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Colorectal Cancer™ UPDATE

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

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Colorectal Cancer Update

A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

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

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

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment, and incorporate these data into management strategies in the local and advanced disease settings.
- Counsel appropriate patients about the availability of ongoing clinical trials.
- Evaluate the emerging research data on various adjuvant chemotherapy approaches, including the use of oxaliplatin-containing regimens and the use of capecitabine or intravenous 5-FU, and explain the absolute risks and benefits of these regimens to patients.
- Evaluate emerging research data on various neoadjuvant radiation therapy/chemotherapy approaches to rectal cancer and explain the absolute risks and benefits of these regimens to patients.
- Integrate emerging data on biologic therapies into management strategies for patients with advanced colorectal cancer.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 5 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Grothey, Haller, Fuchs and Meropol on the integration of emerging clinical research data into the management of colorectal cancer.

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UPCOMING EDUCATIONAL EVENTS

American Society of Clinical Oncology 2007 Gastrointestinal Cancers Symposium
January 19-21, 2007
Orlando, Florida
Event website: **asco.org/GI2007**

The Emerging Role of Biologic Therapy in the Management of Gastrointestinal Cancers: A Case-Based Interactive Tumor Panel Discussion
January 20, 2007
Orlando, Florida
Event website: **ColorectalCancerUpdate.com**

Scripps Cancer Center's 27th Annual Conference: Clinical Hematology and Oncology
February 17-20, 2007
San Diego, California
Event website: **scripps.org/CMEGME.asp?ID=99**

NCCN 12th Annual Conference: Clinical Practice Guidelines and Quality Cancer Care
March 14-18, 2007
Hollywood, Florida
Event website: **nccn.org**

American Association for Cancer Research Annual Meeting
April 14-18, 2007
Los Angeles, California
Event website: **aacr.org**

American Society of Clinical Oncology 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Event website: **asco.org**

American Society of Colon and Rectal Surgeons 2007 Annual Meeting
June 2-6, 2007
St Louis, Missouri
Event website: **fascrs.org**

INTERVIEW

Axel Grothey, MD

Dr Grothey is Senior Associate Consultant in the Department of Medical Oncology at the Mayo Clinic in Rochester, Minnesota.

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Track 13 Use of adjuvant fluoropyrimidine monotherapy

Track 14 NSABP-R-04: Preoperative radiation therapy and oral versus intravenous 5-FU with or without oxaliplatin for rectal cancer

Track 15 Use of postoperative adjuvant therapy for rectal cancer

Select Excerpts from the Interview

Track 3

DR LOVE: Can you discuss the OPTIMOX data sets presented at ASCO?

DR GROTHEY: I believe the most important trial in this regard was the OPTIMOX2 trial (Maindrault-Goebel 2006), which was based on a prior trial conducted in France, the OPTIMOX1 trial (Tournigand 2006). OPTIMOX1 was a Phase III trial comparing FOLFOX4 continued until patients either devel-

oped toxicities or their disease progressed to a stop-and-go regimen — with the stop-and-go related to oxaliplatin — meaning that patients were treated with a limited duration of FOLFOX then continued on a maintenance therapy of 5-FU alone, and oxaliplatin was to be reintroduced at a planned interval.

OPTIMOX2 went one step further by introducing the complete chemotherapy-free interval — giving patients a complete break from all treatment until their disease progressed and comparing it to maintenance therapy.

The problem with this trial for our current practice, beyond the fact that it did not include bevacizumab, was that this trial design allowed tumors to grow back to their initial size. Patients who had a response to FOLFOX-based therapy and discontinued FOLFOX after three months of therapy were then followed and tumors were allowed to progress back to their initial presentation. I believe this would currently be quite a hard sell to patients.

Within these limitations, and based on the fact that only 200 patients were assigned in this trial, no significant difference appeared in the duration of disease control as defined by the study. We don't have any data on overall survival yet, and we don't have quality-of-life data, but at least withholding therapy did not appear to harm patients.

Track 4

DR LOVE: How do you make the decision between FOLFOX and FOLFIRI to combine with bevacizumab in the first-line setting?

