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Colorectal Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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Colorectal Cancer Update
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

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

GLOBAL LEARNING OBJECTIVES

- 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 appropriately selected patients about the availability of ongoing clinical trials.
- Evaluate the emerging 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.
- 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 Meropol, Crane and Grothey on the integration of emerging clinical research data into the management of colorectal cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 3 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **www.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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CONTENT VALIDATION AND DISCLOSURES

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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:

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UPCOMING EDUCATIONAL EVENTS

47th Annual Meeting of American Society for Therapeutic Radiology and Oncology
October 16-20, 2005
Denver, Colorado
Event website: **www.astro.org**

Colorectal Cancer: Molecular Pathways and Therapies
October 19-23, 2005
Dana Point, California
Event website: **www.aacr.org/page3506.aspx**

Society for Integrative Oncology 2nd International Conference
November 10-12, 2005
San Diego, California
Event website: **www.integrativeonc.org**

AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics
November 14-18, 2005
Philadelphia, Pennsylvania
Event website: **www.aacr.org/page3525.aspx**

Oncology World Congress
November 16-19, 2005
New York, New York
Event website: **www.oncologycongress.com**

2006 Gastrointestinal Cancers Symposium
January 26-28, 2006
San Francisco, California
Event website: **www.asco.org/meetings**

Editor's Note

In our faces

DR LOVE: The justification for the NSABP-R-04 neoadjuvant rectal cancer study comparing infusional 5-FU to capecitabine is that this type of Phase III randomized trial is necessary to change clinical practice. Your recent *JCO* editorial criticized the use of research resources for this purpose.

DR CRANE: I'm not going to waffle. In this situation, the lack of Phase III data is an excuse — it's not a reason. The point I raised in the editorial is that you can't answer every question with a Phase III trial, and as investigators, we have to choose research questions that are most important. This issue of 5-FU versus 5-FU has been investigated extensively in the last 15 years in randomized cooperative group studies without any benefit to patients. It's a pedestrian question that doesn't need an answer. From my perspective, we do have Phase III data on this question, and it's the X-ACT trial in the adjuvant setting, which in my view showed an advantage for capecitabine over 5-FU.

In the late 1980s, under the entertaining tutelage of coach Jimmy Johnson, the University of Miami football team defied the staid college football establishment. Instead of wearing the required coats and ties to a Fiesta Bowl dinner, the players showed up wearing combat fatigues. Prior to each game, the team stood jaw-to-jaw with their opponents and brashly told them exactly what was about to transpire.

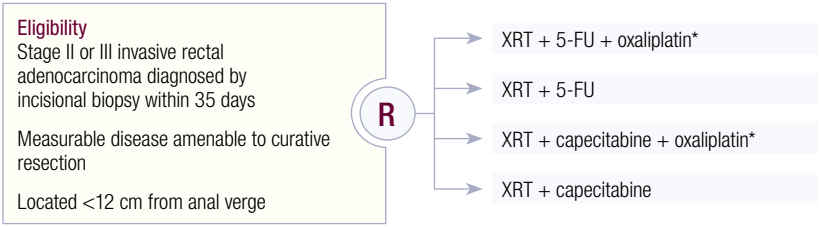
Radiation oncologist Chris Crane was a member of the University of Miami undergraduate student body at that time, and his best friend was the team's placekicker. Perhaps it was his exposure to this type of blunt talk that later led Chris, as a faculty member at MD Anderson Cancer Center, to unflinchingly "tell it like he sees it," including his very public challenge in a *JCO* editorial of the rectal cancer research plans of our most august cooperative group.

I attended the June 2003 NSABP meeting in Orlando when R-04 was presented and discussed and was somewhat surprised and disappointed to hear about the initial plans. In an interview for this program during the meeting, NSABP chair Norman Wolmark defended the study but also noted that the group wished to address additional important research questions in rectal cancer. Shortly after that, the protocol was amended to also evaluate the role of oxaliplatin as

neoadjuvant therapy with combined radiation therapy and either capecitabine or infusional 5-FU (1.1).

1.1 Preoperative Radiotherapy (XRT) Combined with Capecitabine and Oxaliplatin versus Radiotherapy Combined with 5-FU and Oxaliplatin in Patients with Resectable Rectal Cancer

Protocol IDs: NSABP-R-04, NCT00058474
Accrual: 1,606 (Open)



* Protocol amendment to add oxaliplatin is currently under review.

SOURCES: NSABP Protocol R-04, NSABP website.

O'Connell MJ et al. **Update on design of the National Surgical Adjuvant Breast and Bowel Project trial R-04.** *J Clin Oncol* 2005;23(4):933-4. No abstract available

Having been on the medical school faculty of the University of Miami during the Jimmy Johnson, Vinnie Testaverde, Jerome Brown and Michael Irvin era, I can empathize with Chris's desire to shake things up in the name of progress. However, during our conversation at ASCO, we were both much more interested in reflecting on new avenues of clinical research, such as Chris Willett's fascinating translational work in rectal cancer evaluating bevacizumab.

The other two interviewees for this program — medical oncologists Neal Meropol and Axel Grothey — provide a review of other key ASCO developments in colorectal cancer. Probably the most important paper from the meeting was Norm Wolmark's "late-breaking" presentation of the efficacy data from NSABP-C-07 comparing "Roswell Park" bolus 5-FU/leucovorin to the same regimen plus oxaliplatin (FLOX).

These data looked much like the first presentation of the MOSAIC trial two years ago, when the addition of oxaliplatin to infusional 5-FU demonstrated a disease-free survival advantage, prompting the FDA to bless the strategy.

