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Colorectal Cancer™ UPDATE

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

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INTERVIEWS

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CME Certified

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 with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Describe the key clinical and pathologic risk factors that influence clinician selection of the medical and surgical management of colorectal cancer, and apply this information to your practice.
- Develop an evidence-based algorithm for the initial treatment of localized Stage II and III colon cancer, considering the benefits and risks of adjuvant systemic therapy.
- Appraise the evidence on the evolving role of lifestyle modifications and their impact on the risk of colon cancer recurrence.
- Identify the existing data and emerging research focusing on the optimal management of locally advanced rectal cancer, incorporating the concepts of pre- and postoperative concomitant chemoradiation therapy and the utility of additional adjuvant systemic therapy.
- Explain the practical applicability of emerging clinical research data and ongoing trials seeking to clarify the value of concomitant molecular targeted therapy in the adjuvant treatment setting.
- Evaluate how the evidence supporting multiple sequential treatment approaches to recurrent or de novo advanced colorectal cancer applies to patient care.
- Utilize currently available biologic and clinical markers for predicting response to targeted therapy.
- Discuss the risks and benefits of neoadjuvant or adjuvant systemic therapy for colorectal cancer with appropriate patients with potentially curable hepatic metastases.
- Counsel appropriately selected patients about the availability of ongoing clinical trial participation.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 1 of *Colorectal Cancer Update* is to support the learning objectives by offering the perspectives of Drs O'Connell, Marshall and Meyerhardt on the integration of emerging clinical research data into the management of colorectal cancer.

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CREDIT DESIGNATION STATEMENT

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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** 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**.

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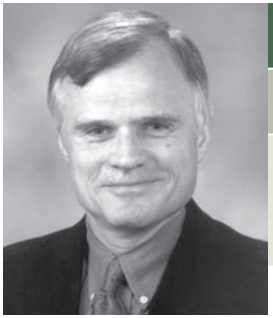


INTERVIEW

Michael J O'Connell, MD

Dr O'Connell is Associate Chairman of the National Surgical Adjuvant Breast and Bowel Project (NSABP) in Pittsburgh, Pennsylvania.

Tracks 1-15

Select Excerpts from the Interview

Track 3

DR LOVE: Would you discuss the background and design of the NSABP-R-04 trial evaluating neoadjuvant treatment for rectal cancer?

DR O'CONNELL: The NSABP-R-04 study is evaluating different methods of combined-modality neoadjuvant treatment using continuous infusion 5-FU

combined with radiation therapy preoperatively as the standard, and it's investigating whether capecitabine would be equally effective as 5-FU in a noninferiority analysis.

The trial is also evaluating whether the addition of oxaliplatin in the preoperative setting might increase the pathological response rates and improve long-term local control (1.1).

DR LOVE: Do you have any predictions about what we will see with the study?

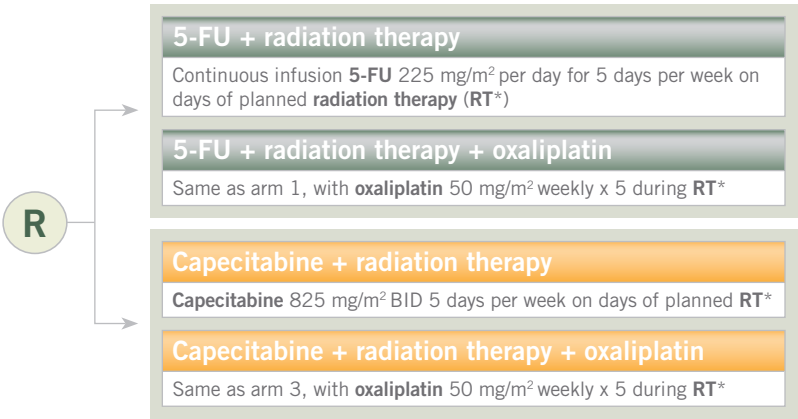
DR O'CONNELL: We hope it will be possible to use an oral agent along with radiation therapy to be equally effective without the need for a central venous catheter and the ambulatory infusion pump.

With the known radiation-sensitizing effect of oxaliplatin and its activity combined with fluorinated pyrimidines in colorectal cancer, I believe it's reasonable that the addition of oxaliplatin might improve local control. Obviously we have to run the trial and examine the results.

1.1

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

Protocol ID: NSABP-R-04; 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.

Track 4

DR LOVE: What are the key research issues surrounding adjuvant systemic therapy?

DR O'CONNELL: The major question is whether the addition of targeted agents — bevacizumab and the anti-endothelial growth factor receptor (EGFR) monoclonal antibodies cetuximab or panitumumab — to chemotherapy will improve the long-term therapeutic outcome. I believe we will have a definitive answer about whether bevacizumab adds to the adjuvant treatment of Stage II and Stage III colon cancer within the next two or three years.

