinal Cancers Symposium in Orlando in January 2007. The format of this recording session was simple — the meeting was divided into seven segments, and for each segment, a faculty member was asked to introduce a major controversy in systemic management of this disease, and this was followed by group discussion. To heighten the pace of the meeting, we provided 150 networked portable computers to audience members and faculty, who participated in our so-called "oncology chat room" where questions and cases were presented and discussed. I also interviewed each faculty member individually to learn about the clinical research database they would be reviewing for the attendees and to further explore their perspectives on the seven key issues we addressed. This monograph summarizes key faculty comments and the result of the audience polling during the conference.

— Neil Love, MD
NLove@ResearchToPractice.com

FACULTY AFFILIATIONS

Richard M Goldberg, MD
Professor and Chief
Division of Hematology/Oncology
Associate Director
University of North Carolina
Lineberger Comprehensive
Cancer Center
Chapel Hill, North Carolina

Axel Grothey, MD
Senior Associate Consultant
Department of Medical Oncology
Mayo Clinic
Rochester, Minnesota

Daniel G Haller, MD
Professor of Medicine
Abramson Cancer Center at the
University of Pennsylvania
Philadelphia, Pennsylvania

Howard S Hochster, MD
Professor of Medicine and
Clinical Pharmacology
NYU Cancer Institute
New York, New York

Neal J Meropol, MD
Director, Gastrointestinal
Cancer Program
Director, Gastrointestinal Tumor Risk
Assessment Program
Divisions of Medical Science and
Population Science
Fox Chase Cancer Center
Philadelphia, Pennsylvania

Alan P Venook, MD
Professor of Clinical Medicine
Associate Chief
Division of Medical Oncology
University of California
San Francisco
San Francisco, California

Norman Wolmark, MD
Professor and Chairman
Department of Human Oncology
Allegheny General Hospital
Professor, Drexel University
College of Medicine
Chairman, National Surgical
Adjuvant Breast and Bowel Project
Pittsburgh, Pennsylvania

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: John H Brebner, Richard Kaderman, PhD, Neil Love, MD, Douglas Paley, Michelle Paley, MD, Margaret Peng, Lilliam Sklaver Poltorack, PharmD, Ginelle Suarez, Erin Wall and Kathryn Ault Ziel, PhD — no real or apparent conflicts of interest to report; Sally Bogert, RNC, WHCNP — shareholder of Amgen Inc and Genentech BioOncology. Research To Practice receives education grants from Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Biogen Idec, Genentech BioOncology/OSI Pharmaceuticals Inc, Genomic Health Inc, 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 Goldberg — Consulting Fees: Amgen Inc, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, Genentech BioOncology, ImClone Systems Inc, Pfizer Inc, Sanofi-Aventis. **Dr Grothey** — Consulting Fees: Amgen Inc, Genentech BioOncology, Roche Laboratories Inc, Sanofi-Aventis. **Dr Haller** — Consulting Fees: Genentech BioOncology, Roche Laboratories Inc, Sanofi-Aventis; Contracted Research: Bristol-Myers Squibb Company, Roche Laboratories Inc, Sanofi-Aventis. **Dr Hochster** — Consulting Fees: Amgen Inc, Genentech BioOncology, Roche Laboratories Inc, Sanofi-Aventis; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: Amgen Inc, Eli Lilly and Company, Genentech BioOncology, Sanofi-Aventis. **Dr Meropol** — Consulting Fees: Amgen Inc, Genentech BioOncology, Pfizer Inc; Contracted Research: Genentech BioOncology. **Dr Venook** — Consulting Fees: Sanofi-Aventis; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: Amgen Inc, Sanofi-Aventis; Contracted Research: Amgen Inc, Genentech BioOncology. **Dr Wolmark** — No financial interests or affiliations to disclose.

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.

SECTION 1

Neoadjuvant Chemoradiation Therapy of Rectal Cancer — Discussant: Daniel G Haller, MD

Tracks 1-9

Track 1 Use of oxaliplatin as a radiosensitizer, systemic therapy or both

Track 2 NSABP-R-04: Preoperative radiation therapy and capecitabine or 5-FU with or without oxaliplatin for operable rectal cancer

Track 3 Use of preoperative versus postoperative chemotherapy in rectal cancer

Track 4 Importance of preoperative staging in the determination of optimal therapy for rectal cancer

Track 5 Preoperative chemoradiation therapy with oxaliplatin for select patients with locally advanced rectal cancer

Track 6 Rationale for NSABP-R-04 design

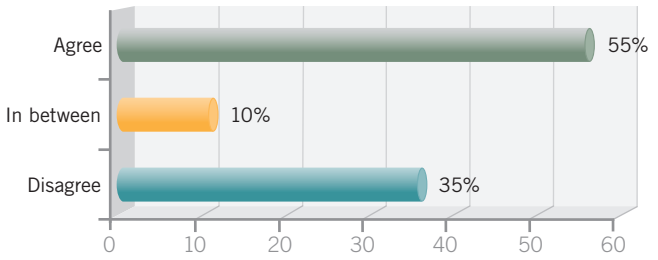
Track 7 Preoperative staging and the use of neoadjuvant chemoradiation therapy versus postoperative chemotherapy

Track 8 Incorporating biologic agents in preoperative therapy of rectal cancer

Track 9 Use of preoperative oxaliplatin-containing chemoradiation therapy for rectal cancer

AUDIENCE POLL QUESTION 1

For select patients with locally advanced rectal cancer, oxaliplatin combined with a fluoropyrimidine and radiation therapy should be offered in the neoadjuvant setting as a nonprotocol option.*



*** Percent of audience participants according to medical specialty: Medical oncologists 65%, Pharmacists 7%, Surgeons 6%, Nurses 4%, Radiation oncologists 3%, Other 15%**

Track 1

DR LOVE: Dan, how would you respond to this poll question about oxaliplatin as neoadjuvant therapy — agree, disagree or in between?

DR HALLER: I would say "in between" because I wear two different hats: one as a person who conducted a Phase I/II trial in this area and uses it off protocol and another as the GI Intergroup co-chair with a protocol (NSABP-R-04; [1.2]) specifically addressing this question.

Separate Phase I or II studies evaluating this regimen have been conducted worldwide (1.1), and some clear conclusions have emerged. First, it is evident that you can add oxaliplatin to a fluoropyrimidine and radiation therapy on a weekly or biweekly schedule or once every three weeks and at different doses. The dose depends on whether you consider oxaliplatin a radiosensitizer, a systemic agent or both. That is, you're administering adjuvant therapy and local therapy to make the radiation therapy work better.

If you want to use oxaliplatin as a radiosensitizer, you probably want to use it more frequently, as in CALGB-89901 (Ryan 2006). If you believe it's more of a systemic agent, you certainly want to administer the maximal dose.

It turns out if you administer oxaliplatin weekly, not everybody gets through all the dosing. So although the total dose that could be delivered is high, the actual dose administered with the weekly regimens is much lower than with the every two-week or every three-week regimens. We have defaulted to a weekly regimen because CALGB data suggested that oxaliplatin was more of a radiosensitizer.

In the German preoperative trial, the pathologic complete response (CR) rate was found to correlate with disease-free survival (Rödel 2005). For patients who have received radiation therapy alone or radiation therapy with 5-FU, the pathologic CR rate is in the range of about eight to 10 percent (Sauer 2004). In the 5-FU/oxaliplatin studies, the pathologic CR rates range anywhere from about 18 percent to 48 percent.

Track 2

DR LOVE: Can you discuss the NSABP-R-04 trial design?

DR HALLER: The primary comparison in NSABP-R-04 was capecitabine versus infusional 5-FU (1.2). It started to become a fairly pedestrian question because many physicians had already diverted to using capecitabine. However, it remains an important question because you have to lower the dose of capecitabine from the "standard systemic dose." You need to ensure that you're maintaining — for a patient being treated with curative intent — the same rates obtained with infusional 5-FU.

1.1

Selected Phase II Trials Incorporating Oxaliplatin as Part of Preoperative Chemoradiation Therapy for Locally Advanced/Unresectable Rectal Cancer

Trial	Oxaliplatin dose	Schedule (days)	N	Grade III/IV diarrhea (%)	path CR (%)
CALGB-89901 (2006)	60 mg/m^2	1, 8, 15, 22, 29, 36	32	33	25
Aschele et al (2005)	60 mg/m^2	1, 8, 15, 22, 29, 36	25	16	28
Pinto et al (2004)	60 mg/m^2	1, 8, 15, 22, 29, 36	26	14	12
Alonso et al (2004)	60 mg/m^2	1, 8, 15, 22, 29, 36	52	7.5	23
Machiels et al (2005)	50 mg/m^2	1, 8, 15, 22, 29	40	30	14
Rödel et al (2007)	50 mg/m^2	1, 8, 22, 29,	104	12	16
Rödel et al (2003)	50/60 mg/m^2	1, 8, 22, 29,	32	12.5	19
Glynne-Jones et al (2005)	130 mg/m^2	1, 29	94	9	17
Carraro et al (2002)	25 mg/m^2	1-4 15(2x) 29-32	22	27	25

SOURCES: Ryan DP et al. *J Clin Oncol* 2006;24(16):2557-62. **Abstract**; Aschele C et al. *Ann Oncol* 2005;16(7):1140-6. **Abstract**; Pinto C et al. *Proc ASCO* 2004;**Abstract 3557**; Alonso V et al. *Proc ASCO* 2004;**Abstract 3607**; Machiels JP et al. *Ann Oncol* 2005;16(12):1898-905. **Abstract**; Rödel C et al. *J Clin Oncol* 2007;25(1):110-7. **Abstract**; Rödel C et al. *J Clin Oncol* 2003;21(16):3098-104. **Abstract**; Glynne-Jones R et al. *Proc ASCO* 2005;**Abstract 3527**; Carraro S et al. *Int J Radiation Oncology Biol Phys* 2002;54(2):397-402. **Abstract**

DR LOVE: What is the dosing schedule for capecitabine in NSABP-R-04?

DR HALLER: It's 825 mg/m^2 twice a day on Monday through Friday. As the study was just about to be launched, the whole oxaliplatin issue came along. Many of us thought the trial would be better as a two-by-two design asking two important questions. We will have the definitive answer from NSABP-R-04, but I would guess that the oxaliplatin combinations would have better pathologic CR rates. Whether that translates into better long-term outcomes — including acute and late toxicities, sphincter preservation, type of surgery and overall survival — is where NSABP-R-04 comes into play.