DR GROTHEY: If we are treating in the neoadjuvant potentially curative setting, an abundance of data support FOLFOX over FOLFIRI and oxaliplatin over irinotecan, particularly the recent data coming from MD Anderson about the effects of liver toxicity on therapy and postoperative, postliver resection mortality or morbidity (Vauthey 2006).

Outside of that, I believe whether you use FOLFOX or FOLFIRI is "a wash." Outside of a clinical trial, I talk to my patients about which toxicity they would prefer. It's either the neurotoxicity or the higher risk of developing early onset diarrhea. From an efficacy point of view, FOLFOX and FOLFIRI are not different in the palliative setting.

DR LOVE: We don't have direct comparisons of FOLFOX/bevacizumab versus FOLFIRI/bevacizumab, but can you make any indirect conclusions from the BICC-C trial data and the TREE trial data?

DR GROTHEY: Yes. The TREE trials (Hochster 2006, 2005) and the BICC-C trial (Fuchs 2006) were similar. The TREE-1 and BICC-C trials both started the year before bevacizumab was approved, so both trials did not include bevacizumab in their first phase, and both trials evaluated what is the best fluoropyrimidine, in combination with either oxaliplatin in the TREE trials or irinotecan in the BICC-C trial.

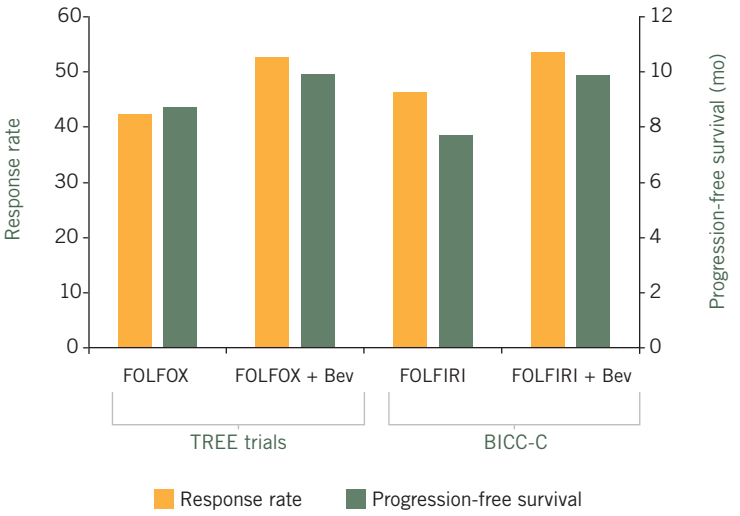
After bevacizumab was approved in the United States, the TREE trial, which evaluated oxaliplatin combinations, was amended to include bevacizumab in all three treatment arms. The capecitabine dose in arm three was reduced to account for toxicities observed in TREE-1, and the BICC-C trial discontinued the capecitabine and irinotecan arm and added bevacizumab to FOLFIRI and IFL.

What we have now is a cross-trial comparison. When you compare FOLFOX and FOLFIRI with bevacizumab in TREE-2 and in the BICC-C trial, it's interesting to see that the progression-free survival in both trials — a cross-trial comparison for FOLFOX with bevacizumab and FOLFIRI with bevacizumab — was 9.9 months, exactly identical. The response rates were 54 to 55 percent, almost identical (1.1).

We have data on FOLFOX with bevacizumab in terms of overall survival, which was 26 months in TREE-2. For FOLFIRI with bevacizumab, the endpoint for overall survival in the BICC-C Phase II trial had not yet been reached, but the survival curve suggested that it will be beyond two years. So we have similar data on FOLFIRI and FOLFOX using almost all efficacy parameters.

1.1

Comparative Response Rates in Trials that Evaluated FOLFOX or FOLFIRI with and without Bevacizumab for First-Line Treatment of Metastatic Colon Cancer: TREE and BICC-C Trials



SOURCES: Grothey A. Presentation. Best of ASCO 2006, Beverly Hills; Hochster HS et al. Presentation. ASCO 2006;**Abstract 3510**; Fuchs C et al. ASCO 2006;**Abstract 3506**.