The NSABP-C-08 study has randomly assigned about 2,700 patients with Stage II and III colon cancer to receive a modified FOLFOX6 regimen for six months, as the control, or the same treatment with bevacizumab for a year (1.2). The trial completed accrual a year ago. The primary endpoint is three-year disease-free survival. Of course, if there's a striking benefit, we might hear that early. But by 2009 at the latest we should have a definitive analysis of that trial.

DR LOVE: Where are we right now with safety data from that trial?

DR O'CONNELL: We will report this at ASCO 2008. We did not see an increase in GI perforations among these patients in the adjuvant setting, who are different from patients with advanced disease. Only two or three perforations were recorded in the entire study.

Second, we did not see an increase in arterial thrombotic strokes or heart attacks in this group of patients, who are more medically fit and younger than patients with advanced disease.

We did see a slight increase in wound infections, which was statistically significant and should be taken into consideration. It was of modest degree, perhaps two or three percent versus one percent, but with the numbers of patients we had, that difference was statistically significant.

1.2

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

Protocol ID: NSABP-C-08
Target accrual: 2,632 (Closed)

Eligibility

- Resected Dukes B or C colon cancer

Study Contact

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

* Modified FOLFOX6

SOURCE: NCI Physician Data Query, January 2008.

Track 6

DR LOVE: Would you discuss the AVANT adjuvant study evaluating FOLFOX and CAPOX with bevacizumab?

DR O'CONNELL: AVANT is comparing FOLFOX alone, FOLFOX with bevacizumab or CAPOX with bevacizumab to learn whether substituting the oral agent, capecitabine, for the continuous infusion 5-FU/leucovorin will be as effective (1.3).

I understand that more than 3,500 patients have entered that trial and that the accrual was recently completed. Like the NSABP-C-08 trial, it's also using a three-year disease-free survival endpoint, so it will be about three years before we have data from that study.

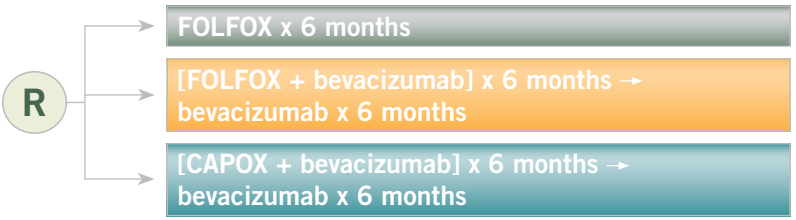
DR LOVE: Do you believe CAPOX is a reasonable clinical option in the adjuvant setting right now?

DR O'CONNELL: You could make that argument. My impression is that CAPOX is as effective as FOLFOX in the advanced-disease setting. That was proved by the NO16966 trial in the metastatic setting that's been presented on several occasions (Cassidy 2006). The toxicity profiles are acceptable, and the efficacy in advanced disease is the same. Yes, I believe this would be a reasonable option in clinical practice now.

1.3

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

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



Eligibility

- Stage II or III colon cancer
- Curative surgery within the past 4 to 8 weeks
- No clinically significant cardiovascular disease*

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

SOURCE: NCI Physician Data Query, January 2008.

Track 14

DR LOVE: Can you summarize the ACCENT data you presented at the 2007 ASCO meeting?

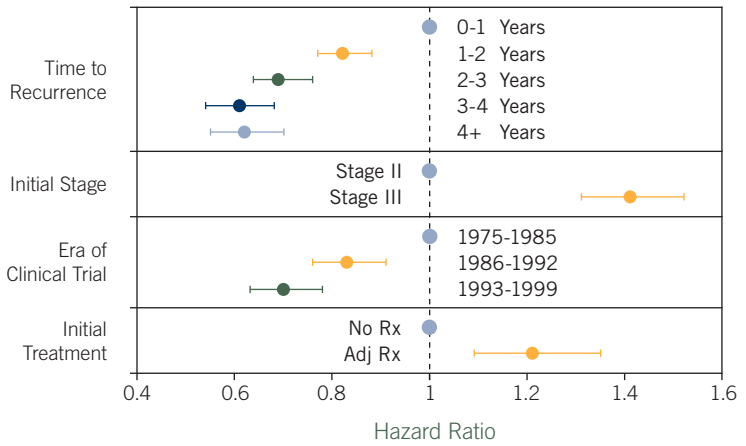
DR O'CONNELL: The ACCENT database includes clinical data from 18 adjuvant therapy studies. Dan Sergeant, from the Mayo Clinic, is the coordinating statistician. The goal of the work I presented was to evaluate the combined data from these studies to determine if the characteristics of the primary tumor might predict the behavior of the cancer if it recurred months or years later.

We found that two factors turned out to be strongly prognostic. One of these was stage. Cancer that recurred years after patients with Stage II primary colon cancer had their tumors removed had a much more indolent natural history than the cancer recurring in patients who'd had Stage III cancer. Stage III — node-positive — cancer had a more rapid natural history when it recurred (O'Connell 2007; [1.4]).

What possibilities might explain this? One is that a difference exists in the biology of Stage II versus Stage III disease. If that were the case, you should be able to examine the patients with Stage II and III disease using a molecular analysis and observe different patterns. However, we haven't observed this type of difference between Stage II and Stage III colon cancer.