Immediately following this talk, Rich Goldberg jumped to the microphone and asked whether these data meant that oncologists "can send our infusional pumps back to the manufacturer." Norm — as always, the wry pundit — replied, "I don't know why you would ask a surgeon, but the data speak for themselves. We've demonstrated that adding oxaliplatin to a weekly 5-FU bolus template shows a benefit that is of similar magnitude to an infusional 5-FU regimen. I would hope people would examine these data and make their own decisions."

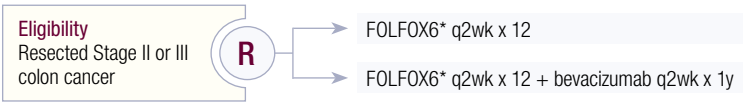
There were also many questions about the relevance of these findings with the FLOX regimen and how they impact the current NSABP adjuvant trial C-08, which uses FOLFOX as the control arm versus FOLFOX plus bevacizumab.

During the same 2003 interview with Norm at the NSABP meeting when we talked about R-04, he elaborated on the group's plans at that time for C-08. The study was intended to be a three-by-two factorial design comparing in the first randomization FOLFOX versus FLOX versus CAPOX (capecitabine plus oxaliplatin), followed by a second randomization to bevacizumab or control. Subsequently, with considerable input (and muscle) from CTEP and the FDA, the study was simplified to its current design (1.2).

The downsizing of C-08 means that an answer about the role of adjuvant bevacizumab will be obtained more quickly; however, if an advantage is observed for adding the anti-VEGF agent, physicians and patients will then have to decide if the results can be generalized to more user-friendly regimens, including capecitabine.

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

Protocol ID: NSABP-C-08
Target Accrual: 2,632 (Open)



* Modified FOLFOX6

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

SOURCE: NCI Physician Data Query, June 2005.

Many similar dilemmas exist in other common solid tumors, including the following:

1. *Should chemotherapy regimens with proven safety and efficacy in metastatic non-small cell lung cancer be utilized in the adjuvant setting if no specific adjuvant data exist for that regimen (for example, docetaxel/carboplatin)?*
2. *Can chemotherapeutic agents other than paclitaxel/carboplatin be combined with bevacizumab for metastatic non-small cell lung cancer (for example, doublets such as docetaxel/carboplatin or gemcitabine/carboplatin)?*
3. *Can agents other than paclitaxel be combined with bevacizumab in metastatic breast cancer (for example, docetaxel,* nab *paclitaxel, capecitabine or vinorelbine)?*

Chris Crane's "in your face" critique of R-04 brings into question the entire concept of evidence-based medicine, which in my opinion means utilizing credible laboratory and clinical research data as the basis for treatment decisions. However, credible evidence goes well beyond the realm of Phase III studies.

Chris's point is that we often have extensive Phase II data on capecitabine, including safety findings, and Phase III trials from similar settings, and that these data may form enough of an evidence base to change practice without going through the expense and delay of implementing large Phase III studies.

The other major colorectal randomized trial reported at ASCO that ties into the concept of "How much evidence is enough to change practice?" was ECOG-E3200. Discussed on the last issue of this audio series by principal investigator Bruce Giantonio, the E3200 data set reinforced the initial findings reported last November via an NCI press release and during Bruce's ASCO GI presentation in January.

Essentially, this study demonstrated a progression-free and overall survival benefit for the addition of bevacizumab to FOLFOX in the second-line metastatic setting. What is interesting about the E3200 data is that oncologists had already made a leap of faith and have been utilizing this regimen up front for more than a year based on positive data combining bevacizumab with 5-FU alone and with IFL. The FDA made this leap much easier by approving bevacizumab with any infusional 5-FU regimen.

The delicate balance between regulatory bodies like the FDA, third-party payers including Medicare, clinical researchers and medical oncologists in practice represents an imperfect system that every now and then benefits when gadflies like "The U's" Chris Crane shake things up a bit and make us reconsider where we've been, where we are and where we're headed.

— Neil Love, MD
NLove@ResearchToPractice.net

Select publications

Crane CH, Sargent DJ. **Substitution of oral fluoropyrimidines for infusional fluorouracil with radiotherapy: How much data do we need?** *J Clin Oncol* 2004;22(15):2978-81.
No abstract available

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.** Presentation. ASCO 2005;**Abstract 3501**.

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.** Presentation. ASCO 2005;**Abstract 2**.

Twelves C et al. **Updated efficacy findings from the X-ACT phase III trial of capecitabine (X) vs bolus 5-FU/LV as adjuvant therapy for patients (pts) with Dukes' C colon cancer.** Presentation. ASCO 2005;**Abstract 3521**.

Wolmark N et al. **A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07.** Presentation. ASCO 2005;**Abstract LBA3500**.

NSABP-C-07: Phase III adjuvant study of 5-FU/leucovorin plus or minus oxaliplatin

Design and efficacy data

In the NSABP-C-07 trial, patients with Stage II and III colon cancer who had undergone resection with curative intent were randomly assigned to receive either the Roswell Park regimen of 5-FU/leucovorin given weekly for six out of eight weeks over approximately a six-month period or the same regimen plus oxaliplatin for three weeks during each eight-week cycle.

Data presented at ASCO 2005 showed that disease-free survival improved with the addition of oxaliplatin. The magnitude of benefit seemed quite comparable to that seen in the MOSAIC study, which led the presenter to conclude that this regimen is an acceptable adjuvant therapy for patients with Stage II or III colon cancer (Wolmark 2005; de Gramont 2005; [2.1]).