Track 9

DR LOVE: How are you approaching patients in the adjuvant setting in terms of nonprotocol therapy?

DR GROTHEY: Recently we have moved from 5-FU to FOLFOX as standard of care in the adjuvant setting for colon cancer and, for most purposes, also in rectal cancer. So the new question is how to integrate the biologic agents that we know work in the palliative setting — cetuximab and bevacizumab. Both of these biologics have demonstrated efficacy in established colorectal cancer tumors, but it has not been determined whether they play any role in the adjuvant setting.

We can't immediately transfer all our knowledge and our experience from the palliative setting into the adjuvant setting. This was demonstrated by the relative failure of irinotecan to show benefit in the adjuvant setting (Saltz 2004), whereas in the palliative setting FOLFOX and FOLFIRI are equivalent.

Cetuximab is an EGFR antibody, and bevacizumab is a VEGF inhibitor. Both are being tested in the United States in ongoing cooperative group trials. NSABP-C-08 is evaluating FOLFOX with or without bevacizumab as adjuvant therapy for Stage II and III colon cancer. NCCTG-N0147 is evaluating FOLFOX with or without cetuximab in the adjuvant setting.

ECOG has a Stage II trial (E5202) observing patients at molecular high risk as defined by microsatellite instability and loss of heterozygosity at the 18q chromosome. Those patients will be randomly assigned to FOLFOX with or without bevacizumab — analogous to the C-08 trial.

For every patient that we see right now in the adjuvant setting, Stage II and Stage III, there is an adjuvant trial available (1.2). These trials are being mirrored by European trials that are similar in design: The AVANT trial is evaluating bevacizumab, and the PETACC trial is evaluating cetuximab.

Track 14

DR LOVE: In rectal cancer, the NSABP is evaluating the use of capecitabine versus continuous infusion 5-FU with or without oxaliplatin. What do we know about both of these questions?

DR GROTHEY: The NSABP-R-04 trial was initially designed simply to compare capecitabine to continuous infusion 5-FU, but over time this question became more and more secondary. We want to optimize not only local control but also the systemic effects of therapy so that micrometastases can be treated as early as possible. So evaluating an oxaliplatin-based combination made sense because we also know that oxaliplatin is a good radiosensitizer and has systemic efficacy at a dose of 50 mg/m^2 on a weekly basis.

The standard of care right now outside of a clinical trial would be to use continuous infusion 5-FU. A growing body of evidence suggests that

capecitabine at a dose of 825 mg/m^2 BID from Monday to Friday with weekend breaks throughout radiation can be safely administered, and this regimen has similar efficacies in Phase II cross-trial comparisons. ■

1.2

Selected Ongoing Adjuvant Trials of Cetuximab or Bevacizumab for Patients with Resected Colon Cancer

Trial	Target accrual	Eligibility	Treatment
NCCTG-N0147	2,300	Stage III	FOLFOX +/- cetuximab†
ECOG-E5202	3,610	Stage II	FOLFOX +/- bevacizumab*
AVANT	3,450	Stage II or III	FOLFOX +/- bevacizumab,* CAPOX + bevacizumab*
PETACC-8	2,000	Stage III	FOLFOX +/- cetuximab

* Bevacizumab-containing arm(s) to receive maintenance therapy with bevacizumab following combination therapy

† Arms that include irinotecan closed to enrollment as of 6/1/2005

SOURCE: NCI Physician Data Query, November 2006.

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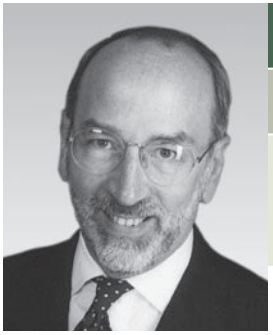

INTERVIEW

Daniel G Haller, MD

Dr Haller is Professor of Medicine at the Abramson Cancer Center at the University of Pennsylvania in Philadelphia, Pennsylvania.