1.4

Prognostic Factors for Survival Following Recurrence: Findings from the ACCENT Data Set of More Than 20,000 Patients with Colon Cancer Who Participated in Large Adjuvant Clinical Trials



SOURCE: With permission from O'Connell MJ et al. **Survival following recurrence in patients with adjuvant colon cancer: Findings from the 20,800-patient ACCENT dataset.** *Proc ASCO* 2007;**Abstract 4009**.

DR LOVE: Then how do you explain what's going on?

DR O'CONNELL: Perhaps patients with Stage III disease are further along in the natural history of their disease at the time of diagnosis. They may have more microscopic disease.

The results are profound — in fact, the difference in median survival from the time of diagnosis of metastatic disease, between earlier Stage II and Stage III, was 5.7 months (O'Connell 2007). That's more than the difference made by any therapeutic regimen in any Phase III trial of chemotherapeutic agents in this disease.

The second major prognostic factor was the time it took for the original cancer to come back. If the tumor recurred quickly — within the first year — the prognosis was poor, suggesting aggressive disease.

However, if the tumor recurred four or five years later, the course of disease tended to be more indolent. We've observed this difference in our practices for many years (O'Connell 2007; [1.4]). ■

SELECT PUBLICATIONS

Bokemeyer C et al. **Cetuximab plus 5-FU/FA/oxaliplatin (FOLFOX-4) versus FOLFOX-4 in the first-line treatment of metastatic colorectal cancer (mCRC): OPUS, a randomized phase II study.** *Proc ASCO* 2007;**Abstract 4035**.

Cassidy J et al. **First efficacy and safety results from XELOX-1/NO16966, a randomized 2x2 factorial phase III trial of XELOX vs FOLFOX + bevacizumab or placebo in first-line metastatic colorectal cancer (MCRC).** *Proc ESMO* 2006;**Abstract LBA3**.

Giantonio BJ et al. **Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200.** *J Clin Oncol* 2007;25(12):1539-44. **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**

National Cancer Institute (NCI). **Conquering colorectal cancer: A blueprint for the future.** April 2000. No abstract available

O'Connell MJ et al. **Survival following recurrence in patients with adjuvant colon cancer: Findings from the 20,800-patient ACCENT dataset.** *Proc ASCO* 2007;**Abstract 4009**.

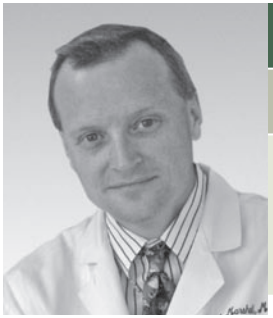
O'Dwyer PJ et al; Gastrointestinal Scientific Leadership Council of the Coalition of Cancer Cooperative Groups. **Priorities in colorectal cancer research: Recommendations from the Gastrointestinal Scientific Leadership Council of the Coalition of Cancer Cooperative Groups.** *J Clin Oncol* 2007;25(16):2313-21. **Abstract**

Saltz L et al. **Bevacizumab in combination with XELOX or FOLFOX4: Updated efficacy results from XELOX-1/NO16966, a randomized phase III trial in first-line metastatic colorectal cancer.** *Proc ASCO* 2007;**Abstract 4028**.

Sobrero AF et al. **Randomized Phase III trial of cetuximab plus irinotecan versus irinotecan alone for metastatic colorectal cancer in 1298 patients who have failed prior oxaliplatin-based therapy: The EPIC trial.** *Proc AACR* 2007;**Abstract LB-2**.

Van Cutsem E et al. **Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): The CRYSTAL trial.** *Proc ASCO* 2007;**Abstract 4000**.

Willett CG et al. **Surrogate markers for antiangiogenic therapy and dose-limiting toxicities for bevacizumab with radiation and chemotherapy: Continued experience of a phase I trial in rectal cancer patients.** *J Clin Oncol* 2005;23(31):8136-9. **Abstract**



INTERVIEW

John L Marshall, MD

Dr Marshall is Chief of Hematology and Oncology and Director of Developmental Therapeutics and GI Oncology at Georgetown University's Lombardi Comprehensive Cancer Center in Washington, DC.

Tracks 1-17

Select Excerpts from the Interview

Track 6

DR LOVE: What are your thoughts on the six-year follow-up of the MOSAIC trial presented at the 2007 ASCO meeting, particularly with regard to stage?

DR MARSHALL: We know that a fluoropyrimidine adds a benefit of two to three percent for the average patient with Stage II disease, but those data from the MOSAIC trial — which was not designed to evaluate Stage II and Stage III disease separately — are repeatedly being split and brought back together.

The message has become confused as to the benefit of adjuvant therapy and the definition of high-risk versus low-risk disease.