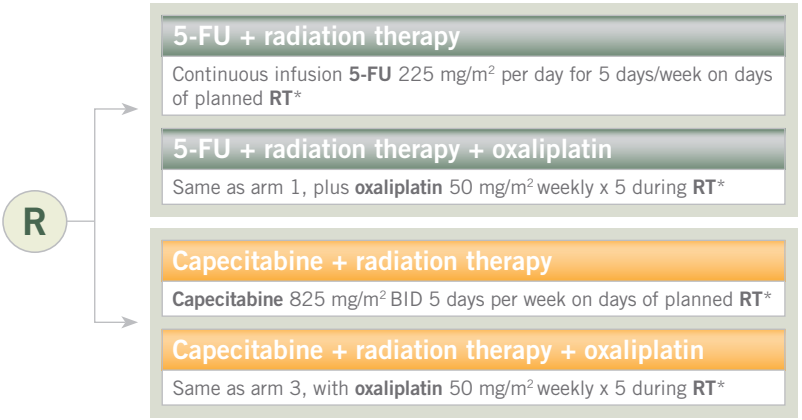
DR LOVE: What do we know about the safety and tolerability of adding oxaliplatin to a fluoropyrimidine in the neoadjuvant setting?

DR HALLER: In most of the studies, more diarrhea occurred with the weekly regimen, which is why more doses were dropped (1.1). Patients received more

1.2

Preoperative Radiation Therapy (RT) Combined with Capecitabine and Oxaliplatin versus Radiation Therapy Combined with 5-FU and Oxaliplatin for Patients with Resectable Rectal Cancer

Protocol IDs: NSABP-R-04, NCT00058474
Target accrual: 1,606



* 4,500 cGy in 25 fractions over five weeks with a 540-cGy boost in three fractions for non-fixed tumors or a 1,080-cGy boost in six fractions for fixed tumors

SOURCE: NSABP-R-04 Protocol, October 27, 2005.

oxaliplatin when it was administered less frequently because they didn't face dose reductions and delays.

In treating patients with rectal cancer, it's important that you not interfere with the radiation therapist administering treatment at the standard dose and schedule. If you had six treatment interruptions for hospitalizations and such, you may see an inferior outcome because the radiation therapy was unintentionally administered in a split-course fashion.

Track 5

DR LOVE: Axel, what are your thoughts about the audience's response to the poll question?

DR GROTHEY: I was intrigued that approximately two thirds of the people here tonight would consider oxaliplatin — at least for some patients — outside of a clinical trial, in the neoadjuvant setting with, so far, only Phase II data. The question I pose to Dan is, do we really need the data from the NSABP-R-04 study if two thirds of us are already using this approach?

DR HALLER: We certainly know that capecitabine is a feasible agent, but the dose that you can administer during radiation therapy is considerably lower than the dose you would normally administer systemically to most patients. So I do want to see that the lower capecitabine dose is equivalent to infusional 5-FU.

Track 9

DR LOVE: Rich, are there situations in which you would use oxaliplatin in this setting?

DR GOLDBERG: We participated in the CALGB study, and I had several patients who showed good responses to oxaliplatin and 5-FU on protocol. I participate in the NSABP-R-04 trial, but I don't use oxaliplatin in this setting off study.

DR GROTHEY: I've used oxaliplatin outside of clinical trials in the neoadjuvant setting for patients with large tumors for whom I wanted to use the radiosensitization activity of oxaliplatin. Also, for patients who present with presumably curable metastatic disease, this utilizes the most active therapy up front and still provides patients with the benefits of local tumor control, preservation of sphincter function, et cetera.

DR HOCHSTER: For a couple of patients who have presented in my practice like that, we've used FOLFOX without bevacizumab and saved radiation therapy for postoperative treatment. The question is about the combination with radiation. What will the increased acute and the long-term toxicities be when you add these agents and a biologic together with radiation therapy? ■

SELECT PUBLICATIONS

Aschele C et al. **Pre-operative FU-based chemoradiation +/- weekly oxaliplatin in locally advanced rectal cancer. Preliminary safety findings of the STAR (Studio Terapia Adiuvante Retto)-01 randomized trial.** *Proc Gastrointestinal Cancers Symposium* 2007;**Abstract 233**.

Bosset JF et al; EORTC Radiotherapy Group Trial 22921. **Chemotherapy with preoperative radiotherapy in rectal cancer.** *N Engl J Med* 2006;355(11):1114-23. **Abstract**

Goldberg RM et al. **Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer.** *J Clin Oncol* 2006;24(25):4085-91. **Abstract**

Mohiuddin M et al. **Randomized phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer: Radiation Therapy Oncology Group Trial 0012.** *J Clin Oncol* 2006;24(4):650-5. **Abstract**

Rödel C et al. **Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer.** *J Clin Oncol* 2005;23(34):8688-96. **Abstract**

Ryan DP et al. **Phase I/II study of preoperative oxaliplatin, fluorouracil, and external-beam radiation therapy in patients with locally advanced rectal cancer: Cancer and Leukemia Group B 89901.** *J Clin Oncol* 2006;24(16):2557-62. **Abstract**

Sauer R et al; German Rectal Cancer Study Group. **Preoperative versus postoperative chemoradiotherapy for rectal cancer.** *N Engl J Med* 2004;351(17):1731-40. **Abstract**

SECTION 2

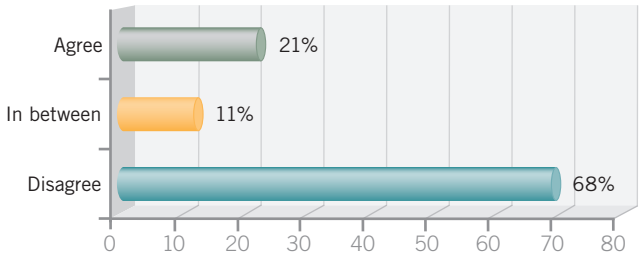
Potential Complications of Treatment with Bevacizumab — Discussant: Alan P Venook, MD

Tracks 1-8

Track 1	Use of bevacizumab for patients with prior arterial events	Track 5	Dose of bevacizumab, use of aspirin and risk of thromboembolic events or bleeding
Track 2	Potential mechanisms underlying bevacizumab-associated arterial thromboembolic events	Track 6	Balancing risks and benefits of bevacizumab
Track 3	Surgery after treatment with bevacizumab	Track 7	Perspectives on the long-term use of bevacizumab in the adjuvant and metastatic settings
Track 4	Reversible posterior leukoencephalopathy syndrome (RPLS) and bevacizumab	Track 8	Treatment of bevacizumab-associated hypertension

AUDIENCE POLL QUESTION 2

With informed patient consent, it is reasonable to use bevacizumab for patients with metastatic disease who have experienced a recent arterial event.



Track 1

DR LOVE: Alan, how would you respond to the poll question — agree, disagree or in between?

DR VENOOK: I don't believe a global "no" or "yes" is the right answer when asked this question. With every treatment decision, we weigh the benefits and risks of therapy.

Clearly the evidence suggests that patients who've had prior arterial thromboembolic events (ATEs) are at greater risk for developing subsequent events when treated with bevacizumab (2.1), and one should remember that the

2.1

Incidence of Arterial Thromboembolic Events (ATEs) in a Pooled Analysis of Five Randomized, Controlled Trials of Bevacizumab with Chemotherapy in Metastatic Cancer and the Relation of Baseline Risk Factors for ATEs to Survival in a Study of Bevacizumab and Chemotherapy in Metastatic Colorectal Cancer

	Incidence of ATEs (%) (from pooled analysis)[1]		Hazard ratio (95% CI) (from a single study in colorectal cancer)[2]	
Baseline risk factor (% of population)	Control	Bev	PFS	OS
All patients (100)	1.7	3.8	0.54 (0.45-0.66)	0.66 (0.54-0.81)
None (63)	1.0	1.8	0.53 (0.43-0.66)	0.73 (0.57-0.94)
≥65 years old* (3.5)	2.5	7.1	0.57 (0.41-0.80)	0.61 (0.42-0.89)
History of ATEs* (8.5)	3.4	15.7	0.61 (0.29-1.28)	0.38 (0.19-0.77)
≥65 years old and history of ATEs (6.5)	2.2	17.9	0.55 (0.22-1.37)	0.59 (0.27-1.28)

CI = confidence interval; Bev = bevacizumab; PFS = progression-free survival; OS = overall survival

* These groups are not mutually exclusive

SOURCES: [1] Skillings JR et al. *Proc ASCO* 2005;**Abstract 3019**; [2] Hurwitz H et al. *N Engl J Med* 2004;350(23):2335-42. **Abstract**

contemporary bevacizumab studies excluded patients who had experienced a variety of ATEs within a specific time frame, usually a year.

Therefore, I believe it's prudent to think twice before treating a patient who's had a myocardial infarction (MI) or ATE in the past year. Still, it's a relative contraindication because the average patient will benefit from bevacizumab, and if you examine the data, you'll see that the incidence of an ATE is only about four percent (Hedrick 2006).

When I examine this issue, I consider a couple of angles. One, what is the goal of therapy? If you believe that an excellent response to treatment might render a patient curable and free of disease, then you want to give that patient the best shot, and that might be a reason to use bevacizumab even with a relative contraindication.

On the other hand, if a patient has massive metastatic disease and the goal is clearly palliative, you might think twice about using bevacizumab if that patient is marginal in terms of risk factors for these events.

DR LOVE: Alan, what about the patient on anticoagulation receiving bevacizumab?

DR VENOOK: While a bit of a myth suggests that patients who are anticoagulated can't safely receive bevacizumab, a fair amount of data indicates that's not

2.2

Bevacizumab and Grade III/IV Bleeding Events in Patients Receiving Concurrent Anticoagulation Therapy

	All patients (AVF2107)		Patients receiving concomitant FDAC*	
	IFL (n = 396)	IFL + bev (n = 392)	IFL (n = 30)	IFL + bev (n = 53)
Grade III/IV bleeding (%)	2.5	3.1	6.7	3.8

FDAC = Full-dose anticoagulation
Patients receiving FDAC were excluded from Phase III Trial AVF2107.
* Patients diagnosed with a thrombotic event and subsequently treated with FDAC while on therapy drug

SOURCE: Hambleton J et al. *Proc ASCO* 2004;**Abstract 3528**.

the case. I see patients who do not receive bevacizumab because of a perceived contraindication that I believe to be incorrect. A prime example is the patient who's been anticoagulated for a coronary stent placed five years ago. I see no contraindication to bevacizumab when treating a patient like that.

DR LOVE: Do we know what that misperception is based on?

DR VENOOK: I presume that at the beginning of the studies, there was global concern regarding clotting and bleeding. The existing data set is a retrospective collation of results on patients who were anticoagulated, so it's flawed by the questions of patient selection and why they were anticoagulated.

However, Julie Hambleton has compiled data that I believe compellingly demonstrate that if bevacizumab is otherwise indicated, the patient who's been anticoagulated can safely receive bevacizumab (Hambleton 2004, 2005; [2.2, 2.3]).

Track 4

DR LOVE: Have you seen any cases of reversible posterior leukoencephalopathy syndrome (RPLS)?

DR VENOOK: I've never seen it — although I did have a couple of patients with unexplained neurologic syndromes before we knew that RPLS existed, so it's possible that we have seen it but didn't know.

It appears to be a capillary leak syndrome in patients receiving bevacizumab. It may be related to the more severe hypertension that some patients develop on this agent. It's described as a diminished mentation, a seizure-like activity and lip smacking.