Toxicity data

The toxicity data from C-07 suggest that both arms had substantial Grade III and IV toxicities, but how those compare with a FOLFOX regimen or an infusional 5-FU-based regimen is uncertain at this point. In the C-07 trial, they used a lower total dose of oxaliplatin than MOSAIC, which is an important distinction. The long-term neurotoxicity with FOLFOX may be worse than that seen with the FLOX regimen used in C-07.

I believe we need more detailed information about toxicity before adopting the C-07 oxaliplatin regimen into routine clinical practice. The C-07 data do provide an alternative for patients in whom we would like to use an oxaliplatin-containing regimen but for one reason or another are not able to use infusional 5-FU. However, for most other patients, I am more comfortable using FOLFOX because we have longer follow-up and more data on acute toxicity with this regimen.

Dr Meropol is the 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.

2.1 NSABP-C-07 Phase III Study Comparing Adjuvant 5-FU/Leucovorin with or without Oxaliplatin

Three-year disease-free survival: FLOX versus FULV

FLOX* (n = 1,200)	FULV† (n = 1,207)	*p*-value	HR (95% CI)	Risk reduction
76.5%	71.6%	<0.004	0.79 (0.67-0.93)	21%

Overall toxicity data

	FLOX	FULV
Grade III	50%	41%
Grade IV	10%	9%

* FLOX = weekly IV bolus 5-FU/LV + oxaliplatin; † FULV = weekly IV bolus 5-FU/LV

"The overall toxicity was greater for the FLOX arm, but not that much greater. ... The most troubling toxicity related with oxaliplatin is neurotoxicity. The scale that we used for measuring neurotoxicity was the NCI Sanofi scale and I remind you that Grade III neurotoxicity in this scale is paresthesias, dysesthesias, with pain or interference with activities of daily living.

"Now, 85 percent of the oxaliplatin-treated group had some degree of toxicity throughout the three cycles during treatment. Twelve months after the cessation of therapy, this percentage dropped to 29 percent. What is of greater interest is the fact that only eight percent of the oxaliplatin-treated patients had Grade III neurotoxicity, and that this dropped to 0.5 percent 12 months after the cessation of therapy.

"These percentages are lower than those reported in the MOSAIC trial, perhaps because we use a lower cumulative dose of oxaliplatin. The CO-7 cumulative dose was 765 mg/m^2 compared to about a gram in the MOSAIC study. Eighty-six percent of patients received full-dose oxaliplatin during cycle 1, 68 percent received full dose during cycle 2 and 62 percent received full dose during cycle 3. An overall 73 percent received protocol-stipulated cumulative dose."

SOURCE: Wolmark N et al. **A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07**. Presentation. ASCO 2005;**Abstract LBA3500**.

Rationale for comparing capecitabine to 5-FU

A Phase III study presented at ASCO 2005 compared capecitabine/oxaliplatin to 5-FU/oxaliplatin as first-line therapy in patients with metastatic colorectal cancer, and with early follow-up, it appears overall survival is very similar with these two regimens (Arkenau 2005; [2.2]). For patients who are clearly in a palliative mode, particularly for patients in whom surgical resection is not going to be feasible with curative intent, I believe that study lends some credence to the option of capecitabine/oxaliplatin rather than infusional 5-FU-based therapy.

The data evaluating capecitabine in combination with irinotecan and oxaliplatin suggest that we probably do need to conduct large-scale equivalence studies comparing those regimens to their infusional 5-FU counterparts. I believe that only the large-scale investigations will clearly delineate the toxicity differences between the capecitabine-based regimens and the 5-FU-based regimens, which will become important when selecting treatments for our patients.

Another reason for doing such comparison studies in patients with metastatic disease is to determine whether one of the approaches is superior in terms of major antitumor responses — the types of responses that might lead to resectability of liver metastases, for example, with curative intent. It's plausible that only a small difference, if any, in overall survival exists between capecitabine and 5-FU-based combination regimens; however, if significant responses can be seen early with one regimen versus another, this might impact a small percentage of patients who ultimately can be cured.

2.2 Phase III Trial Comparing Capecitabine Plus Oxaliplatin (CAPOX) versus Infusional 5-FU/Folinic Acid Plus Oxaliplatin (FUFOX) for Metastatic Colorectal Cancer

Efficacy parameter	CAPOX (n = 238)	FUFOX (n = 230)	HR (95% CI)	*p*-value
Response rate	47%	49%	—	0.70
Median progression-free survival	7.0 months	8.0 months	1.19 (0.97-1.48)	0.11
Overall survival	16.3 months	17.2 months	1.05 (0.79-1.41)	0.72

SOURCE: Arkenau H et al. **Infusional 5-FU/FA plus oxaliplatin (FUFOX) versus capecitabine plus oxaliplatin (CAPOX) as first-line treatment for metastatic colorectal cancer: Safety and efficacy analysis from a phase III trial of the German AIO**. Presentation. ASCO 2005;**Abstract 3507**.

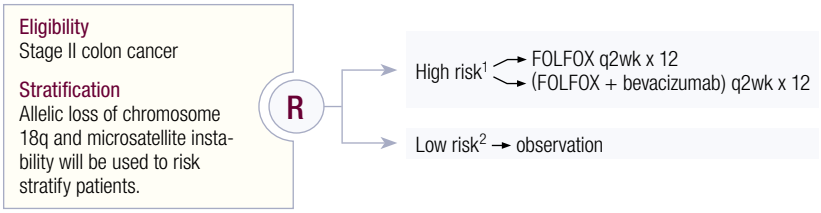
ECOG-E5202: Adjuvant trial assigning treatment based on molecular phenotypes

The Eastern Cooperative Oncology Group is poised to activate a Phase III study, ECOG-E5202, in which patients will be assigned treatment based on molecular phenotype (2.3). All the patients with Stage II disease will have their tumors assessed for microsatellite instability and 18q deletions in real time. The patients whose molecular phenotypes suggest an extremely good prognosis will be followed for relapse and survival but will receive no adjuvant therapy. The patients who fall into the higher-risk group will then be randomly assigned to receive either FOLFOX or FOLFOX plus bevacizumab.