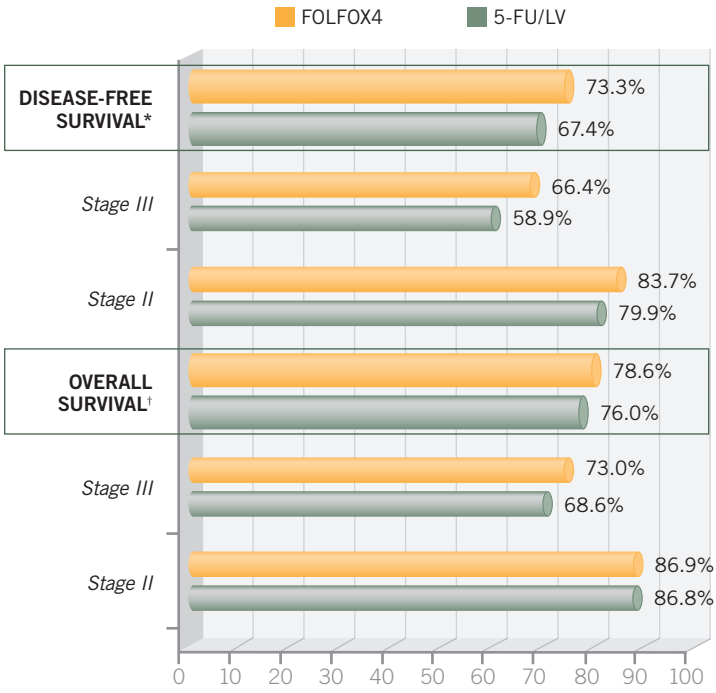
The FDA approved the FOLFOX regimen only for patients with Stage III disease, and we cried foul. Now in the six-year follow-up reported at ASCO, we see these super-split-out data and suddenly we see no disease-free survival benefit with oxaliplatin for patients with low-risk Stage II colon cancer and no overall survival benefit in Stage II disease (de Gramont 2007b; [2.1]).

I applaud NSABP for not revealing the split-out data from NSABP-C-07, the Phase III study of fluorouracil and leucovorin with or without oxaliplatin for patients with Stage II or III colon cancer (Kuebler 2007).

They reported the data in a single set, which was positive for the addition of oxaliplatin. The magnitude of benefit was the same as what was seen in the MOSAIC trial for the overall population.

2.1

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



FOLFOX4 = oxaliplatin, leucovorin, fluorouracil; 5-FU = 5-fluorouracil; LV = leucovorin

* Five-year follow-up; † Six-year follow-up

SOURCE: De Gramont A et al. *Proc ASCO* 2007b;**Abstract 4007**.

Track 11

DR LOVE: What are your thoughts on the iBET trial and the question of whether to continue bevacizumab on disease progression?

DR MARSHALL: At the 2007 ASCO meeting, Axel Grothey presented data from the BRiTE registry demonstrating a significant improvement in survival

2.2

Survival with and without Bevacizumab Beyond Progression in the BRiTE Registry

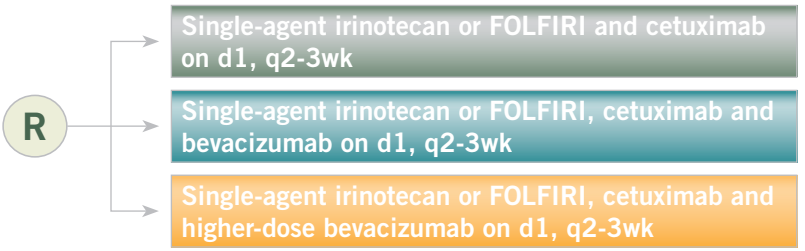
Outcomes	Bevacizumab beyond progression (n = 642)	No bevacizumab beyond progression (n = 531)
Overall survival	31.8 mo	19.9 mo
One-year survival	87.7%	77. 3%
Survival beyond first progressive disease	19.2 mo	9.5 mo

SOURCE: Grothey A et al. *Proc ASCO* 2007;**Abstract 4036**.

2.3

The iBET Trial: A Phase III Study of Irinotecan-Based Therapy and Cetuximab with or without Bevacizumab in Metastatic Colon Cancer After Disease Progression on First-Line Therapy

Protocol IDs: SWOG-S0600, NCT00499369
Target accrual: 1,260 (Open)



Eligibility

- Confirmed metastatic disease with disease progression following first-line therapy with bevacizumab and FOLFOX, OPTIMOX or XELOX
- No prior irinotecan or cetuximab
- Zubrod PS 0-2
- No uncontrolled hypertension (ie, SBP > 150 mmHg or DBP > 90 mmHg)

Study Contacts

SWOG
Philip Gold, MD
Tel: 206-386-2121

NCCTG
Axel Grothey, MD
Tel: 507-284-2511

SOURCE: NCI Physician Data Query, January 2008.

for patients who received bevacizumab beyond progression compared to those who did not (Grothey 2007; [2.2]), and it's a strikingly positive finding.