I believe the real issue is distinguishing RPLS from a stroke or a bleed. We are now more likely to perform scans on patients who have unexplained neurologic problems. It's possible that some of the strokes reported early on with bevacizumab may have been this syndrome, and we didn't work them up adequately. Again, I've never seen a case, possibly because we err on the side of stopping bevacizumab if patients are having suspicious symptoms.

2.3

Management of Arterial Thromboembolic Events During Treatment with Bevacizumab and Chemotherapy for Metastatic Colorectal Cancer

"Serious adverse events are uncommon with the addition of bevacizumab to chemotherapy, but potentially life-threatening events (GI perforation and ATEs) have occurred in a small number of patients.

Patients ≥65 years and those with a history of ATEs should be monitored closely for ATEs, but data from the pivotal phase III trial indicate that there is a marked survival advantage from bevacizumab even in these patients (eg, overall survival is longer by 9.4 months in patients aged ≥65 years treated with IFL plus bevacizumab than in those treated with IFL plus placebo).

Patients who develop an ATE can be treated with full-dose anticoagulation therapy without any increase in the risk of bleeding."

SOURCE: Hurwitz H, Saini S. *Semin Oncol* 2006;33(5 Suppl 10):26-34. **Abstract**

Track 6

DR LOVE: Rich, how do you feel about the use of bevacizumab in older patients?

DR GOLDBERG: We don't have data to suggest that bevacizumab is tolerated less well by older people, unless they have a history of an ATE *and* are over 65, so I recommend it routinely without consideration for age, but I do consider the patient's arterial thrombotic history.

DR HOCHSTER: In the toxicity analysis, the risk for patients over the age of 65 was increased, and the risk for patients with a recent arterial event was increased (2.1). The risk for patients with both was increased the most, but they all had the same survival benefit (2.1, 2.3). Part of my discussion with patients such as these is to tell them, "Your risk of having another arterial event may be up to 10 percent, but this is also likely to prolong your life by 33 percent."

DR MEROPOL: For me, the scenario that sometimes plays out is the patient for whom cure is not possible and we're discussing prolongation of survival. Patients may not be willing to take on the added risk of a thrombotic complication with bevacizumab if they're in a high-risk group in the front-line setting.

However, in the second- or third-line setting, when we know that bevacizumab can also improve survival after failure of front-line therapy, the tradeoff

may be different. It may be the last chance to receive bevacizumab, and they might be more willing to take the risk as they get further along.

Track 7

DR LOVE: Alan, what do we know about the duration of therapy with bevacizumab and the risk of complications?

DR VENOOK: Given that bevacizumab is being used by some as maintenance therapy, it's important to determine whether risks, such as for ATEs, are increased with long-term use. This is uncharted territory. Most of the data we have are from patients with advanced disease who have received 12 months of bevacizumab *at most*.

I believe one of the important endpoints of the NSABP-C-08 trial will be whether there are any long-term consequences from using bevacizumab for a year in patients with Stage II or Stage III colon cancer. Meanwhile, we should be cautious about assuming that long-term use of bevacizumab is beneficial for patients and should be continued indefinitely.

DR GROTHEY: We need to start a registry of patients coming off NSABP-C-08 and other trials and follow them long term in order to capture those events and determine the risks of long-term therapy. ■

SELECT PUBLICATIONS

De Gramont A et al. **Targeted agents for adjuvant therapy of colon cancer.** *Semin Oncol* 2006;33(Suppl 11):42-5. **Abstract**

Hambleton J et al. **Safety of low-dose aspirin (ASA) in a pooled analysis of 3 randomized, controlled trials (RCTs) of bevacizumab (BV) with chemotherapy (CT) in patients (pts) with metastatic colorectal cancer (mCRC).** *Proc ASCO* 2005;**Abstract 3554**.

Hambleton J et al. **Bevacizumab does not increase bleeding in patients with metastatic colorectal cancer receiving concurrent anticoagulation.** *Proc ASCO* 2004;**Abstract 3528**.

Hedrick E et al. **Safety of bevacizumab plus chemotherapy as first-line treatment of patients with metastatic colorectal cancer: Updated results from a large observational registry in the US (BRiTE).** *Proc ASCO* 2006;**Abstract 3536**.

Hochster HS. **Bevacizumab in combination with chemotherapy: First-line treatment of patients with metastatic colorectal cancer.** *Semin Oncol* 2006;33(5 Suppl 10):8-14. **Abstract**

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**.

Kabbinavar FF et al. **Combined analysis of efficacy: The addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer.** *J Clin Oncol* 2005;23(16):3706-12. **Abstract**

Skillings JR et al. **Arterial thromboembolic events (ATEs) in a pooled analysis of 5 randomized, controlled trials (RCTs) of bevacizumab (BV) with chemotherapy.** *Proc ASCO* 2005;**Abstract 3019**.

SECTION 3

Planned Chemotherapy-Free Holidays in the Management of Metastatic Colorectal Cancer — Discussant: Axel Grothey, MD

Tracks 1-6

Track 1 Planned "holidays" from oxaliplatin or irinotecan during treatment with FOLFOX or FOLFIRI

Track 2 Incorporation of biologic therapies in chemotherapy-free intervals and maintenance strategies

Track 3 Complete treatment-free intervals versus maintenance therapy and the role of biologic therapies

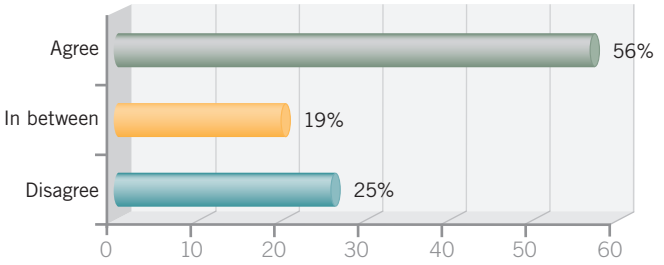
Track 4 Considerations in defining the end of treatment holidays

Track 5 Peripheral neuropathy and the decision to discontinue or reintroduce oxaliplatin

Track 6 Failure to utilize maintenance therapy: Impact on progression-free survival in XELOX-1/NO16966

AUDIENCE POLL QUESTION 3

Patients who have significant responses to FOLFOX/bevacizumab and FOLFIRI/bevacizumab should have planned discontinuation of oxaliplatin or irinotecan prior to the development of significant toxicity.



Track 1

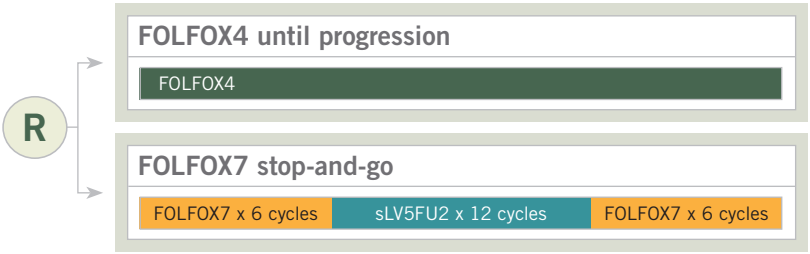
DR LOVE: Axel, what are your thoughts about this poll question?

DR GROTHEY: I was happy about the audience answers because I have been trying to educate physicians to stop treatment before patients develop toxicities.

For an oxaliplatin-based regimen, this approach has evolved, and it's already

3.1

OPTIMOX1: A Randomized Study of FOLFOX4 or FOLFOX7 with Oxaliplatin in a Stop-and-Go Fashion in Advanced Colorectal Cancer — A GERCOR Study



	FOLFOX4	Stop-and-go FOLFOX7	*p*-value
RR (%)	58.5	59.2	>0.05
PFS	9.0 months	8.7 months	0.47
DDC	9.0 months	10.6 months	0.89
OS	19.3 months	21.2 months	0.49
Grade III/IV neurotoxicity (%)	17.9	13.3	0.12

SOURCE: Tournigand C et al. *J Clin Oncol* 2006;24(3):394-400. **Abstract**

the standard approach based on the Phase III data from the OPTIMOX1 trial, which demonstrated we can safely discontinue oxaliplatin without compromising efficacy (Tournigand 2006; [3.1]).

For irinotecan, we have limited information based on the Italian GISCAD trial presented at ASCO 2006. Discontinuation of irinotecan-based therapy — in an on-and-off schedule of two months on FOLFIRI followed by two months off FOLFIRI (a complete chemotherapy break) — did not influence progression-free survival or toxicity (Labianca 2006; [3.2]), which was interesting.

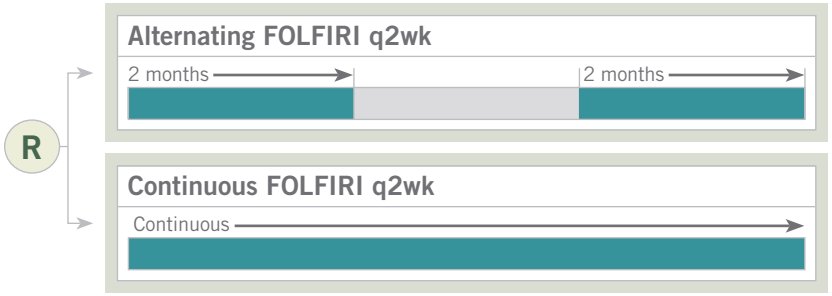
The data are more solid for an oxaliplatin-based regimen, which is what we use more often as first-line therapy in the United States. Because oxaliplatin is associated with cumulative toxicity, it makes sense to "OPTIMOXize" FOLFOX, meaning to stop oxaliplatin after a certain number of cycles.

At the 2007 ASCO GI Symposium, Aimery de Gramont discussed the history of the OPTIMOX trials and updated the results from the OPTIMOX2 trial. The problem Aimery faced when he developed the FOLFOX regimen was that more patients stopped oxaliplatin-based therapy because of toxicity than because of disease progression (Green 2005).

3.2

GISCAD Trial: A Randomized Trial of Alternating versus Continuous FOLFIRI in Advanced Colorectal Cancer

Enrollment: 336
Median follow-up: 27 months



	Arm A	Arm B	HR (95% CI)
Relative response	29%	35%	—
PFS	8.8	7.3	1.00 (0.74 - 1.36)
OS	16.9	17.6	1.11 (0.83 - 1.48)

SOURCE: Labianca R et al. *Proc ASCO* 2006;**Abstract 3505**.

So the OPTIMOX1 trial in patients with metastatic colorectal cancer compared the continuation of FOLFOX4 until disease progression or toxicity to a stop-and-go strategy for oxaliplatin, which used induction therapy with six cycles of FOLFOX7 followed by six months of maintenance therapy with 5-FU/leucovorin and planned reintroduction of FOLFOX7. He demonstrated that when you stop oxaliplatin for six months, this does not compromise overall outcome in terms of the response rate, progression-free survival, duration of disease control and overall survival (Tournigand 2006; [3.1]).