I believe it's premature to use molecular diagnostics to select adjuvant therapy for colon cancer outside of a clinical trial. In this study, the analyses will be conducted by a CLIA-approved laboratory that is highly skilled in performing these studies and, in fact, was responsible for the initial observations related to microsatellite instability and 18q status as prognostic and predictive markers.

2.3 Prospective Study Evaluating the Role of Chromosome 18q Status and Microsatellite Instability as Prognostic Markers of Response to Adjuvant Therapy

Protocol ID: ECOG-E5202
Accrual: 3,000 (Pending)



[1] High risk = microsatellite stability with 18q loss of heterozygosity or microsatellite instability with 18q loss of heterozygosity; [2] low risk = microsatellite stability with retention of 18q alleles or low-frequency microsatellite instability with retention of 18q alleles or high-frequency microsatellite instability with or without retention of 18q alleles

SOURCE: Baddi L, Benson A 3rd. **Adjuvant therapy in stage II colon cancer: Current approaches.** *Oncologist* 2005;10(5):325-31. No abstract available

ECOG-E3200: FOLFOX with or without bevacizumab

Design and efficacy data

ECOG-E3200 sought to determine whether bevacizumab, when added to chemotherapy in the second- or third-line setting for metastatic disease, would improve survival. Eligible patients had previously received 5-FU and irinotecan either together or in sequential fashion but had not yet received oxaliplatin.

Initially, patients were randomly assigned to one of three treatment arms, either FOLFOX4 alone or FOLFOX4 plus bevacizumab or bevacizumab alone. However, the Data Safety Monitoring Board of ECOG closed the single-agent bevacizumab arm before completion of accrual because of its inferiority to the other arms, so just the two FOLFOX arms continued until the completion of the study.

The data presented at ASCO 2005 showed that FOLFOX plus bevacizumab improved survival when compared to the other two arms, with a median survival benefit of approximately two months, and the survival benefit was associated with an improvement in response rate (Giantonio 2005; [2.4]).

The FOLFOX plus bevacizumab arm had a response rate of approximately 20 percent, versus approximately 10 percent in the FOLFOX arm. The data also showed bevacizumab to have nominal activity, at least in terms of response rate, in patients with advanced colon cancer who had failed prior chemotherapy.

Clinical implications of ECOG-E3200

ECOG-E3200 does validate the concept that bevacizumab adds to the benefit of an oxaliplatin-containing regimen, just as it did with an irinotecan-containing regimen. For clinicians who may not have been comfortable using FOLFOX plus bevacizumab in the front-line setting because there were no data with

that combination, those data now exist, and while they were second-line data, I believe they validate the benefit of adding bevacizumab to FOLFOX. If a physician prefers FOLFOX as their front-line chemotherapy backbone, they can now feel comfortable adding bevacizumab.

2.4 ECOG-E3200: FOLFOX with or without Bevacizumab in the Treatment of Metastatic Disease

"The addition of bevacizumab to FOLFOX-4 resulted in a statistically significant improvement in overall survival. At a median follow-up of 28 months, the median overall survival for patients treated with bevacizumab and FOLFOX-4 was 12.9 months compared to 10.8 months for those treated with FOLFOX alone. The p-value for this comparison was 0.0018 and the hazard ratio for death for those treated with the combination was 0.76. The median overall survival for patients treated with bevacizumab alone was 10.2 months.

"In addition, the combination of bevacizumab and FOLFOX-4 resulted in a statistically significant improvement in progression-free survival. The median progression-free survival for the patients treated with the combination was 7.2 months, compared to 4.8 months for those treated with FOLFOX alone. The p-value for this comparison was less than 0.0001 and the hazard ratio for progression was 0.64. The median progression-free survival for the patients who received bevacizumab alone was 2.7 months."

SOURCE: 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.** Presentation. ASCO 2005;**Abstract 2**.

BOND-2 trial: Bevacizumab/cetuximab with or without irinotecan

The BOND-2 trial is a first effort in colon cancer to combine anti-VEGF and anti-EGFR agents by combining bevacizumab and cetuximab in patients with metastatic colorectal cancer (2.5). Patients who had previously received irinotecan and had progressive disease were randomly assigned to either receive irinotecan again with both cetuximab and bevacizumab or cetuximab/bevacizumab without further chemotherapy (Saltz 2005). It's important to note that the patients on this study had not received cetuximab or bevacizumab previously.

The response data in both arms of this trial appear to be better than one might have expected, based on historical controls with cetuximab monotherapy or cetuximab plus irinotecan in this type of pretreated patient population. The BOND-2 study validates this combined approach in terms of moving it into large-scale randomized studies to truly determine whether the combination of bevacizumab plus cetuximab is superior to sequential therapies containing one of these antibodies, followed by another regimen containing the other.