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Track 2 US BRiTE registry trial: Side effects and toxicity of bevacizumab in clinical practice

Track 3 Predicting risk of bevacizumab-associated arterial thrombotic events

Track 4 Acquired hypertension as a predictor of response to bevacizumab

Track 5 Cetuximab-associated rash: Implications for adjuvant therapy

Track 6 Preoperative versus postoperative chemoradiation therapy for rectal cancer

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Track 8 Rationale for incorporating oxaliplatin with preoperative radiation therapy for rectal cancer

Track 9 Selection of oral versus infusional fluoropyrimidine therapy

Track 10 Geographic variability in the tolerability of fluoropyrimidines

Track 11 Use of preoperative response to chemoradiation therapy to determine postoperative adjuvant therapy for rectal cancer

Select Excerpts from the Interview

Track 2

DR LOVE: Can you discuss the findings of the US BRiTE registry trial?

DR HALLER: I believe American oncologists are doing a wonderful job of selecting patients. The BRiTE registry showed that the toxicity profile of bevacizumab for the average patient in the community is similar to those in clinical trials. This is important information to have. Sometimes we worry that patients in trials are so extraordinarily selected that toxicity findings will not apply to our patients.

We know that 20 percent of patients with metastatic disease should not receive bevacizumab because of the high risk of arterial thrombotic events, perforation or other adverse events. I believe 80 percent might be the correct number of patients to be receiving bevacizumab.

DR LOVE: Where are we in terms of understanding the side effects and toxicity of bevacizumab?

DR HALLER: We know that the toxicity profile we saw in the AVF2107 trial is somewhat predictive of what we see in clinical practice (Hurwitz 2003; Hedrick 2006; [2.1]). As a practitioner, that is comforting — I can tell a patient what to expect.

2.1

Selected Adverse Events Associated with Bevacizumab in the BRiTE Registry

Adverse event*	BRiTE registry (N = 1,960)	AVF2107 IFL + BV arm† (n = 402)
Hypertension requiring medication	16.4%	11.0%†
Grade III or IV bleeding event	2.2%	3.1%
Gastrointestinal perforation	1.7%	1.5%
Arterial thromboembolic event	1.5%	4.0%
Postoperative bleeding or wound-healing complications	1.4%	2.1%‡

* Patients may have experienced more than one type of BV-associated adverse event.
† Grade III hypertension
‡ Serious adverse events in IFL + BV and 5-FU + BV arms (n = 616)

SOURCE: Hedrick E et al. *Proc ASCO* 2006;**Abstract 3536**.

Track 8

DR LOVE: The NSABP-R-04 trial, which originally compared preoperative capecitabine and radiation therapy to continuous infusion 5-FU and radiation therapy, has now been amended to include oxaliplatin. What do we know about neoadjuvant oxaliplatin?

DR HALLER: Our preclinical rationale is something we have inferred from laboratory evidence — that platinates will be synergistic with radiation therapy. This is why platinums and fluoropyrimidines have been used in head and neck cancer, lung cancer, cervical cancer and other settings.

Our clinical rationale stems from two US trials, CALGB 89901 and ECOG 1297 (Ryan 2006; Rosenthal 2003). These trials incorporated infusional 5-FU and either biweekly or weekly oxaliplatin and showed pathologic complete response rates in the mid 20 percent range, compared to about 10 percent in other trials, including the German study with preoperative 5-FU and radiation therapy (Sauer 2004).

Indeed, across a series of Phase I-II trials, we see reliable pathologic complete response rates from the midteens up to about 40 percent. To me, the consistency of the data is important.

At our institution, we collected data from a large series of patients who were not enrolling in a study but received preoperative 5-FU with or without oxaliplatin. When we examined these cases retrospectively, we saw that the patho-

logic complete response rates were equivalent to those seen in the ECOG trial (Dolinsky 2006).

The data were so intriguing to our radiation oncologists and surgeons that they hesitated to refer a patient unless they believed the patient might receive oxaliplatin as part of a "standard" regimen.

Track 10

DR LOVE: Can you summarize the fascinating and long-awaited data that you presented at ASCO on the side effects of fluoropyrimidines and geography?