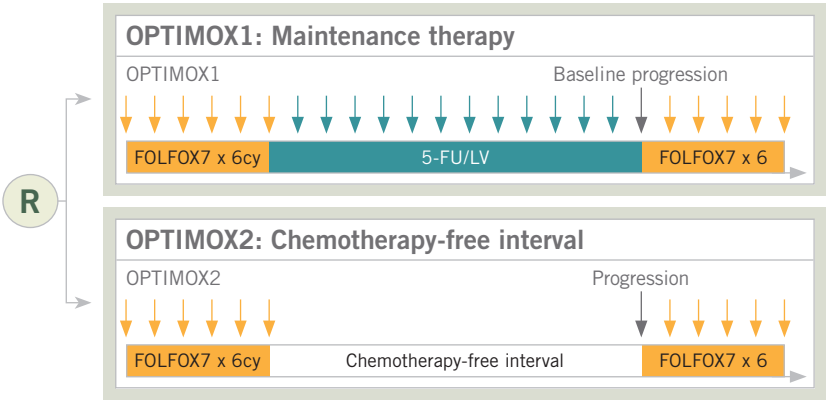
The OPTIMOX2 trial randomly assigned patients with metastatic colorectal cancer to an OPTIMOX1-like treatment arm of induction, maintenance, reintroduction or a treatment arm consisting of induction, a complete chemotherapy-free interval and reintroduction. It was a Phase II trial comparing maintenance therapy to a complete break of any tumor-directed therapy (Maindrault-Goebel 2006; [3.3]).

The response rates were the same for the patients treated with maintenance therapy and those treated with a chemotherapy-free interval because they received the same induction therapy regimen. There is no question, and response occurs early (Maindrault-Goebel 2006).

It's clear that when you receive some tumor-targeted therapy (ie, chemo-

3.3

OPTIMOX2: Randomized Phase II Study of Maintenance Therapy or Chemotherapy-Free Intervals After FOLFOX for Patients with Metastatic Colorectal Cancer (MRC): A GERCOR Study



Eligibility

- Unresectable or measurable metastasis
- No adjuvant CT < 6 months prior
- WHO PS ≤ 2
- No peripheral sensory neuropathy

	OPTIMOX1 (n = 100)	OPTIMOX2 (n = 102)	*p*-value
RR	61%	61%	NR
Progression-free survival	8.7 months	6.9 months	0.009

SOURCE: Maindrault-Goebel F et al. *Proc ASCO* 2006;**Abstract 3504**.

therapy that can inhibit tumor growth), progression-free survival is significantly longer than if you stop therapy completely (Maindrault-Goebel 2006; [3.3]).

If progression-free survival is your primary endpoint, you must be sure patients receive their therapy and only discontinue the treatment components that create toxicity.

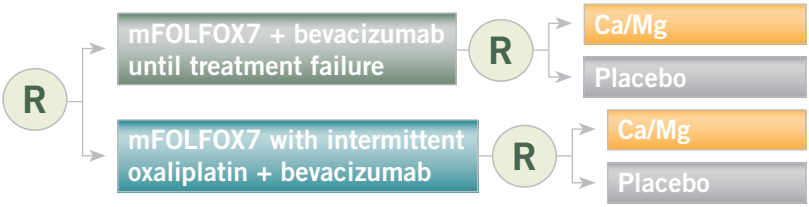
DR LOVE: How is this approach being integrated into the current randomized trials in the metastatic setting?

DR GROTHEY: We still have a hard time adopting this stop-and-go approach in our ongoing Phase III trials that use an oxaliplatin-based regimen up front. At some point patients will discontinue treatment not for progression but for toxicity, which then affects overall outcome if not dealt with in the right way. Right now, the ongoing Intergroup trial is being amended to include a more or less OPTIMOX-like approach as the standard.

3.4

CONcePT: Combined Oxaliplatin Neurotoxicity Prevention Trial

Protocol ID: NCT00129870
Target accrual: 270



Ca/Mg = calcium gluconate/magnesium sulfate

Eligibility

- Metastatic measurable colorectal cancer
- No prior therapy for metastatic disease
- No peripheral neuropathy > Grade I
- No uncontrolled hypertension
- No significant history of bleeding within six months

Study contact

Gilbert Jirau-Lucca, MS, Study Director, Sanofi-Aventis

SOURCE: clinicaltrials.gov, April 2007.

Track 2

DR LOVE: What do we know about incorporating biologics into this type of strategy?

DR GROTHEY: We have limited data about how biologics would affect this concept of maintenance therapy or chemotherapy-free intervals. We're currently conducting a trial led by the Mayo Clinic, which is evaluating a FOLFOX regimen with bevacizumab in a stop-and-go design.

In this trial, patients receive FOLFOX and bevacizumab for four months or eight cycles (3.4). Then we apply a planned discontinuation of oxaliplatin while 5-FU/bevacizumab is continued for four months, followed by the reintroduction of oxaliplatin.

This trial has accrued more than half of the target accrual goal, so we should have some data next year to determine whether continuing biologics as an integral component of maintenance therapy allows us to deliver more treatment and delay tumor progression without affecting toxicity.

Currently, various trials use biologic agents in the maintenance phase to delay tumor progression. The idea is, you might induce a response by using conven-

tional chemotherapy in combination with one or two biologic agents and maintain the response by using biologic agents to allow for a long-term delay in progression and limit toxicity.

Tracks 3-4

DR LOVE: Neal, in practice do you use treatment-free intervals or prefer some type of maintenance therapy?

DR MEROPOL: In general, I provide complete treatment-free holidays. It is a tremendous added benefit for the patient not to have to come in to the office.

While we have no secure data addressing the survival impact of a complete holiday, in the absence of data to the contrary and with the data from the OPTIMOX1, OPTIMOX2 and GISCAD studies suggesting no detriment, at least in short-term outcomes, I'm pretty comfortable discussing with a patient the possibility of a complete holiday from treatment.

DR HALLER: A question I have for the panel members is, what defines the end of the holiday, assuming you don't want to wait until the patient is symptomatic?

DR GOLDBERG: So many different considerations are relevant — including the patient's psychology. For some patients, the thought that they have cancer and are not actively on treatment is so detrimental to their quality of life that they'd rather put up with the toxicities and the office visits.

DR VENOOK: I favor absolute holidays, but they are not appropriate for everyone. Palliation means trying to improve the patient's quality of life, and stopping therapy can often help to do that. However, the issue is complex, and my default position is probably to continue the chemotherapy. Also, we need a data set on whether discontinuing bevacizumab will be a problem. ■

SELECT PUBLICATIONS

Green E et al. **Detailed analysis of oxaliplatin-associated neurotoxicity in Intergroup trial N9741.** *Proc Gastrointestinal Cancers Symposium* 2005;**Abstract 182**.

Labianca R et al. **Alternating versus continuous "FOLFIRI" in advanced colorectal cancer (ACC): A randomized "GISCAD" trial.** *Proc ASCO* 2006;**Abstract 3505**.

Maindrault-Goebel F et al. **OPTIMOX2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC). A GERCOR study.** *Proc ASCO* 2006;**Abstract 3504**.

Pasetto LM et al. **Oxaliplatin-related neurotoxicity: How and why?** *Crit Rev Oncol Hematol* 2006;59(2):159-68. **Abstract**

Saltz LB et al. **Bevacizumab (Bev) in combination with XELOX or FOLFOX4: Efficacy results from XELOX-1/NO16966, a randomized phase III trial in the first-line treatment of metastatic colorectal cancer (MCRC).** *Proc Gastrointestinal Cancers Symposium* 2007;**Abstract 238**.

Tournigand C et al. **OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer — A GERCOR study.** *J Clin Oncol* 2006;24(3):394-400. **Abstract**

SECTION 4

Treatment of Patients Presenting with Synchronous Primary and Metastatic Colon Cancer — Discussant: Norman Wolmark, MD

Tracks 1-6

Track 1 Incidence and treatment of patients presenting with synchronous primary and metastatic colon cancer

Track 2 NSABP-C-10: FOLFOX6 with bevacizumab for patients with unresectable Stage IV colon cancer and a synchronous asymptomatic primary tumor

Track 3 Clinical endpoints in NSABP-C-10: Events related to the intact primary tumor

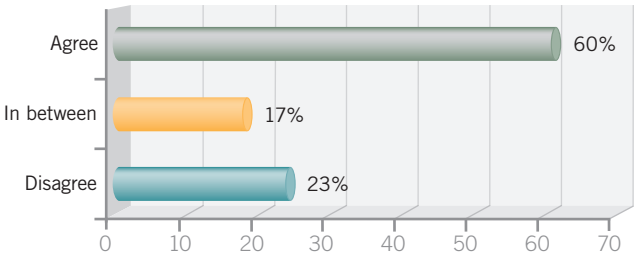
Track 4 Treatment of patients with an intact primary tumor and synchronous metastatic disease

Track 5 Treatment approach for patients with rectal cancer and simultaneous metastatic disease

Track 6 Considerations in the addition of cetuximab to first-line chemotherapy

AUDIENCE POLL QUESTION 4

For asymptomatic patients presenting with primary colon cancer and metastatic disease, the management strategy of choice is enrollment in the NSABP-C-10 trial evaluating FOLFOX/bevacizumab.



Track 1

DR LOVE: Norm, can you review the background to the NSABP-C-10 trial?

DR WOLMARK: As surgeons, we have all been taught that the appropriate treatment when patients present with a simultaneous primary colonic tumor and metastatic disease is to resect the primary lesion. I have actively participated in this practice and taught medical students and residents that if you leave the primary tumor, then you will end up with inordinate rates of

obstruction, perforation and bleeding, and you will pay a greater price later than you would by performing the operation sooner.

Of course, this was a carryover from an era when therapy for metastatic disease didn't have the same benefits as it does currently. We wanted to know the magnitude of the issue and whether it really is a problem today to leave the primary intact, and we hope to answer those questions with the NSABP-C-10 trial.

Tracks 2-3

DR LOVE: What are the design and eligibility for the NSABP-C-10 trial?

DR WOLMARK: This is a Phase II trial evaluating FOLFOX6 with bevacizumab in patients who present with untreated primary colon cancer and concomitant metastatic disease not considered surgically resectable for cure (4.1). Patients do not undergo surgery unless down the road an obstruction or perforation makes it necessary for their safety. Patients with liver metastases amenable to hepatic resection or resection and ablation to render them "disease free" are ineligible for this study.

Some other, subtle criteria relate to the treatment, similar to the criteria for the NSABP-C-08 trial that evaluated adjuvant fluorouracil, leucovorin and oxaliplatin with or without bevacizumab. For example, we don't want patients whose risk would be increased with the use of bevacizumab, such as patients with active ulcer disease or arterial events or MIs within the past six months.

DR LOVE: What are the primary endpoints for the study?

DR WOLMARK: The endpoints consist of monitoring the rate of operations for complications of the primary tumor, such as bleeding, perforation, fistula or obstruction, or death related to the primary tumor.

The trial is powered specifically to determine outcomes relative to the primary tumor. If the incidence of events is less than 25 percent, the therapeutic intervention will be considered a success, but if the event rate is higher, it will be considered unsuccessful.