2.5 BOND-2: Phase II Randomized Trial Comparing Cetuximab/Bevacizumab with or without Irinotecan in Patients Who have Failed Irinotecan

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

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

Select publications

Arkenau H et al. **Infusional 5-fluorouracil/folinic acid plus oxaliplatin (FUFOX) versus capecitabine plus oxaliplatin (CAPOX) as first-line treatment of metastatic colorectal cancer (MCRC): Results of the safety and efficacy.** Presentation. ASCO 2005;**Abstract 3507**.

Baddi L, Benson A 3rd. **Adjuvant therapy in stage II colon cancer: Current approaches.** *Oncologist* 2005;10(5):325-31. No abstract available

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**

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.** Presentation. ASCO 2005;**Abstract 3501**.

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.** Presentation. ASCO 2005;**Abstract 2**.

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

Kabbinavar F et al. **Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.** *J Clin Oncol* 2003;21(1):60-5. **Abstract**

Lenz HJ et al. **Activity of cetuximab in patients with colorectal cancer refractory to both irinotecan and oxaliplatin.** Presentation. ASCO 2004;**Abstract 3510**.

Mancuso A, Sternberg CN. **Colorectal cancer and antiangiogenic therapy: What can be expected in clinical practice?** *Crit Rev Oncol Hematol* 2005;55(1):67-81. **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**.

Starling N, Cunningham D. **Cetuximab in previously treated colorectal cancer.** *Clin Colorectal Cancer* 2005;5(Suppl 1):28-33. **Abstract**

Wolmark N et al. **A Phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07.** Presentation. ASCO 2005;**Abstract LBA3500**.

Phase III trials comparing capecitabine to infusional 5-FU

Our editorial in the *Journal of Clinical Oncology* questioned whether we need more data on substituting oral fluoropyrimidines for infusional fluorouracil with radiotherapy for rectal cancer (Crane 2004).

The X-ACT study, an adjuvant trial in patients with node-positive colon cancer, compared 5-FU/leucovorin versus capecitabine. Trial data that were initially presented at ASCO in 2004 demonstrated that capecitabine is an acceptable alternative and, in fact, may be better than IV 5-FU/leucovorin (Cassidy 2004).

I believe capecitabine is basically interchangeable with intravenous 5-FU and that the argument not to use it because of a lack of Phase III data is an excuse, not a reason. I also think that reimbursement issues are a factor. The "5-FU versus 5-FU question" has been investigated over the last 15 years in randomized cooperative group studies involving 4,000 patients, costing $10 million and without any benefit to any patients currently. While I believe we always need Phase III data, we do have Phase III data answering this question from the X-ACT trial.

The NSABP designed R-04 to compare capecitabine with venous infusional fluorouracil in patients receiving preoperative radiotherapy for locally advanced rectal cancer, but I don't believe such a trial is necessary. There was a meeting about this, and the study design was changed to incorporate oxaliplatin, which I believe is our only opportunity to understand whether that drug will benefit such patients. The final design is a two-by-two randomization of infusional 5-FU versus capecitabine with a second randomization to oxaliplatin or not.

I believe everyone will agree that the amended design is better. If I had to guess what this trial would show, my guess is that capecitabine will be equally effective but less toxic than infusional 5-FU and that oxaliplatin will improve response but not long-term outcome.

Dr Crane is an Associate Professor, Program Director and Section Chief of the Gastrointestinal Section in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Selection of agents for preoperative chemoradiation therapy

In most cases, single-agent capecitabine is adequate for preoperative chemoradiation. When another agent is added, such as irinotecan or oxaliplatin, we introduce levels of toxicity that, in my view, are not acceptable. The exception may be the worst cases — such as patients with large T3 tumors and positive nodes or obstructing T4 lesions where resection would be difficult. In such cases, I believe oxaliplatin improves the response rate, but I'm not sure that will translate to a meaningful clinical benefit for the whole population. It's clear that oxaliplatin and irinotecan add gastrointestinal toxicity on the order of 25 to 30 percent and some hematologic toxicity.

At MD Anderson, we use capecitabine rather than infusional 5-FU in this setting. Capecitabine is more convenient, and while the toxicity profiles of the agents are similar, I believe the quality of life for the patients and the doctors and nurses is improved with capecitabine. Patients can remain active during treatment with capecitabine, and they don't have a risk of infection or a five to 10 percent risk of thrombosis from a peripheral line.

At ASCO 2005, European data were presented from a randomized trial comparing preoperative radiotherapy with versus without 5-FU for the treatment of T3-4 rectal cancer (Gerard 2005). While in the United States, the standard is to give some form of 5-FU. This study failed to demonstrate a huge impact with 5-FU — with only single-digit improvements — so 5-FU may not even be necessary.

Neoadjuvant bevacizumab in the treatment of rectal cancer

Bevacizumab has been proven in many disease sites to improve the effects of chemotherapy. Approximately three years ago, before it was approved with radiation therapy, we had the opportunity to investigate this agent. We conducted a Phase I trial of 50 patients with pancreatic cancer (ID02-146) who received capecitabine, radiation therapy and bevacizumab, and the results were very exciting. In the patients who received five mg/kg of bevacizumab every two weeks, which was the final recommended dose, we saw a 50 percent partial response rate. Six of the 12 patients had their tumors shrink by 50 percent, which is a "high bar" endpoint for pancreatic cancer.

The regimen was well tolerated, and the RTOG is now conducting a Phase II study with bevacizumab, capecitabine and radiation therapy in patients with locally advanced pancreatic cancer that cannot be surgically excised (RTOG-0411). At MD Anderson, we currently have a neoadjuvant Phase II study with the same regimen in patients presenting with locally advanced rectal cancer (2003-0832; [3.1]).