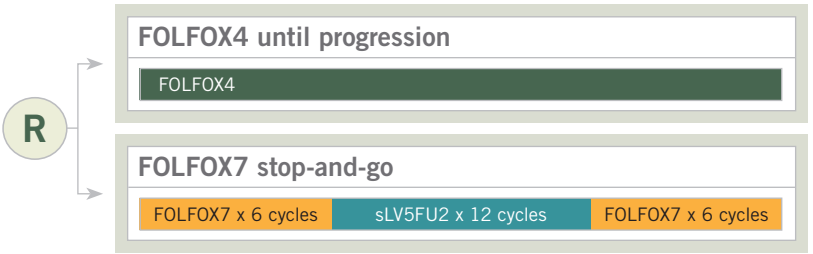
We're all soft-pedaling the data, using the fact that these are registry data and not from a prospective randomized trial as a rationale for enrolling patients on the iBET trial. Accrual to the trial is slow, and I believe a bias for continuing bevacizumab is already emerging. In addition, two of the three arms in the iBET trial include bevacizumab, and I predict that when the patients in the nonbevacizumab arm develop progression, they'll receive bevacizumab in the third line, so in the end all the patients will receive bevacizumab beyond progression (2.3).

Track 14

DR LOVE: In our recent Patterns of Care survey, we asked physicians about how they utilize planned drug "holidays" for patients on FOLFOX or FOLFIRI with bevacizumab. We found that, whereas 70 percent of the clinical investigators would continue 5-FU and bevacizumab during the break, only 29 percent of practicing oncologists do so. They were more likely to stop all drugs or simply continue with one agent. What do you think of these findings?

2.4

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	NS
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	0.1

DDC = duration of disease control

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

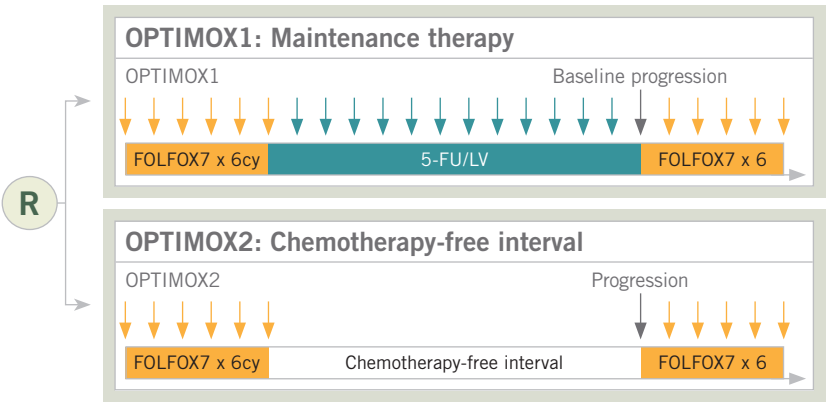
DR MARSHALL: I believe your data reflect the lag involved in getting the message out. If you had conducted that survey a year earlier, before the OPTIMOX2 data, I expect the responses would have been more homogeneous, with everyone feeling comfortable stopping all medications during the holiday. In OPTIMOX1, patients were randomly assigned to continuous FOLFOX or six cycles of FOLFOX, then 5-FU/leucovorin only, restarting the oxaliplatin when their disease progressed. The data showed that the latter schedule was as effective and it was a little less toxic, with less neurotoxicity (2.4).

Then the OPTIMOX2 trial, presented at ASCO 2007, compared the winning arm from OPTIMOX1 to a complete holiday — that is, stopping all drugs after six cycles of FOLFOX — and the drugs were not restarted until the disease had regrown to the baseline status. Both a progression-free and an overall survival benefit were seen among the patients who continued to receive 5-FU/leucovorin through the holiday (2.5).

I am still surprised that the OPTIMOX2 data showed that four months or so of 5-FU/leucovorin affected overall survival. However, everyone left ASCO

2.5

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



Eligibility

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

	OPTIMOX1 (n = 99)	OPTIMOX2 (n = 103)	*p*-value
OS	26 months	19 months	0.0549
RR	60%	59%	NR
Progression-free survival	36 weeks	29 weeks	0.08

SOURCE: Maindrault-Goebel F et al. *Proc ASCO* 2007;**Abstract 4013**.

with the message that the patients have to receive something during the holiday. Although the data do indicate that a holiday may be valuable, we need to determine how to optimize that holiday. The data do tell us that waiting until tumors regrow to their baseline size is probably not the right thing to do. Clinically, we restart the chemotherapy at the first sign of progression.

DR LOVE: What is your initial approach in the front-line metastatic setting?

DR MARSHALL: I generally use FOLFOX with bevacizumab, and I reassess the patients after a few months. When the disease stops responding, I usually continue the bevacizumab on an every three-week schedule and, for most patients, I continue 5-FU in the form of capecitabine. My preferred recipe is continuous, low-dose capecitabine. I also have many patients to whom I administer every other-week capecitabine right from the beginning. ■

SELECT PUBLICATIONS

De Gramont A et al. **Adjuvant therapy for stage II and III colorectal cancer.** *Semin Oncol* 2007a;34(2 Suppl 1):37-40. **Abstract**

De Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of 6 years.** *Proc ASCO* 2007b;**Abstract 4007**.