We plan to accrue 90 patients, and to safeguard patients, we are using a Simon two-stage design. Initially we will enroll 30 patients, in order to have 26 evaluable patients, and then the trial goes into hiatus so that we can determine the event rate. If 10 or more patients have experienced an event — death from the primary or surgery or bleeding, perforation, fistula or obstruction related to the primary — the trial will be stopped. If fewer than 10 patients have experienced an event, the study will continue and we will enter the next 60 patients.

In addition, these are patients who are deemed inoperable, so a tertiary endpoint is to determine how many patients can be converted from inoper-

4.1 **Phase II Trial of FOLFOX with Bevacizumab for Patients with Unresectable Stage IV Colon Cancer and a Synchronous Asymptomatic Primary Tumor**

Protocol ID: NSABP-C-10
Target Accrual: 90 (Open)

Eligibility
Asymptomatic primary colon cancer
Unresectable metastases

→ [FOLFOX6 + bevacizumab] every 14 days*

* Courses repeat in the absence of disease progression or unacceptable toxicities.

Study Contact

National Surgical Adjuvant Breast and Bowel Project
Laurence McCahill, MD
Tel: 802-656-2963

SOURCE: NCI Physician Data Query, February 2007.

able to operable, in terms of metastatic disease and the primary, with a modern regimen such as FOLFOX6 with bevacizumab.

Track 4

DR LOVE: Axel, how do you treat patients with metastatic colorectal cancer and an intact primary tumor?

DR GROTHEY: The BRiTE registry followed prospectively approximately 2,000 patients treated with chemotherapy and bevacizumab for metastatic colorectal cancer, and about 16 percent of those patients had the primary intact.

They revealed that 3.4 percent of these patients experienced gastrointestinal perforations, which is about twice as high as in the overall registry population, but of course they eliminated the risks of primary surgery, so it's a tradeoff.

Currently, I believe that if the metastases are the dominating life-threatening factor, I start with chemotherapy right away, with the primary intact. Also, I do use bevacizumab in that situation.

DR LOVE: Dan, if it were breast cancer, we would leave the primary intact and use it as an indicator lesion for systemic therapy of metastases. Does that strategy make sense in colorectal cancer?

DR HALLER: I believe it does. However, this approach is highly individualized, so it's between the patient and the surgeon to make the final decision. If a patient has a nonobstructing, nonbleeding primary tumor, more often than not, we leave in place.

DR LOVE: Rich, how do you manage these cases?

DR GOLDBERG: My default position is not to operate on patients who present with widely metastatic disease unless they're obstructed or bleeding, and I have been willing to administer bevacizumab.

DR LOVE: Do you see any difference in response to therapy in the primary tumor compared to what you typically see with metastatic disease?

DR GOLDBERG: The primaries seem to be quite responsive, and it's been interesting to follow them.

DR WOLMARK: That's precisely why I believe the NSABP-C-10 trial will provide us with useful information.

DR GROTHEY: This point that the primary tumor can respond to therapy is important because some surgeons don't believe that. Norm, you're an exception, but I routinely hear at the Mayo Clinic that primaries don't respond and we need to perform surgery. That is not true.

DR HOCHSTER: That's been our experience also. In fact, a couple of patients who've undergone post-therapy colonoscopy have had unobservable primaries, so I believe the primary is often more sensitive than the liver metastases. In terms of bleeding, I have yet to see any patient with metastatic colorectal cancer and an intact primary tumor experience a major bleeding problem.

DR MEROPOL: I agree with the other panel members in that I tend to defer surgery in general, and I'm comfortable using bevacizumab as long as there isn't a lot of bleeding. ■

SELECT PUBLICATIONS

Chen HX et al. **Phase II multicenter trial of bevacizumab plus fluorouracil and leucovorin in patients with advanced refractory colorectal cancer: An NCI Treatment Referral Center Trial TRC-0301.** *J Clin Oncol* 2006;24(21):3354-60. **Abstract**

Cook AD et al. **Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: An analysis of surveillance, epidemiology, and end results data, 1988 to 2000.** *Ann Surg Oncol* 2005;12(8):637-45. **Abstract**

Giantonio BJ et al. **A phase II study of high-dose bevacizumab in combination with irinotecan, 5-fluorouracil, leucovorin, as initial therapy for advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E2200.** *Ann Oncol* 2006;17(9):1399-403. **Abstract**

Hedrick E et al. **Safety of bevacizumab plus chemotherapy as first-line treatment of patients with metastatic colorectal cancer: Updated results from a large observational registry in the US (BRiTE).** *Proc ASCO* 2006;**Abstract 3536**.

Hurwitz HI et al. **Bevacizumab in combination with fluorouracil and leucovorin: An active regimen for first-line metastatic colorectal cancer.** *J Clin Oncol* 2005;23(15):3502-8. **Abstract**

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

Tebbutt NC et al. **Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases.** *Gut* 2003;52(4):568-73. **Abstract**

SECTION 5

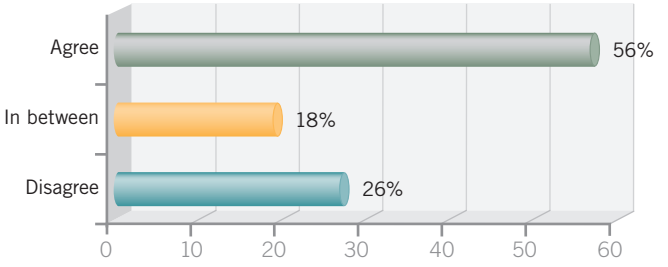
Adjuvant Chemotherapy for Older Patients — Discussant: Richard M Goldberg, MD

Tracks 1-4

Track 1	Selection and use of adjuvant chemotherapy for older patients	Track 3	Case discussion: A 92-year-old with T3N2 (10 positive nodes) colon cancer
Track 2	Chemotherapy tolerance in octogenarians	Track 4	FOLFOX versus FLOX in the adjuvant treatment of older patients with colorectal cancer

AUDIENCE POLL QUESTION 5

In general, for otherwise healthy patients of any age — even those in their seventies or eighties — if adjuvant chemotherapy is to be used, it should include oxaliplatin.



Track 1

DR LOVE: Rich, what are your thoughts on the audience response to this question?

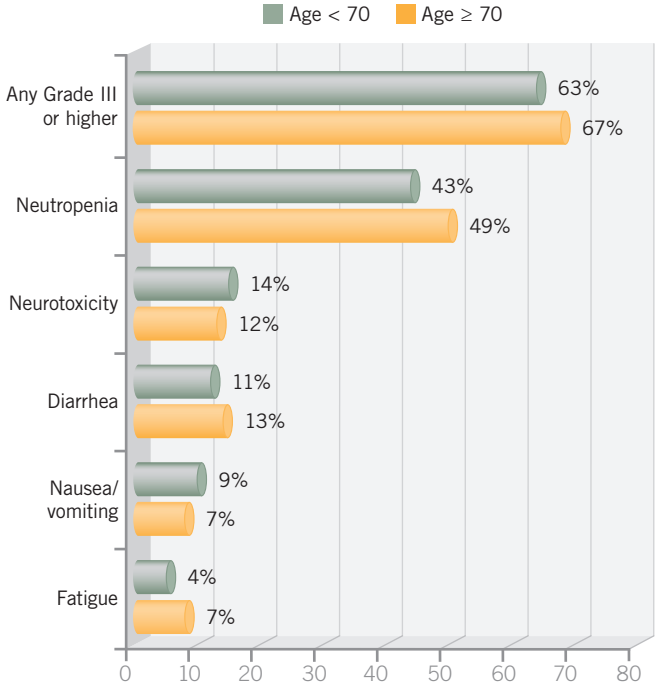
DR GOLDBERG: I am surprised that about one quarter of the participants in the audience are not offering FOLFOX to older patients in the adjuvant setting. I believe the data suggest that as long as you pick your patients carefully, the vast majority can tolerate more aggressive therapy (Goldberg 2006; [5.1]).

DR LOVE: A physician in the audience has submitted a case to you to discuss — a 92-year-old man with 10 positive nodes.

DR GOLDBERG: I would consider the person with 10 positive nodes as someone who is exceedingly unlikely to be cured by surgery either alone

5.1

Select Grade III or Higher Adverse Events in Patients (<70 versus ≥70 Years of Age) Treated with FOLFOX4 in the Adjuvant or Palliative Setting



FOLFOX4 = oxaliplatin and fluorouracil/leucovorin administered bimonthly

SOURCE: Goldberg RM et al. *J Clin Oncol* 2006;24(25):4085-91. **Abstract**

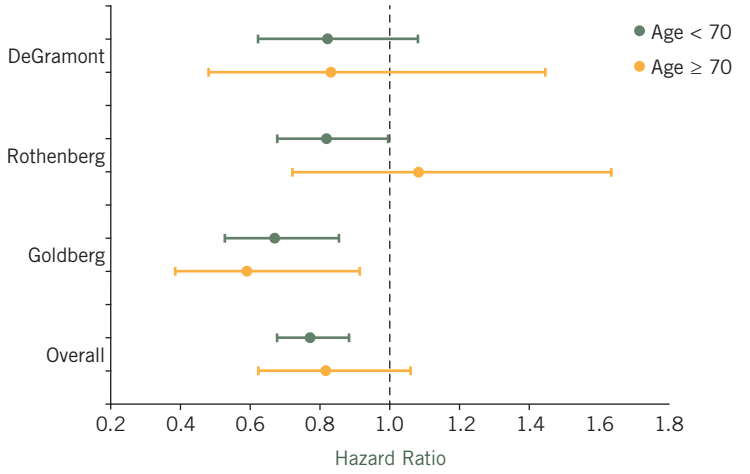
or with adjuvant therapy. If you look at the Gill Model we constructed and published in the *Journal of Clinical Oncology*, for a patient with more than four positive nodes, the five-year survival was around 10 percent without adjuvant therapy and about 25 percent with adjuvant therapy (Gill 2004).

Percentage for percentage, patients with the highest risk of recurrence benefited the most from 5-FU/leucovorin (Gill 2004). Presumably, if you were to use FOLFOX, the benefit of adjuvant chemotherapy would be magnified.

According to the data published by Dan Sargent and the ACCENT (Adjuvant Colon Cancer Endpoints) Group, we know that colorectal cancer tends to recur early, with about 80 percent of the recurrences occurring in the first three years (Sargent 2005).

5.2

Overall Survival by Study for Oxaliplatin and Fluorouracil/Leucovorin Administered Bimonthly versus Control by Age



SOURCE: Goldberg RM et al. **Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer.** *J Clin Oncol* 2006;24(25):4085-91. Reprinted with permission from the American Society of Clinical Oncology. **Abstract**

In somebody with an aggressive tumor like the one you mentioned, I would expect a recurrence earlier rather than later. If the person is otherwise fit, I believe the judicious use of chemotherapy is appropriate.