Investigators at Mass General published a Phase I trial in *Nature Medicine* and presented it at ASCO in 2004. In this trial, patients with primary rectal cancer received neoadjuvant bevacizumab, 5-FU and radiotherapy (Willett 2004a, 2004b). It was initially reported that five out of six patients had either microscopic residual or complete pathologic responses to the preoperative regimen, but I know from personal communication that these results are holding up,

and now 11 out of 12 patients have had this response. In addition, no surgical catastrophes have been encountered following this regimen as long as six weeks elapse before the patient undergoes surgery.

These data open a lot of doors for the future of these patients and chemoradiation in general. In clinical trials, we will be evaluating bevacizumab's ability to enhance the effect of radiation therapy. One of our focuses at MD Anderson is organ preservation, and with bevacizumab, instead of removing radiation therapy, from the neoadjuvant treatment equation, this agent, when used with radiation therapy, may lessen how radical a surgery needs to be. I want to stress that this is investigational, but the responses are better, and I believe they will also translate into better local control.

3.1 Active Clinical Trials Evaluating Bevacizumab Combined with Radiation in the Neoadjuvant Treatment of Rectal Cancer

Protocol ID	Phase	Protocol schema	Eligibility
2003-0832 (T3-4)	II	Bevacizumab + capecitabine + radiotherapy	Rectal cancer
DFCI-02025 (Stage II/III)	I	Bevacizumab + fluorouracil + radiotherapy	Rectal cancer

SOURCE: NCI Physician Data Query, July 2005.

Select publications

Cassidy J et al. **Capecitabine (X) vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT study): Efficacy results of a phase III trial.** Presentation. ASCO 2004;**Abstract 3509**.

Crane CH, Sargent DJ. **Substitution of oral fluoropyrimidines for infusional fluorouracil with radiotherapy: How much data do we need?** *J Clin Oncol* 2004;22(15):2978-81. No abstract available

Gerard J et al. **Preoperative (preop) radiotherapy (RT) + 5 FU/folinic acid (FA) in T3-4 rectal cancers: Results of the FFCD 9203 randomized trial.** Presentation. ASCO 2005;**Abstract 3504**.

Hofheinz RD et al. **Phase I trial of capecitabine and weekly irinotecan in combination with radiotherapy for neoadjuvant therapy of rectal cancer.** *J Clin Oncol* 2005;23(7):1350-7. **Abstract**

Nygren P et al. **Targeted drugs in metastatic colorectal cancer with special emphasis on guidelines for the use of bevacizumab and cetuximab: An Acta Oncologica expert report.** *Acta Oncol* 2005;44(3):203-17. **Abstract**

O'Connell MJ et al. **Update on design of the National Surgical Adjuvant Breast and Bowel Project trial R-04.** *J Clin Oncol* 2005;23(4):933-4. No abstract available

Rodel C, Sauer R. **Neoadjuvant radiotherapy and radiochemotherapy for rectal cancer.** *Recent Results Cancer Res* 2005;165:221-30. **Abstract**

Willett CG et al. **Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.** *Nat Med* 2004a;10(2):145-7. **Abstract**

Willett CG et al. **Phase I study of neoadjuvant bevacizumab, 5-fluorouracil, and radiation therapy followed by surgery for patients with primary rectal cancer.** *Proc ASCO* 2004b;**Abstract 3589**.

Axel Grothey, MD

EDITED COMMENTS

Clinical trials with adjuvant oxaliplatin in patients with colon cancer

The MOSAIC trial compared FOLFOX4 to infusional 5-FU/leucovorin, and three-year disease-free survival was superior in patients treated with adjuvant FOLFOX with oxaliplatin (Andre 2004). An improvement in disease-free survival is a surrogate marker for overall survival, according to the analysis by Dan Sargent (Sargent 2004). At that point, we had one trial demonstrating that the addition of oxaliplatin to a 5-FU-based regimen could have benefit in the adjuvant therapy of colon cancer.

This year, a trial of a bolus 5-FU regimen with oxaliplatin supported this idea. The results from NSABP-C-07 were more positive than most experts expected. NSABP-C-07 randomly assigned patients with Stage II or III colon cancer to receive the Roswell Park regimen of 5-FU/leucovorin (three cycles of an eight-week regimen) with or without oxaliplatin 85 mg/m^2 administered weeks one, three and five (FLOX; [Wolmark 2005]).

FOLFOX versus FLOX

Compared to the FOLFOX4 regimen used in the MOSAIC adjuvant trial, the FLOX regimen in NSABP-C-07 had the same duration of therapy but a lower cumulative dose of oxaliplatin (765 mg/m^2 versus 1,020 mg/m^2). Although the dose intensity of oxaliplatin was lower and a bolus 5-FU regimen was used as the backbone for the FLOX regimen, they found an increase in the three-year disease-free survival that was almost identical to that in the MOSAIC trial — about a five percent absolute increase (Wolmark 2005).

This suggests that the addition of oxaliplatin to any 5-FU-based regimen is of benefit in the adjuvant setting. Secondly, it shows we probably have two alternatives to choose from — FOLFOX or FLOX. Interestingly, we have the same effect with a lower cumulative dose of oxaliplatin. In the MOSAIC trial, the median dose intensity of oxaliplatin was only 81 percent (Andre 2004). Patients did not receive the six-month cumulative dose of oxaliplatin. The question is, can we use just four months or three months of therapy?