DR HALLER: As American oncologists, we all thought we were doing something wrong. What was it about our patients that made them appear to suffer so much more toxicity from capecitabine than the patients described in trials? Dr Hans Schmoll and I co-chaired a study that compared CAPOX with either the Roswell or the Mayo Clinic 5-FU regimens in 1,800 patients with Stage III colon cancer (Schmoll 2005). When we evaluated toxicity differences by region, we saw on the surface that the US population clearly had more toxicity.

When we combined our data with two trials of the Mayo Clinic regimen versus capecitabine in advanced disease (Hoff 2001; van Cutsem 2001), the toxicity profile was consistent across the board. We then reviewed historically the IMPACT data (IMPACT 1995), which were a compilation of 5-FU and leucovorin regimens versus surgery alone in colon cancer, and saw that Europeans had less toxicity with any 5-FU and leucovorin regimen.

At ASCO this year Dr Schmoll presented toxicity data for the CAPOX study (Schmoll 2006), and I presented a poster on capecitabine in both the metastatic and adjuvant settings with or without oxaliplatin (Haller 2006).

For US patients versus non-US patients, the hazard ratios were about 1.8 for almost any toxicity you could name, including myelosuppression, a nonself-reported toxicity, and some self-reported toxicities such as diarrhea and mucositis (2.2).

2.2 Regional Differences in Tolerability of Fluoropyrimidines

Adjusted relative risk (95% CI) for US vs non-US patients

	First-line MCRC	Adjuvant colon cancer
Grade III/IV AEs	1.75 (1.34-2.29)	1.48 (1.10-1.99)
Grade III/IV GI AEs	1.74 (1.27-2.37)	1.68 (1.23-2.30)
Grade III/IV neutropenia	1.46 (0.98-2.18)	1.44 (0.90-2.30)

AE = adverse event; CI = confidence interval; GI= gastrointestinal

SOURCE: With permission. Haller DG et al. *Proc ASCO* 2006;**Abstract 3514**.

So it is no longer unclear whether Americans have more toxicity — it is now a known truth. Possible explanations for these differences include differences in pharmacogenetic factors or differences in external environmental factors, such as diet. Dr Carmen Allegra has shown that certain foods or supplements — and American diets are very high in folates — may be contributing to toxicity. ■

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INTERVIEW

Charles S Fuchs, MD, MPH

Dr Fuchs is Associate Professor of Medicine at the Dana-Farber Cancer Institute of Harvard University in Boston, Massachusetts.

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Track 2 Use of irinotecan-containing regimens in the adjuvant setting

Track 3 Effects of physical activity on patients with colon cancer

Track 4 Influence of regular aspirin use on survival for patients with colon cancer

Track 5 Potential mechanisms of aspirin, diet and exercise on risk of cancer recurrence

Track 6 Feasibility of prospectively evaluating aspirin, diet or exercise in clinical trials

Track 7 Counseling patients about dietary and lifestyle modifications

Track 8 Selection of adjuvant chemotherapy for patients with Stage II disease

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Track 3

DR LOVE: Can you review your data evaluating exercise in the adjuvant trial of IFL (CALGB-C89803)?

DR FUCHS: In CALGB-C89803, which was a negative trial in terms of the primary endpoint (Saltz 2004), we provided patients with a 16-page questionnaire about diet and lifestyle. Patients completed the questionnaire, which was validated through various studies such as the Nurses' Health Study. In the CALGB trial, the surveys were administered midway through adjuvant therapy and about six months after its completion (Meyerhardt 2006a, b).

Compliance with the questionnaire was excellent — about 95 percent of the patients completed it. Physical activity was highly protective and associated with a significant improvement in disease-free survival. The more physically

active the patient, the better the disease-free and overall survival (Meyerhardt 2006a).

DR LOVE: Did the physical activity occur during chemotherapy?

DR FUCHS: It was during and after chemotherapy. We measured it at two time points. If the patients walked an average of about six hours per week, they had a 47 percent improvement in disease-free survival (Meyerhardt 2006a).