In my own practice, if I'm concerned about the patient tolerating therapy, I'll often use infusional 5-FU/leucovorin without a bolus for the first cycle. If they tolerate it, which most of them do, then I'll add oxaliplatin. I would rather experiment and be more aggressive with these patients than use single-agent therapy.

DR LOVE: Do you hear any other questions from physicians who treat colorectal cancer about the use of adjuvant chemotherapy in elderly patients?

DR GOLDBERG: One of the questions I'm asked is, "What about the use of oxaliplatin for the patient who is older and has diabetes?" My feeling is that in most patients the neurologic toxicity associated with oxaliplatin is not an on-off switch — it's something that is "dialed up" over time.

As long as you're attentive and talk to patients about it, I believe you can safely use oxaliplatin for people with a risk of sensory neuropathy. You simply have to lower your threshold for backing off from the drug.

Track 2

DR LOVE: What are your thoughts on treating octogenarians with chemotherapy?

DR GOLDBERG: Patients in their eighties are vastly underrepresented in clinical trials, so we don't have many objective data to rely on. Rather, we're extrapolating from people in their seventies.

Having said that, I have a patient in my practice who's 91 years old that I treated with FOLFOX and bevacizumab. When she came in to my office with a walker due to arthritis, someone could have criticized my treatment choice, but I kept a low threshold for discontinuing the therapy, and she tolerated it just fine.

DR LOVE: Alan, we see in Adjuvant Online! that as the patient's age increases, the absolute benefit of adjuvant therapy decreases because of competing causes of mortality. What are your thoughts about this issue?

DR VENOOK: Age is a factor in your decision-making and in how aggressively you follow patients. However, age by itself should not be a reason not to offer patients treatment (5.2). One problem with the clinical trials is that we get our trial data on 80-year-old Olympic athletes, and whether that's relevant to the patient in your office is a different question.

Track 4

DR LOVE: Norm, what about FLOX versus FOLFOX in the elderly?

DR WOLMARK: I would stick to the regimen that has been demonstrated to be effective, regardless of age, and I believe more data are available with FOLFOX than with FLOX.

DR GROTHEY: The NSABP-C-07 FLOX data added nicely to the oxaliplatin story in the sense that we have learned that regardless of the 5-FU backbone — whether it's bolus or infusional — oxaliplatin adds benefit in the adjuvant setting, whereas the irinotecan story turned the other way. We hope to see that soon with capecitabine, but we don't know that yet. ■

SELECT PUBLICATIONS

Gill S et al. **Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: Who benefits and by how much?** *J Clin Oncol* 2004;22(10):1797-806. **Abstract**

Goldberg RM et al. **Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer.** *J Clin Oncol* 2006;24(25):4085-91. **Abstract**

Sargent DJ et al. **Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: Individual patient data from 20,898 patients on 18 randomized trials.** *J Clin Oncol* 2005;23(34):8664-70. **Abstract**

SECTION 6

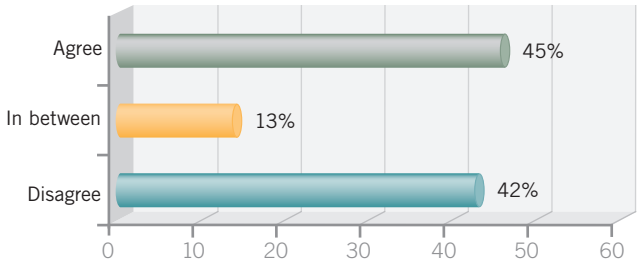
Adjuvant Chemotherapy for Patients with Stage II Colon Cancer — Discussant: Neal J Meropol, MD

Tracks 1-6

Track 1	Adjuvant chemotherapy for patients with Stage II colon cancer
Track 2	Differences in physician perceptions of benefit from adjuvant therapy in breast and colon cancer
Track 3	Patients' perceptions of potential benefit from adjuvant therapy
Track 4	Patients' expectations regarding toxicity and side effects of chemotherapy
Track 5	Risk-benefit considerations and impact on patient preferences for adjuvant chemotherapy
Track 6	Survey of patients' and physicians' perspectives on preferences for adjuvant therapy

AUDIENCE POLL QUESTION 6

Patients with Stage II colon cancer should be referred to a medical oncologist and offered adjuvant chemotherapy as an option even if no high-risk factors are present.



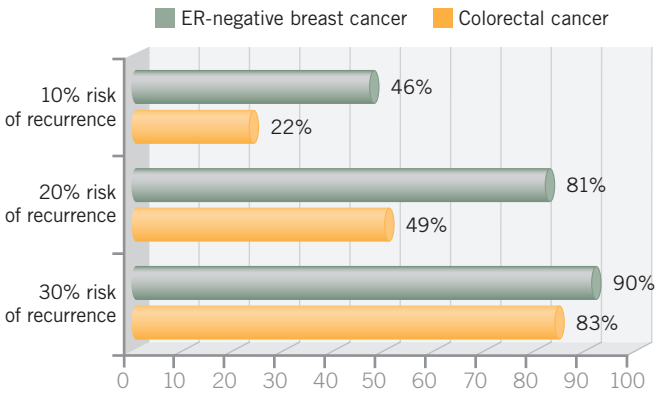
Track 1

DR LOVE: Neal, what do we know about the impact of adjuvant chemotherapy on patients with Stage II colon cancer?

DR MEROPOL: The management of Stage II colon cancer is a difficult decision-making scenario, insofar as the prognosis is good with surgery alone and the potential benefit of adjuvant therapy for the population as a whole is marginal. If you were to treat all patients who have Stage II colon cancer with adjuvant therapy, the absolute benefit would probably be in the range of five percent or less for the most active chemotherapy regimen (Andre 2004; de Gramont 2005).

6.1

Survey of 150 practicing oncologists: How likely are you to recommend adjuvant chemotherapy to a 60-year-old healthy woman with colon cancer or breast cancer and the following estimated five-year risk of recurrence? (Responses of "very likely")



SOURCE: Love N et al. Gastrointestinal Cancers Symposium 2007;**Abstract 239**.

The challenges are in defining which patients are at the greatest risk of relapse from the group of patients with Stage II disease and in selecting those patients for adjuvant therapy because their potential for benefit is greater.

Patients have different values with regard to the tradeoffs of the potential benefits and side effects. This requires a discussion about the option of adjuvant therapy — the potential hazards, which are well defined, and the potential benefits, which are less well defined for any individual.

The doctor and patient have to come to an agreement and understanding about what is best for that individual patient. With regard to your question about whether all patients with Stage II colon cancer should be referred to a medical oncologist, my answer is that all of those patients should engage in a discussion about adjuvant therapy and whether it's right for them.

Track 2

DR LOVE: When we ask oncologists nationally, "What are you likely to recommend to a woman who has a 10 or 20 percent risk of relapse from breast cancer?" the vast majority say they're likely to recommend chemotherapy, but in colon cancer, far fewer docs say they would treat a patient with colon cancer and the same risk for relapse (6.1). What do you think explains these differences?

6.2

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**.

DR MEROPOL: I believe part of it is cultural and part of it is data driven. With regard to the data in breast cancer, prospective randomized studies involving thousands of patients have conclusively shown and defined the small benefit from the addition of adjuvant therapy for an individual who's at low risk of relapse.

In colon cancer, we don't have those kinds of data. We have extrapolations from a higher-risk situation and pooled analyses that either show no benefit or marginal benefit (Benson 2004; Figueredo 2004; Gill 2004).

The most compelling data with regard to patients with Stage II colon cancer are from the MOSAIC trial, in which patients with Stage II disease seem to have a benefit of a few percent in three- and four-year disease-free survival with FOLFOX over 5-FU/leucovorin (Andre 2004; de Gramont 2005; [6.2]).

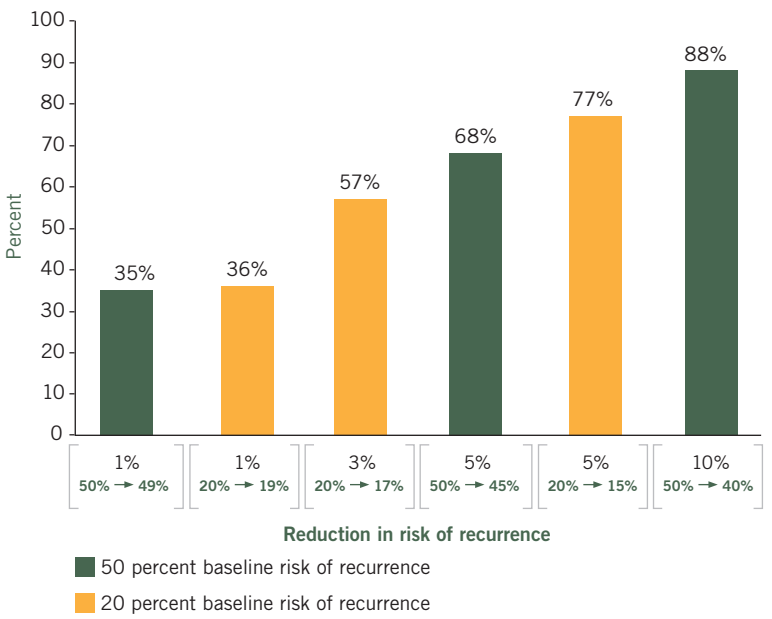
The overall survival data have not been reported yet. So we don't have the long-term follow-up, but we do know there's an attendant risk of long-term neurotoxicity, which affects decisions about the use of this therapy when the gain is marginal in terms of overall survival.

Track 6

DR LOVE: We asked 150 people who had received adjuvant chemotherapy for colorectal cancer in the last five years, "How much benefit would you want to receive in order to go through chemotherapy again?" Approximately one third of them would go through chemotherapy again for a one percent reduction in relapse rate, and more than half of them would go through therapy for a three percent reduction (6.3).

6.3

Percent of Patients with Colorectal Cancer Who Would Receive Adjuvant Chemotherapy Again for Various Reductions in Risk of Recurrence



SOURCE: Love N et al. Gastrointestinal Cancers Symposium 2007; **Abstract 239**.

DR WOLMARK: I believe that from a biologic standpoint, we have no reason to think that Stage II patients are a unique subset relative to their responsiveness to adjuvant therapy. It's just that they're at lower risk for recurrence.

What your analysis, Neil, has shown is very useful. The heterogeneity between breast and colon cancer does not lie in the tumor or in the patient. Patients want to be treated for the same low risk, whether they have breast or colon cancer. The heterogeneity lies in the fact that, traditionally, the medical oncologist who specializes in colorectal cancer is less enthusiastic about adjuvant therapy.

The irksome part from my perspective is not that all Stage II patients should be treated — it's that all Stage II patients should be apprised of the benefit of adjuvant chemotherapy.

I believe what we need to resolve this issue is a tool that allows us to evaluate patients beyond the traditional factors we've used to decide which patients with early-stage colorectal cancer to treat. We need an assay equivalent to Onco*type*

DX™, and I believe we're making significant progress relative to that.