De Gramont A et al. **Reintroduction of oxaliplatin is associated with improved survival in advanced colorectal cancer.** *J Clin Oncol* 2007c;25(22):3224-9. **Abstract**

Grothey A et al. **Association between exposure to bevacizumab (BV) beyond first progression (BBP) and overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): Results from a large observational study (BRiTE).** *Proc ASCO* 2007;**Abstract 4036**.

Hecht JR et al. **An interim analysis of efficacy and safety from a randomized controlled trial of panitumumab with chemotherapy plus bevacizumab (Bev) for metastatic colorectal cancer (MRCR).** Presentation. World Congress on Gastrointestinal Cancer 2007. No abstract available

Kuebler JP et al. **Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: Results from NSABP C-07.** *J Clin Oncol* 2007;25(16):2198-204. **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* 2007;**Abstract 4013**.

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**.

Schmoll HJ et al. **Final safety findings from a randomized phase III trial of capecitabine + oxaliplatin (XELOX) vs bolus 5-FU/LV as adjuvant therapy for patients (pts) with stage III colon cancer.** *Proc ASCO* 2006;**Abstract 3569**.

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**

Tyagi P, Grothey A. **Commentary on a phase III trial of bevacizumab plus XELOX or FOLFOX4 for first-line treatment of metastatic colorectal cancer: The NO16966 trial.** *Clin Colorectal Cancer* 2006;6(4):261-4. **Abstract**

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

INTERVIEW

Jeffrey A Meyerhardt, MD, MPH

Dr Meyerhardt is Assistant Professor of Medicine at Harvard Medical School's Department of Medical Oncology in the Gastrointestinal Cancer Treatment Center at Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-9

Track 1 Initial observational study evaluating the relationship between obesity and treatment outcomes

Track 2 Correlation between physical activity and disease-free survival (patients in CALGB-89803)

Track 3 Association of dietary patterns with cancer recurrence and survival in Stage III colon cancer (patients in CALGB-89803)

Track 4 Trials evaluating the effects of diet and exercise in other tumor types

Track 5 Trials evaluating the impact of diet and exercise on clinical outcomes for patients with colorectal cancer

Track 6 Weight fluctuation in patients diagnosed with colon or breast cancer

Track 7 Risk of colon cancer recurrence for patients receiving hormone replacement therapy

Track 8 Counseling patients on diet and exercise to improve overall health and cancer outcomes

Track 9 Future directions for colorectal cancer research

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Can you discuss the data that you presented at ASCO 2005 evaluating the impact of physical activity on colon cancer recurrence and survival mined from the CALGB-89803 trial of 5-FU/leucovorin versus IFL?

DR MEYERHARDT: Patients on this trial completed two questionnaires: the first one at approximately three months into chemotherapy and the second around six months after completing therapy.

We created a metric called metabolic equivalent task (MET), which is basically a measure of energy expenditure for nine different activities, such as walking, jogging or biking. For each, patients were asked whether they engaged in the activity and, if so, how often and for how many minutes.

Then we created categories of multiples of three MET hours per week. For example, sitting still for an hour is equivalent to one MET hour, or walking for

one hour at two to three miles per hour each week is equivalent to three MET hours per week. The reference range was less than three MET hours per week.

We found that colon cancer survivors who engaged in at least 18 MET hours of exercise per week had approximately a 50 percent reduction in the risk of disease recurrence or mortality, or a 50 percent improvement in the disease-free survival rate, compared to those in the reference range (Meyerhardt 2006; [3.1]).

DR LOVE: How much exercise would equal 18 MET hours?

DR MEYERHARDT: Walking at a pace of two to three miles per hour for one hour six times a week equals 18 MET hours. Of course there are ways to do it more efficiently or in less time.

Jogging or running for an hour equals seven or ten MET hours, respectively. Most of the patients on the study did some combination of exercise rather than one single aerobic activity.

DR LOVE: What caveats should be considered when reviewing these data?

DR MEYERHARDT: Obviously our study was observational and we did not randomly assign patients to one level of physical activity or another. Also, one could argue that the healthier patients are the patients who are able to exercise more.

To minimize the bias from patients who were becoming sicker, we didn't count events, recurrences or deaths within six months of the activity assessment in the primary analysis. Even extending this restriction to 12 and 24 months, we continued to observe a positive effect of exercise.

3.1

Colorectal Cancer-Specific and Overall Mortality by Level of Postdiagnosis Physical Activity

MET hours per week	No. of patients at risk	Colorectal cancer-specific mortality*		Overall mortality*	
		HR	**95% CI**	**HR**	**95% CI**
<3	167	Referent		Referent	
3-8.9	146	0.92	0.50 to 1.69	0.77	0.48 to 1.23
9-17.9	97	0.57	0.27 to 1.20	0.50	0.28 to 0.90
≥18	144	0.39	0.18 to 0.82	0.43	0.25 to 0.74
p for trend		0.008		0.003	

MET = metabolic equivalent task
HR = hazard ratio
CI = confidence interval

* Adjusted for body mass index, stage of disease (I, II, III), grade of tumor differentiation, colon or rectal primary, age at diagnosis, year of diagnosis, receipt of chemotherapy (yes, no, unknown), time from diagnosis to physical activity measurement, change in body mass index before and after diagnosis, smoking status (current, past, never)

SOURCE: Meyerhardt JA et al. *J Clin Oncol* 2006b;24(22):3527-34. **Abstract**

DR LOVE: What is the potential biologic explanation for your findings?