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The fact that adjuvant FLOX was at least in the same range of efficacy as adjuvant FOLFOX is surprising because of the data from the TREE-1 and TREE-2 trials just reported at ASCO (Hochster 2005). Those trials compared modified FOLFOX6, CAPOX and bFOL (a bolus 5-FU/leucovorin/oxaliplatin regimen developed by Howard Hochster at NYU). In these sequential Phase II trials, bFOL was clearly the inferior regimen in terms of response rate. Therefore, it's interesting that the FLOX regimen of bolus 5-FU/leucovorin/oxaliplatin could be effective in the adjuvant setting.

Overall, FLOX appears to be more toxic than FOLFOX, but the incidence of Grade III neurotoxicity was lower with FLOX in NSABP-C-07 (eight percent; [Wolmark 2005]) than with FOLFOX4 in the MOSAIC trial (12 percent; [Andre 2004]), mainly because the target cumulative dose was lower.

In my practice, I would still use adjuvant FOLFOX as the standard of care in the adjuvant setting because it's more tolerable, but I would probably stop the oxaliplatin as soon as patients report Grade II neurotoxicity. I would try to reach four months of therapy (eight cycles), which is tolerable for most patients. In former adjuvant settings, we have tried to push to toxicity because we thought we needed duration of therapy and dose intensity for the benefit. NSABP-C-07 might indicate that we don't have to push beyond a certain cumulative dose of oxaliplatin.

MOSAIC trial update

The recent ASCO update demonstrates that the difference in disease-free survival is maintained over time. After four years of follow-up, the absolute difference in disease-free survival is 8.6 percent in patients with Stage III disease. In patients with Stage II disease, we're seeing a difference of around three or more percent, which is not yet statistically significant. The survival difference is in the range of two percent (de Gramont 2005; [4.1]).

We will not necessarily see a significant difference in overall survival yet, because as soon as a patient relapses, we have active treatments that keep the patients alive. One interesting tidbit from Dr de Gramont's presentation was that those patients who did relapse after adjuvant FOLFOX apparently did not respond as well to systemic chemotherapy (de Gramont 2005). This might indicate that those patients who relapse after adjuvant FOLFOX are probably a poor-prognosis group of patients who don't respond to chemotherapy as well in the palliative setting.

When we consider the actual toxicity differences between 5-FU/leucovorin and FOLFOX4 in the MOSAIC trial, the most critical point is that we don't see a difference in mortality. We have 0.5 percent of patients dying on therapy in both arms. FOLFOX4 is associated with neutropenia, but patients don't necessarily experience neutropenia as a clinical symptom unless they have febrile neutropenia, which occurred in only about two percent of the patients.

The key difference is in neurotoxicity. We've seen that the vast majority of patients experience reversibility of these neurotoxicity symptoms. A few patients

are left with Grade II or Grade III neurotoxicity more than two years after chemotherapy, but it's a minority (de Gramont 2005).

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

	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. **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**. Presentation. ASCO 2005;**Abstract 3501**.

Adjuvant therapy for patients with Stage II disease

Patients with high-risk Stage II disease should be offered adjuvant FOLFOX. We have reliable and well-validated risk factors to tell us which patients are at higher risk: patients with T4/N0 tumors, an inadequate number of lymph nodes sampled (<10), obstruction or perforation at clinical presentation, angiolymphatic invasion in their tumor specimen or undifferentiated tumors.

These tumor characteristics could lead us to treat those patients with adjuvant FOLFOX. A nonplanned, exploratory subgroup analysis of the MOSAIC adjuvant trial evaluated those patients with high-risk Stage II disease and demonstrated that they have exactly the same benefit as patients with Stage III colon cancer (Hickish 2004). For me, that analysis also says that if you don't have these risk factors, you probably do not benefit from adjuvant chemotherapy.

Update of the X-ACT adjuvant trial

The trial randomly assigned patients to receive capecitabine or the Mayo Clinic 5-FU regimen, which is probably an inferior regimen. Based on this comparison, in almost 2,000 patients with Stage III disease, capecitabine didn't appear to be inferior and may be better (Twelves 2005a; [4.2]).

In the recent update of the trial, the curves for disease-free survival and overall survival look better. There was a nonstatistically significant absolute difference in the range of three percent for three-year disease-free survival and overall survival favoring capecitabine (Twelves 2005b). Superiority was never

an endpoint of the trial, but we can conclude that capecitabine is a substitute for bolus 5-FU/leucovorin.

The safety analysis in this mainly European patient population showed that 2,500 mg/m^2 per day of capecitabine was more tolerable than the Mayo Clinic regimen. About 57 percent of patients required capecitabine dose modifications (Twelves 2005a), which is more or less what we experience in clinical practice. The need for dose reductions is probably higher in the United States. In my personal view, we should start with the established dose but keep a close eye on the patient and reduce the dose until the patient can tolerate the capecitabine.

4.2 X-ACT Trial: Safety and Efficacy of Capecitabine as Adjuvant Therapy

"This randomized phase 3 trial showed that disease-free survival among patients who received oral capecitabine was at least equivalent to that among those who received fluorouracil plus leucovorin by intravenous bolus as adjuvant treatment for stage III colon cancer. Predefined multivariate analyses reinforced the primary efficacy findings. Although unadjusted analyses of disease-free survival and overall survival showed noninferiority of capecitabine to fluorouracil plus leucovorin, the multivariate analyses suggested that treatment with capecitabine improved the efficacy outcomes. ...

"The significantly lower incidence and delayed onset of fluoropyrimidine-related grade 3 or 4 toxic effects with capecitabine as compared with fluorouracil plus leucovorin supports the favorable safety data reported with regard to patients with metastatic disease. Overall, there were significantly lower incidences of neutropenia and stomatitis and lower rates of nausea, vomiting, alopecia, and diarrhea in the settings of adjuvant treatment and metastatic disease with capecitabine. ...