DR HOCHSTER: I agree that every patient with Stage II cancer would benefit from seeing a medical oncologist. Even if they decide against adjuvant therapy, they reap other benefits, such as discussions about the risk of colorectal cancer for relatives and how they can be screened. Patients also need to know how their health-related issues for the next 25 years will be different as a result of their having colorectal cancer, particularly in terms of future screening so that if they're the one patient in five who develops recurrence, we can capture it when it's likely to be curative. ■

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**

Barrier A et al. **Stage II colon cancer prognosis prediction by tumor gene expression profiling.** *J Clin Oncol* 2006;24(29):4685-91. **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**

Chung KY, Kelsen D. **Adjuvant therapy for stage II colorectal cancer: Who and with what?** *Curr Treat Options Gastroenterol* 2006;9(3):272-80. **Abstract**

Cronin DP et al. **Patterns of care for adjuvant therapy in a random population-based sample of patients diagnosed with colorectal cancer.** *Am J Gastroenterol* 2006;101(10):2308-18. **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**.

Figueredo A et al. **Adjuvant therapy for stage II colon cancer: A systematic review from the Cancer Care Ontario Program in Evidence-Based Care's gastrointestinal cancer disease site group.** *J Clin Oncol* 2004;22(16):3395-407. **Abstract**

Funaioli C et al. **Does biomolecular characterization of stage II/III colorectal cancer have any prognostic value?** *Clin Colorectal Cancer* 2006;6(1):38-45. **Abstract**

Gill S et al. **Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: Who benefits and by how much?** *J Clin Oncol* 2004;22(10):1797-806. **Abstract**

Gray RG et al. **QUASAR: A randomized study of adjuvant chemotherapy (CT) vs observation including 3238 colorectal cancer patients.** *Proc ASCO* 2004;**Abstract 3501**.

Hickish T et al. **Stage II patients in the "MOSAIC" trial evaluating oxaliplatin/5-FU/LV as adjuvant treatment of colon cancer: A subpopulation analysis.** *Ann Oncol* 2004;15 (Suppl 3):III76;**Abstract 284P**.

Love N et al. **How well do we communicate with our patients? A survey of patients who received adjuvant chemotherapy for colorectal cancer.** Gastrointestinal Cancers Symposium 2007;**Abstract 239**.

Lanza G et al. **Immunohistochemical test for MLH1 and MSH2 expression predicts clinical outcome in stage II and III colorectal cancer patients.** *J Clin Oncol* 2006;24(15):2359-67. **Abstract**

Morris M et al. **Survival rates for stage II colon cancer patients treated with or without chemotherapy in a population-based setting.** *Int J Colorectal Dis* 2007;[Epub ahead of print]. **Abstract**

SECTION 7

Treatment of Patients with Potentially Curable Hepatic Metastases — Discussant: Howard S Hochster, MD

Tracks 1-9

Track 1 Preoperative therapy for patients undergoing potentially curative resection of hepatic metastases

Track 2 Chemotherapy with bevacizumab and an anti-EGFR antibody or cetuximab for potentially resectable metastatic disease

Track 3 Therapeutic approach for patients with "borderline resectable" metastatic disease

Track 4 Clinical trials evaluating biologic doublets in the metastatic setting

Track 5 Potential impact of converting unresectable hepatic metastases to resectable disease

Track 6 Novel biologic strategies and agents in colorectal cancer

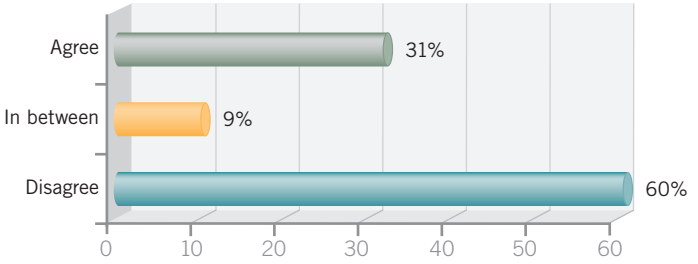
Track 7 Tumor location and vascularity and the resectability of hepatic metastases

Track 8 Use of FOLFOX with either bevacizumab or cetuximab for potentially resectable metastatic disease

Track 9 Therapeutic options for patients with peritoneal metastases and liver disease

AUDIENCE POLL QUESTION 7

One reasonable nonprotocol option for patients with colorectal cancer treated preoperatively with curative intent is combination chemotherapy with bevacizumab and an anti-EGFR antibody.



Tracks 1-2

DR LOVE: Howard, do you recommend preoperative chemotherapy for patients with potentially resectable hepatic metastases?

DR HOCHSTER: If a patient has a clearly resectable liver lesion or two, we have a discussion with the patient and the surgeon as to whether it makes more sense to do surgery first or to administer induction chemotherapy and

7.1

EORTC-40983: Phase III Trial of Neoadjuvant FOLFOX4 for Resectable Colorectal Cancer (CRC) Liver Metastases

Accrual: 364 (Closed)

- Potentially resectable liver metastases of CRC
- No extrahepatic disease
- No previous chemotherapy with oxaliplatin

R → FOLFOX4 → surgery → FOLFOX4

R → Surgery

Primary endpoints: Progression-free survival, overall survival

Response to chemotherapy (RECIST)

Efficacy parameter	
Complete response (CR)	6/182 (3.3%)
Partial response (PR)	64/182 (35.2%)
Stable disease (SD)	61/182 (33.5%)
Clinical benefit (CR + PR + SD)	131/182 (71.9%)
Progressive disease	14/182 (7.7%)
Not available	37/182 (20.3%)

SOURCE: Gruenberger T et al. *Proc ASCO* 2006;**Abstract 3500**.

then go for surgery.

I believe administering chemotherapy first is an option, and while we don't have data showing that induction chemotherapy improves survival, we hope the EORTC-40983 trial will show that eventually.

In this Phase III trial, patients with potentially resectable liver metastases were randomly assigned to receive three months of FOLFOX before and three months of FOLFOX after surgery or to undergo surgery without chemotherapy (Gruenberger 2006b; [7.1]).

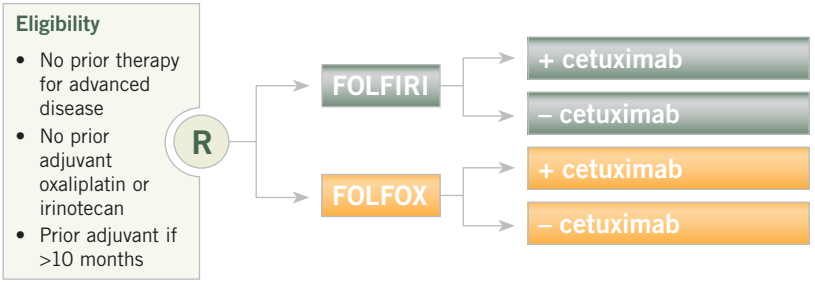
If the trial demonstrates a survival benefit for chemotherapy, then we will know to treat these patients with chemotherapy up front. However, you have to bear in mind that the systemic therapy in the trial is FOLFOX alone, not FOLFOX with bevacizumab.

DR LOVE: How do you treat the patient who has either unresectable liver disease or one or two metastases in the lung in addition to the liver metastases?

DR HOCHSTER: In those cases, I prefer FOLFOX with bevacizumab because that combination has the highest response rate. The first-line data from the somewhat abbreviated SWOG study show that cetuximab also improves the

7.2

CALGB-80203: Preliminary Results of a Phase III Study of FOLFIRI or FOLFOX with or without Cetuximab for Untreated Metastatic Colorectal Cancer



CALGB-80203: Response by Treatment

Response	FOLFIRI (n = 58)	FOLFIRI + cetuximab (n = 55)	FOLFOX (n = 58)	FOLFOX + cetuximab (n = 53)
CR + PR	22 (36%)	26 (44%)	24 (40%)	35 (60%)
SD	23 (38%)	19 (32%)	18 (30%)	15 (26%)

SOURCE: Venook A et al. *Proc ASCO* 2006;**Abstract 3509**.

response rate when combined with chemotherapy, so we have two antibodies that increase the response rate over chemotherapy alone.

The CALGB-C80203 study, presented by Alan Venook at ASCO 2006, was supposed to accrue 2,200 patients but was stopped early after enrolling approximately 280. The design was a two-by-two randomization of FOLFOX versus FOLFIRI with or without cetuximab. The addition of cetuximab showed approximately a 10 to 20 percent increase in the response rate for both arms, so this study also suggests that the addition of cetuximab to first-line chemotherapy improves the response rate (Venook 2006; [7.2]).

Data from the large European study, the CRYSTAL trial, should also be available soon. This trial compares FOLFIRI with or without cetuximab for first-line therapy. According to the recent press release, cetuximab did increase progression-free survival, which was the primary endpoint.

Track 4

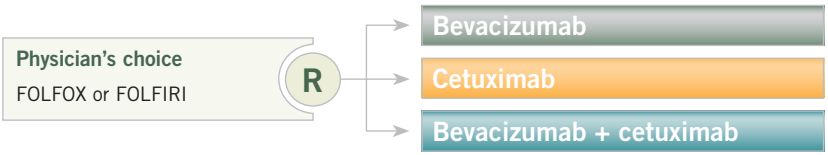
DR LOVE: Can you review the BOND-2 trial?

DR HOCHSTER: This was a Phase II, NCI consortium trial that we partici-

7.3

CALGB-C80405: Chemotherapy and Biologic Agents Alone or in Combination in the Treatment of Metastatic CRC

Target accrual: 2,300 (533 as of 3/28/07)



Select Eligibility Criteria

- Untreated metastatic disease
- No CNS metastases or carcinomatous meningitis
- No prior treatment with an agent that targets VEGF or EGF receptors
- More than 12 months since adjuvant 5-FU with or without oxaliplatin or irinotecan

Study Contacts

Cancer and Leukemia Group B
Alan Venook, MD, Protocol Chair
Tel: 415-353-7065; 800-888-8664

Southwest Oncology Group
Charles Blanke, MD, FACP, Protocol Chair
Tel: 503-494-1556

SOURCES: CTSU protocol list March 2007; NCI Physician Data Query, March 2007.

pated in with Leonard Saltz at Memorial. The trial evaluated patients whose disease had progressed on an irinotecan regimen but who had not received bevacizumab previously. Patients who received both bevacizumab and cetuximab had approximately a 20 percent response rate, as compared to 11 percent among patients who received cetuximab only.

The toxicities were as expected from either antibody, with no unexpected or synergistic toxicities (Saltz 2005). They saw vascular side effects and perforations from the bevacizumab and skin toxicities from the cetuximab.

DR LOVE: What other ongoing studies are evaluating the double antibody approach?

DR HOCHSTER: Two studies are examining this strategy in the front-line setting. The PACCE study is a first-line study of FOLFOX or FOLFIRI with bevacizumab in one arm versus bevacizumab and panitumumab in the second arm. It has already completed accrual, and data should be available in the next year.

The other study is the CALGB Intergroup study, C80405, which is a three-arm study powered for survival, so it is a much bigger study. The physician selects either FOLFOX or FOLFIRI, and then patients are randomly assigned to bevacizumab alone, cetuximab alone or the combination of the two (7.3).