One might argue that the physically active patients were healthier and the patients who were inactive had occult cancer. We considered that and repeated the analysis by excluding all of the events in the first six months after completing the questionnaire, and we found the same results (Meyerhardt 2006a). We also repeated the analysis for the patients with colon cancer in the Nurses' Health Study who had completed the same questionnaire, and the findings were identical (Meyerhardt 2006b).

Track 8

DR LOVE: How do you approach the decision about adjuvant chemotherapy off protocol, particularly for patients with Stage II disease?

DR FUCHS: I use the clinical features we are familiar with, such as perforation and obstruction and the number of lymph nodes sampled. I try to pool together patients I don't believe would benefit from adjuvant therapy, those with whom I'm comfortable using a fluoropyrimidine alone and those for whom I would use FOLFOX.

In patients with higher-risk disease — those with few lymph nodes analyzed or those with adherence to or invasion of adjacent structures who might have obstruction or perforation — I'm comfortable using FOLFOX. I have to admit, however, that I'm still willing to use fluoropyrimidine monotherapy for patients with more standard-risk disease, although I know some of my colleagues routinely use FOLFOX in all circumstances.

Although the proportional benefit of FOLFOX is fairly consistent across patients with Stage II or Stage III disease, I also want to consider the absolute benefits, in a particularly low-risk setting. Is the addition of oxaliplatin, with its inherent neuropathy risk, necessary in patients for whom the absolute benefit is not so great?

DR LOVE: When you are going to use fluoropyrimidine monotherapy, do you bring up the possibility of capecitabine?

DR FUCHS: I do. The X-ACT study is a compelling effort (Twelves 2005; [3.1]), although the majority of the patients were enrolled in Europe. Dan Haller has clearly demonstrated that the toxicity associated with capecitabine differs on each side of the Atlantic (Haller 2006). Although you can use 2,500 mg/m^2 per day in Europe with reasonable tolerability, it is difficult to use those doses in the United States. The quandary is that this is an adjuvant setting and

we want to use the standard dose used in the X-ACT trial, yet most patients in North America don't tolerate that dose.

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

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

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

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

Track 11

DR LOVE: How do you approach patients who present with synchronous primary and metastatic colon cancer?

DR FUCHS: I consider the possibility of not sending them to up-front surgery. If the tumor is on the right side, where the risk of obstruction is reasonably low, if they don't demonstrate any obstructive symptoms and if there isn't any obvious bleeding and I'm not concerned about perforation, sending them for a resection would just delay the start of systemic therapy.

I would start them on a regimen of chemotherapy with bevacizumab without sending them for a resection. Some are concerned about the possibility that perforation might occur if the primary is in place, but those data have not been borne out. ■

SELECT PUBLICATIONS

Chlebowski RT et al. **Dietary fat reduction in postmenopausal women with primary breast cancer: Phase III Women's Intervention Nutrition Study (WINS).** Presentation. ASCO 2005;**Abstract 10**.

Haller DG et al. **Tolerability of fluoropyrimidines appears to differ by region.** *Proc ASCO* 2006;**Abstract 3514**.

Meyerhardt JA et al. **Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: Findings from CALGB 89803.** *J Clin Oncol* 2006a;24(22):3535-41. **Abstract**

Meyerhardt JA et al. **Physical activity and survival after colorectal cancer diagnosis.** *J Clin Oncol* 2006b;24(22):3527-34. **Abstract**

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

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

INTERVIEW

Neal J Meropol, MD

Dr Meropol is Director of the Gastrointestinal Cancer Program and Director of the Gastrointestinal Tumor Risk Assessment Program in the Divisions of Medical Science and Population Science at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