DR MEYERHARDT: One explanation is that factors like obesity and lack of physical activity increase one's insulin levels and insulin-like growth factor, both of which have been shown to be mitogens for tumor development, metastasis and angiogenesis.

Thus, if patients avoid obesity or increase their level of physical activity, they may be decreasing those levels. If cancer recurrences result from micrometastatic disease that grows, metastasizes and develops a blood supply, then inhibiting those factors may prevent those events from occurring.

Track 3

DR LOVE: You recently published data evaluating dietary patterns and their association with colon cancer recurrence and mortality in this same CALGB trial. Can you discuss those data?

DR MEYERHARDT: A variety of individual dietary factors are related to colon cancer risk, so we utilized dietary patterns to obtain a general sense of patients' overall dietary intake. The two patterns we used were the "prudent" and "Western" pattern diets.

A Western pattern diet is characterized by higher intake of red meat, fatty foods, sugary foods, desserts and refined grains, whereas a prudent pattern diet has a higher intake of poultry, fruits and vegetables.

3.2

Associations between Colon Cancer Recurrence and Mortality and the Western Dietary Pattern[1]

Parameter	Western dietary pattern by quintile[2]					
	1 (n = 201)	2 (n = 202)	3 (n = 202)	4 (n = 202)	5 (n = 202)	*p* for trend
Disease-free survival[3]	Reference	0.98	1.51	1.64	3.25	<0.001
Recurrence-free survival[3]	Reference	0.92	1.42	1.4	2.85	<0.001
Overall mortality[3]	Reference	0.74	1.38	1.66	2.32	<0.001

[1] Median follow-up of patients was 5.3 years from completion of the first questionnaire and 5.6 years from trial entry.

[2] Higher quintiles are indicative of higher intake of the Western dietary pattern.

[3] Adjusted for sex, age, depth of invasion through bowel wall (T1-2 versus T3-4), number of positive lymph nodes (1-3 versus ≥4), presence of clinical perforation at time of surgery, presence of bowel obstruction at time of surgery, baseline performance status (0 versus 1-2), treatment group, weight change between first and second questionnaire, time-varying body mass index, time-varying physical activity level and time-varying total calories

SOURCE: Meyerhardt JA et al. *JAMA* 2007a;298(7):754-64. **Abstract**

Every patient was scored in both dietary patterns, and the patterns were not correlated with each other. For example, a patient may eat hamburgers every day and still eat a lot of fruits and vegetables, so although they may have a reasonable score on a prudent pattern diet, they can still score high on the Western pattern diet.

Our primary finding was related to the Western pattern diet. Patients who scored on the highest level, indicating a higher intake on the Western pattern diet, had over three times the risk of colon cancer recurrence and mortality compared to those on the lowest level of the Western pattern diet (Meyerhardt 2007; [3.2]).

DR LOVE: What is the biologic interpretation of this data?

DR MEYERHARDT: Similar to what we see with obesity and low physical activity, we know that higher levels of the Western pattern diet increase the risk of diabetes and increase people's C peptide levels, thus modulating insulin and insulin-like growth factors. That is one possible hypothesis for how diet affects micrometastatic disease in the adjuvant setting. ■

SELECT PUBLICATIONS

Chlebowski RT et al. **Dietary fat reduction in postmenopausal women with primary breast cancer: Phase III Women's Intervention Nutrition Study (WINS).** *Proc ASCO* 2005;23;**Abstract 10**.

Dray X et al. **Influence of dietary factors on colorectal cancer survival.** *Gut* 2003;52(6):868-73. **Abstract**

Haydon AM et al. **Effect of physical activity and body size on survival after diagnosis with colorectal cancer.** *Gut* 2006a;55(1):62-7. **Abstract**

Haydon AM et al. **Physical activity, insulin-like growth factor 1, insulin-like growth factor binding protein 3, and survival from colorectal cancer.** *Gut* 2006b;55(5):689-94. **Abstract**

Kesse E et al. **Dietary patterns and risk of colorectal tumors: A cohort of French women of the National Education System (E3N).** *Am J Epidemiol* 2006;164(11):1085-93. **Abstract**

Kim MK et al. **Dietary patterns and subsequent colorectal cancer risk by subsite: A prospective cohort study.** *Int J Cancer* 2005;115(5):790-8. **Abstract**

Meyerhardt JA et al. **Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer.** *JAMA* 2007a;298(7):754-64. **Abstract**

Meyerhardt JA et al. **The impact of dietary patterns on cancer recurrence and survival in patients with stage III colon cancer: Findings from CALGB 89803.** *Proc ASCO* 2007b;**Abstract 4019**.