That's an excellent study, which, if completed, will show the merits of using

an anti-VEGF antibody, an anti-EGF antibody or the combination of the two. That should give us some clear data.

Track 8

DR LOVE: Axel, what do you consider a reasonable approach to treating patients with potentially resectable metastatic disease in practice?

DR GROTHEY: I believe what we are seeking in the neoadjuvant setting is response rate, more than delaying of tumor progression, but we don't want to get to the point where we can no longer see the metastases. I have heard the statement, "The medical oncologist's dream is a surgeon's nightmare." We know that a complete response in a liver metastasis is not a complete response by the pathology criteria.

I can easily see the rationale for using EGF receptor antibodies based on Alan's data and other data (Venook 2006). A consistent response rate benefit occurs when we add cetuximab. However, the data are limited, and we're still waiting on the Phase III first-line trial results with cetuximab.

Whether we should also add bevacizumab is a different question. For now, I believe that in first-line, neoadjuvant therapy, response rate is our surrogate marker for resectability, but how we get there is an area of discussion.

DR LOVE: What do you currently use in clinical practice?

DR GROTHEY: Off study, I've used FOLFOX/bevacizumab, and I've used FOLFOX/cetuximab.

DR LOVE: Alan, how do you feel about double biologic therapy in this setting?

DR VENOOK: One of the endpoints of the Phase III CALGB-C80405 trial, the study of cetuximab and/or bevacizumab with FOLFOX or FOLFIRI in patients with previously untreated metastatic colorectal cancer, is to analyze the number of patients who go to surgery. However, off study, I would not use double biologics, largely due to the insurance issues.

DR LOVE: How do you feel about using FOLFOXIRI in this setting?

DR VENOOK: Data in the literature are conflicting regarding FOLFOXIRI. A paper from the Hellenic Oncology Society in Greece in the *British Journal of Cancer* showed more toxicity and no benefit with FOLFOXIRI when compared to FOLFIRI (Souglakos 2006).

Generally, our approach is to treat these patients with four cycles of FOLFOX/bevacizumab. If at that point the tumor is deemed resectable, we stop the bevacizumab, administer another dose of FOLFOX and then resect six weeks after the last dose of bevacizumab.

We have to be careful not to offer too much treatment to these patients preop-

eratively, or we may eradicate the disease and the surgeon doesn't know where to go, believe it or not. Also, it may result in a fatty liver, and the experienced hepatic surgeon can tell you that the liver is like mush in some of these patients who have been too heavily pretreated. ■

SELECT PUBLICATIONS

Adam R et al. **Chemotherapy and surgery in the treatment of colorectal liver metastases: The golden alliance.** Gastrointestinal Cancers Symposium 2007;Educational summaries:74-5.

Adam R et al. **Tumor progression while on chemotherapy: A contraindication to liver resection for multiple colorectal metastases?** *Ann Surg* 2004;240(6):1052-64. **Abstract**

Barrier A et al. **Stage II colon cancer prognosis prediction by tumor gene expression profiling.** *J Clin Oncol* 2006;24(29):4685-91. **Abstract**

Chung KY, Kelsen D. **Adjuvant therapy for stage II colorectal cancer: Who and with what?** *Curr Treat Options Gastroenterol* 2006;9(3):272-80. **Abstract**

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**

Dealis C et al. **Phase II trial of FOLFOX-6 and bevacizumab in unresectable liver metastasis from colorectal cancer: A preliminary safety analysis.** Gastrointestinal Cancers Symposium 2007;**Abstract 452**.

Gruenberger B et al. **Neoadjuvant chemotherapy including bevacizumab in potentially curable metastatic colorectal cancer.** *Proc ASCO* 2006a;**Abstract 3546**.

Gruenberger T et al. **Tumor response to pre-operative chemotherapy (CT) with FOLFOX-4 for resectable colorectal cancer liver metastases (LM). Interim results of EORTC Intergroup randomized phase III study 40983.** *Proc ASCO* 2006b;**Abstract 3500**.

Hochster HS. **Bevacizumab in combination with chemotherapy: First-line treatment of patients with metastatic colorectal cancer.** *Semin Oncol* 2006;33(5 Suppl 10):8-14. **Abstract**

Hurwitz HI et al. **Bevacizumab in combination with fluorouracil and leucovorin: An active regimen for first-line metastatic colorectal cancer.** *J Clin Oncol* 2005;23(15):3502-8. **Abstract**

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

Lenz H et al. **Pharmacogenomic analysis of a randomized phase II trial (BOND 2) of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer.** Gastrointestinal Cancers Symposium 2007;**Abstract 401**.

Saltz LB et al. **Randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer.** *Proc ASCO* 2005;**Abstract 3508**.

Souglakos J et al. **FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): A multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG).** *Br J Cancer* 2006;94(6):798-805. **Abstract**

Venook A et al. **Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) ± cetuximab for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): CALGB 80203 preliminary results.** *Proc ASCO* 2006;**Abstract 3509**.

Vincenzi B et al. **The new era in the treatment of advanced colorectal cancer patients: The role of monoclonal antibodies.** *Expert Opin Emerg Drugs* 2006;11(4):665-83. **Abstract**

Yoo PS et al. **Liver resection for metastatic colorectal cancer in the age of neoadjuvant chemotherapy and bevacizumab.** *Clin Colorectal Cancer* 2006;6(3):202-7. **Abstract**

POST-TEST

Colorectal Cancer Clinical Investigator Think Tank: *Proceedings from a CME Satellite Symposium at the Gastrointestinal Cancers Symposium in Orlando, Florida*

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **According to the BRiTE registry, the incidence of arterial thromboembolic events associated with bevacizumab is _____ compared with 1.5 percent among patients who did not receive bevacizumab.**
   a. One percent
   b. Four percent
   c. 10 percent
   d. 14 percent
2. **The current standard practice is to stop bevacizumab therapy _____ before surgery to reduce the risk of surgical complications.**
   a. Two to three weeks
   b. Six to eight weeks
   c. Three to four months
   d. Six months
3. **In the OPTIMOX1 trial, induction therapy with six cycles of FOLFOX7 followed by six months of maintenance therapy with 5-FU/leucovorin and planned reintroduction of FOLFOX7 was equivalent to the continuation of FOLFOX4 until disease progression or toxicity in terms of _____.**
   a. Response rate
   b. Progression-free survival
   c. Duration of disease control
   d. Overall survival
   e. All of the above
4. **In the OPTIMOX2 trial, maintenance therapy with 5-FU/leucovorin compared to a chemotherapy-free interval following FOLFOX7 significantly improved _____.**
   a. Response rate
   b. Progression-free survival
   c. Duration of disease control
   d. Overall survival
   e. All of the above
5. **Randomized Phase III trial data have demonstrated that maintenance therapy with bevacizumab following FOLFOX/bevacizumab improves progression-free and overall survival.**
   a. True
   b. False
6. **The ongoing NSABP-C-10 trial evaluates FOLFOX with _____ in patients with synchronous primary lesions and metastatic disease.**
   a. Bevacizumab
   b. Cetuximab
   c. Irinotecan
7. **A pooled analysis of FOLFOX-based trials in the adjuvant and palliative settings demonstrated that patients who are 70 years of age and older have _____ from FOLFOX compared to patients who are younger than 70 years old.**
   a. The same benefit
   b. Less benefit
   c. Almost the same level of toxicity
   d. Both a and c
   e. Both b and c
8. **Current clinical practice guidelines recommend the use of adjuvant chemotherapy for all patients with Stage II colon cancer.**
   a. True
   b. False
9. **In the Phase III trial EORTC-40983, patients with resectable liver metastases are randomly assigned to surgery alone or _____.**
   a. Three months of FOLFOX preoperatively only
   b. Three months of FOLFOX postoperatively only
   c. Three months of FOLFOX pre- and postoperatively
10. **In the randomized trial CALGB-C80203 comparing FOLFOX to FOLFIRI with or without cetuximab, a significant increase occurred in the response rate for both cetuximab-containing arms.**
    a. True
    b. False

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

EVALUATION FORM

Colorectal Cancer Clinical Investigator Think Tank: *Proceedings from a CME Satellite Symposium at the Gastrointestinal Cancers Symposium in Orlando, Florida*

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 Post-test and 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

LEARNING OBJECTIVES

To what extent does this CME activity address the following learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in gastrointestinal cancer treatment and incorporate these data into management strategies. . . . . 5 4 3 2 1 N/A
- Evaluate recent data and ongoing trials on various treatment approaches for localized colon cancer and explain the absolute risks and benefits of adjuvant chemotherapy to patients. . . . . 5 4 3 2 1 N/A
- Integrate emerging data on biologic therapies into the management of advanced colon and rectal cancers. . . . . 5 4 3 2 1 N/A
- Discuss neoadjuvant radiation therapy/chemotherapy approaches for patients with rectal cancer. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Richard M Goldberg, MD	5 4 3 2 1	5 4 3 2 1
Axel Grothey, MD	5 4 3 2 1	5 4 3 2 1
Daniel G Haller, 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
Neal J Meropol, MD	5 4 3 2 1	5 4 3 2 1
Alan P Venook, MD	5 4 3 2 1	5 4 3 2 1
Norman Wolmark, 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 ☐ Downloaded MP3s from website

EVALUATION FORM

Colorectal Cancer Clinical Investigator Think Tank: *Proceedings from a CME Satellite Symposium at the Gastrointestinal Cancers Symposium in Orlando, Florida*

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 4.25 *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 fax both to (800) 447-4310, or mail both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Evaluation online at www.ColorectalCancerUpdate.com/GI_2007/CME.

ASCOGIS007

Colorectal Cancer™ UPDATE

Editor/CME Director	Neil Love, MD
Managing Editor	Kathryn Ault Ziel, PhD
Scientific Director	Richard Kaderman, PhD
Writers	Lilliam Sklaver Poltorack, PharmD Douglas Paley
Continuing Education Administrator for Nursing	Sally Bogert, RNC, WHCNP
Content Validation	Margaret Peng John H Brebner Ginelle Suarez Erin Wall
Director, Creative and Copy Editing	Aura Herrmann
Creative Manager	Fernando Rendina
Graphic Designers	Jason Cunnius Tamara Dabney Shantia Daniel Elisa Stambouli
Senior Production Editor	Alexis Oneca
Traffic Manager	Tere Sosa
Copy Editors	Dave Amber Rosemary Hulce Kirsten Miller Pat Morrissey/Havlin Carol Peschke Susan Petrone
Audio Production	Frank Cesarano
Technical Services	Arly Ledezma
Web Master	John Ribeiro
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.com
For CME Information	Email: CME@ResearchToPractice.com

Colorectal Cancer™

U P D A T E

This program is supported by education grants from Genentech BioOncology and Sanofi-Aventis.

Research To Practice®

Sponsored by Research To Practice.

Last review date: April 2007
Release date: April 2007
Expiration date: April 2008
Estimated time to complete: 4.25 hours