Tracks 1-14

Track 1	Introduction
Track 2	OPTIMOX2: Maintenance therapy versus chemotherapy-free intervals
Track 3	Selection of patients with metastatic disease for an intermittent chemotherapeutic strategy
Track 4	Determination of bevacizumab dose in combination with chemotherapy
Track 5	Societal and economic impact of the cost of cancer therapies
Track 6	Predictors of response to EGFR and VEGF inhibitors
Track 7	Key clinical research questions regarding the use of biologic therapies
Track 8	Use of cetuximab/bevacizumab combination antibody therapy
Track 9	Clinical trials evaluating curative intent strategies for patients with initially unresectable metastatic disease
Track 10	Geographic differences in the tolerability of capecitabine
Track 11	Intensive surveillance for early identification of metastatic disease after adjuvant therapy
Track 12	Changing patterns of metastases in colorectal cancer
Track 13	Selection of adjuvant therapy for elderly patients
Track 14	Selection of an oral versus intravenous fluoropyrimidine as monotherapy

Select Excerpts from the Interview

Track 4

DR LOVE: What are some of the common issues raised to you by oncologists in practice?

DR MEROPOL: One of the questions that has recently been raised is, "What is the appropriate dose of bevacizumab to use with chemotherapy for patients with colon cancer?" The original FDA-approved dose was 5 mg/kg every two weeks, based on the IFL data (Hurwitz 2004).

ECOG-E3200, a study for patients who had not previously received bevacizumab but had failed prior therapy with 5-FU and irinotecan, demonstrated a survival advantage with the administration of FOLFOX and bevacizumab. It is interesting that the dose of bevacizumab in ECOG-E3200 was 10 mg/kg

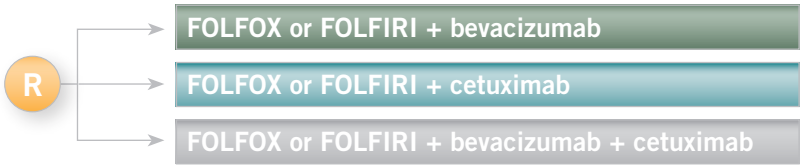
every two weeks (Giantonio 2005).

On the one hand, we have IFL with bevacizumab at 5 mg/kg demonstrating a survival benefit (Hurwitz 2004). Of course, IFL is a chemotherapy regimen we don't use much anymore. I believe most of us who treat many patients with colon cancer are comfortable with 5 mg/kg regardless of the regimen.

More data will be forthcoming from the current Intergroup study (C80405), in which patients will receive chemotherapy (FOLFOX or FOLFIRI) with bevacizumab, cetuximab or the combination as front-line therapy (4.1). This study uses a 5-mg/kg dose of bevacizumab. So we will have additional information about FOLFOX with 5 mg/kg of bevacizumab.

4.1

CALGB-C80405: A Randomized Phase III Study of Bevacizumab and/or Cetuximab with FOLFOX or FOLFIRI for Untreated Advanced Colorectal Cancer



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

Primary Objective

- Overall survival

Secondary Objectives

- Progression-free survival
- Duration of response
- Toxicity
- Resectability of formerly unresectable disease

Target Accrual: 2,300

Current Accrual: 321 (11/10/2006)

Date Activated: September 15, 2005

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: NCI Physician Data Query, October 2006; Cancer Trials Support Unit, November 2006.

Track 7

DR LOVE: What do you think are the most exciting clinical research questions being asked in the current trials?

DR MEROPOL: One of the key questions is whether one should continue bevacizumab after the failure of a front-line regimen containing bevacizumab.

That is, perhaps, the most important clinical question we have in the treatment of metastatic disease.

Studies are in development that we hope will answer this question. One study will randomly assign patients who experience disease progression on a front-line bevacizumab-containing regimen to continue or not continue bevacizumab with their next line of therapy. At this point, I am not continuing bevacizumab with second-line therapy.

Another important question in clinical trials is whether combinations of VEGF and EGFR antibodies as front-line therapy will provide better outcomes in progression-free or overall survival. The question is being evaluated both with cetuximab and panitumumab. A third key clinical question relates to the adjuvant setting. Studies are under way exploring whether bevacizumab or cetuximab should be used in the adjuvant setting. That is incredibly important.

Also, some large-scale studies are exploring whether treatment can be assigned on the basis of molecular markers in the tumors. Two studies at the cooperative group level are taking this approach. In ECOG-E5202, an adjuvant trial for patients with Stage II colon cancer, the markers being used are microsatellite instability and loss of heterozygosity at chromosome 18q. Based on these markers, a decision is made about whether the patient can be safely observed or whether he or she should receive chemotherapy.