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**

Meyerhardt JA et al. **Assessment of a dietary questionnaire in cancer patients receiving cytotoxic chemotherapy.** *J Clin Oncol* 2005;23(33):8453-60. **Abstract**

Pierce JP et al. **Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: The Women's Healthy Eating and Living (WHEL) Randomized Trial.** *JAMA* 2007;298(3):289-98. **Abstract**

Slattery ML et al. **Diet and survival of patients with colon cancer in Utah: Is there an association?** *Int J Epidemiol* 1989;18(4):792-7. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **NSABP-R-04 will evaluate preoperative radiation therapy combined with capecitabine/oxaliplatin versus radiation therapy combined with 5-FU/oxaliplatin for patients with resectable rectal cancer.**
   a. True
   b. False
2. **Patients in NSABP-C-08 are randomly assigned to _____.**
   a. CAPOX with or without bevacizumab
   b. FOLFOX6 with or without bevacizumab
3. **In the Phase III AVANT adjuvant study, patients are randomly assigned to either FOLFOX or _____.**
   a. FOLFOX and bevacizumab
   b. CAPOX and bevacizumab
   c. Both a and b
4. **In the ACCENT database of patients with Stage II and III colorectal cancer, _____ was associated with time from recurrence to death.**
   a. Year of recurrence
   b. Initial tumor stage
   c. Both a and b
   d. None of the above
5. **The iBET trial will randomly assign patients who have failed therapy with bevacizumab and an oxaliplatin-based regimen to _____.**
   a. Cetuximab with an irinotecan-based regimen
   b. Cetuximab with an irinotecan-based regimen and continuation of bevacizumab
   c. Cetuximab with an oxaliplatin-based regimen
   d. Both a and b
   e. Both a and c
6. **In the OPTIMOX2 trial for patients who had received FOLFOX7, maintenance therapy with 5-FU/leucovorin prolonged survival compared to _____.**
   a. Maintenance therapy with bevacizumab
   b. Maintenance therapy with cetuximab
   c. Maintenance therapy with capecitabine
   d. A complete treatment-free holiday
   e. None of the above
7. **Prospectively collected data from the BRiTE registry support the hypothesis that continued use of bevacizumab beyond disease progression is associated with an improved clinical outcome.**
   a. True
   b. False
8. **In the MOSAIC trial, six-year overall survival was greater with adjuvant FOLFOX4 compared to 5-FU/LV among patients with Stage II colorectal cancer.**
   a. True
   b. False
9. **Meyerhardt and colleagues reported that patients with Stage III colon cancer who engaged in at least 18 MET hours of exercise per week had approximately a _____ improvement in disease-free survival rate compared to patients who exercised less than three MET hours per week.**
   a. 10 percent
   b. 25 percent
   c. 50 percent
10. **Which dietary pattern was found to impact a patient's risk of colon cancer recurrence and mortality, as reported by Meyerhardt and colleagues?**
    a. Western pattern (refined grains, processed and red meats, desserts, high-fat dairy products and french fries)
    b. Prudent pattern (fruits, vegetables, whole grains, legumes, poultry and fish)

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

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

- Describe the key clinical and pathologic risk factors that influence clinician selection of the medical and surgical management of colorectal cancer, and apply this information to your practice. . . . . 5 4 3 2 1 N/A
- Develop an evidence-based algorithm for the initial treatment of localized Stage II and III colon cancer, considering the benefits and risks of adjuvant systemic therapy. . . . . 5 4 3 2 1 N/A
- Appraise the evidence on the evolving role of lifestyle modifications and their impact on the risk of colon cancer recurrence. . . . . 5 4 3 2 1 N/A
- Identify the existing data and emerging research focusing on the optimal management of locally advanced rectal cancer, incorporating the concepts of pre- and postoperative concomitant chemoradiation therapy and the utility of additional adjuvant systemic therapy. . . 5 4 3 2 1 N/A
- Explain the practical applicability of emerging clinical research data and ongoing trials seeking to clarify the value of concomitant molecular targeted therapy in the adjuvant treatment setting. . . . . 5 4 3 2 1 N/A
- Evaluate how the evidence supporting multiple sequential treatment approaches to recurrent or de novo advanced colorectal cancer applies to patient care. . . . . 5 4 3 2 1 N/A
- Utilize currently available biologic and clinical markers for predicting response to targeted therapy. . . . . 5 4 3 2 1 N/A
- Discuss the risks and benefits of neoadjuvant or adjuvant systemic therapy for colorectal cancer with appropriate patients with potentially curable hepatic metastases. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trial participation. . . . . 5 4 3 2 1 N/A

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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John L Marshall, MD	5 4 3 2 1	5 4 3 2 1
Jeffrey A Meyerhardt, MD, MPH	5 4 3 2 1	5 4 3 2 1

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CCU108

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