In the metastatic disease study ECOG-E4203, the marker being evaluated is thymidylate synthase (TS). The hypothesis is that if your tumor has a high level of TS, you are more likely to be resistant to 5-fluorouracil. Patients whose tumors have high TS levels, measured by immunohistochemistry, are randomly assigned to FOLFOX/bevacizumab or a non-5-FU-containing regimen (irinotecan/oxaliplatin/bevacizumab). Those whose tumors have a low to intermediate TS level are assigned to FOLFOX/bevacizumab. ■

SELECT PUBLICATIONS

Giantonio BJ et al. **Impact of bevacizumab dose reduction on clinical outcomes for patients treated on the Eastern Cooperative Oncology Group's Study E3200.** *Proc ASCO* 2006;**Abstract 3538**.

Giantonio BJ et al. **High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO* 2005;**Abstract 2**.

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

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**.

Moroni M et al. **Gene copy number for epidermal growth factor receptor (EGFR) and clinical response to antiEGFR treatment in colorectal cancer: A cohort study.** *Lancet Oncol* 2005;6(5):279-86. **Abstract**

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **According to data from the TREE trials and the BICC-C study, respectively, FOLFOX with bevacizumab or FOLFIRI with bevacizumab were associated with improved progression-free survival and response rates compared to chemotherapy alone as first-line treatment of metastatic colon cancer.**
   a. True
   b. False

2. **NSABP trial R-04 evaluates preoperative radiation therapy and capecitabine or continuous infusion 5-FU with or without _____ for patients with operable rectal carcinoma.**
   a. Bevacizumab
   b. Cetuximab
   c. Oxaliplatin
   d. Irinotecan

3. **Which of the following trials is evaluating the use of cetuximab or bevacizumab in combination with FOLFOX for the adjuvant treatment of colon cancer?**
   a. NSABP-C-08
   b. NCCTG-N0147
   c. ECOG-E5202
   d. Both b and c
   e. All of the above

4. **In the BRiTE registry trial, which adverse event occurred with a similar frequency among patients in the clinical setting compared to those in the AVF2107 trial?**
   a. Hypertension requiring medication
   b. Grade III or IV bleeding
   c. Gastrointestinal perforation
   d. All of the above

5. **Compared to non-US patients, US patients experience higher rates of which fluoropyrimidine-associated adverse event?**
   a. All Grade III and IV adverse events
   b. Grade III and IV gastrointestinal adverse events only
   c. Grade III and IV neutropenia only
   d. Grade III and IV neurotoxicity only

6. **A questionnaire administered to patients enrolled in CALGB-C89803 demonstrated that physical activity was associated with an improved _____ in patients with Stage III colon cancer.**
   a. Disease-free survival
   b. Overall survival
   c. Quality of life
   d. Both a and b
   e. All of the above

7. **The X-ACT trial compared adjuvant therapy with _____ to 5-FU/leucovorin in patients with Stage III colon cancer.**
   a. Oxaliplatin
   b. Gemcitabine
   c. Capecitabine
   d. Bevacizumab
   e. Cetuximab

8. **The Intergroup study (N0147) will evaluate adjuvant FOLFOX with or without _____.**
   a. Panitumumab
   b. Cetuximab
   c. Bevacizumab
   d. Erlotinib
   e. Gefitinib

9. **A dose of 5 mg/kg of bevacizumab has been used in all of the clinical trials for patients with colorectal cancer.**
   a. True
   b. False

10. **Which of the following molecular markers are being used in ECOG-E5202?**
    a. Thymidylate synthase
    b. Microsatellite instability
    c. Loss of heterozygosity at chromosome 18q
    d. Both a and b
    e. Both b and c

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
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
Charles S Fuchs, MD, MPH	5 4 3 2 1	5 4 3 2 1
Neal J Meropol, MD	5 4 3 2 1	5 4 3 2 1

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Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
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Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
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CCU506

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Colorectal Cancer™

U P D A T E

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