"Our results support capecitabine as an alternative to fluorouracil plus leucovorin in the adjuvant treatment of colon cancer. Capecitabine or oxaliplatin-based therapy should be considered for all patients requiring adjuvant therapy for colon cancer."

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

Neoadjuvant chemotherapy for patients with rectal cancer

The Mayo Clinic is a conservative institution, and we are using continuous-infusion 5-FU in this situation, but I think the data are compelling that capecitabine can be used as a substitute. Outside of clinical trials, we shouldn't be afraid to use capecitabine. Having said that, this is currently being investigated in NSABP-R-04, which compares radiation therapy with either capecitabine or infusional 5-FU. A second randomization will evaluate the addition of oxaliplatin.

The future involves increasing the efficacy of neoadjuvant chemotherapy because in the end, patients eventually succumb to distant metastases. Adding more effective chemotherapy up front in combination with radiation therapy

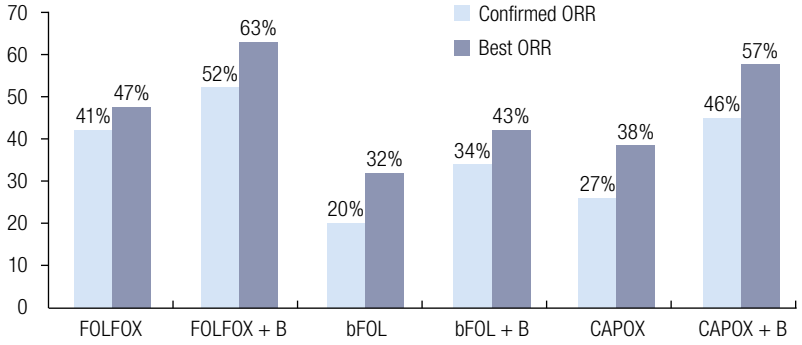
will allow us to maintain systemically active chemotherapy, which might attack micrometastases as early as possible. I'm sure it will enhance the pathologic complete response rate following chemoradiation therapy, which is a predictor for overall survival. Hence, we'll have local control improvement, and with the use of combination chemotherapy early on, we might have an impact on distant metastases.

TREE-1 and TREE-2 trials: First-line therapy for metastatic colorectal cancer

TREE-1 and TREE-2 were sequential trials based on different fluoropyrimidines being tested with oxaliplatin — CAPOX versus modified FOLFOX6 versus bFOL. When bevacizumab became available, the study was amended to include all three different combination regimens plus bevacizumab. What we have seen in TREE-1 and TREE-2 combined is that bFOL was inferior in terms of response rate (Hochster 2005; [4.3]).

In TREE-1, the CAPOX regimen used a high dose of capecitabine (1,000 mg/m^2 twice a day for 14 days), which was associated with the highest rate of diarrhea and hand-foot syndrome during the first 12 weeks of treatment. For TREE-2, the capecitabine dose was reduced to 850 mg/m^2, which led to much better tolerability — lower incidences of diarrhea and hand-foot syndrome — while still maintaining efficacy. In TREE-2, the efficacy of CAPOX plus bevacizumab was comparable to modified FOLFOX6 plus bevacizumab in terms of response rate and definitely better than bFOL plus bevacizumab (Hochster 2005).

4.3 Comparative Response Rates for TREE-1 and TREE-2



$p < 0.004$, from the pooled logistic regression analysis, likelihood ratio test; ORR = overall response rate
B = bevacizumab

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

Continuation of bevacizumab following disease progression

I personally continue bevacizumab because of the idea that it works on normal, genetically stable cells. My hypothesis is that the resistance we observe with FOLFOX/bevacizumab as first-line therapy is to FOLFOX, not to bevacizumab. Bevacizumab enhances the activity of chemotherapy; in colorectal cancer, it has been shown for 5-FU, irinotecan, cetuximab and oxaliplatin.

As we're targeting genetically stable endothelial cells that provide neovascularization to the tumor, I think it makes sense to use it this way. The role of bevacizumab following disease progression, however, is unclear. This is the main reason SWOG and NCCTG will be conducting a trial, the Intergroup Bevacizumab Continuation trial, in which patients who have progressed on FOLFOX/bevacizumab or FOLFOX followed by 5-FU/leucovorin/bevacizumab will be randomly assigned to additional therapy with or without bevacizumab.

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**

Arkenau H et al. **Infusional 5-fluorouracil/folinic acid plus oxaliplatin (FUFOX) versus capecitabine plus oxaliplatin (CAPOX) as first line treatment of metastatic colorectal cancer (MCRC): Results of the safety and efficacy analysis.** Presentation. ASCO 2005;**Abstract 3507**.

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.** Presentation. ASCO 2005;**Abstract 3501**.

Hickish T et al. **FOLFOX4 as adjuvant treatment for stage II colon cancer (CC): Subpopulation data from the MOSAIC trial.** Presentation. ASCO 2004;**Abstract 3619**.

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

Lenz HJ et al. **Activity of cetuximab in patients with colorectal cancer refractory to both irinotecan and oxaliplatin.** Presentation. ASCO 2004;**Abstract 3510**.

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**.

Sargent DJ et al. **Disease-free survival (DFS) vs overall survival (OS) as a primary endpoint for adjuvant colon cancer studies: Individual patient data from 12,915 patients on 15 randomized trials.** Presentation. ASCO 2004;**Abstract 3502**.

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

Twelves C et al. **Updated efficacy findings from the X-ACT phase III trial of capecitabine (X) vs bolus 5-FU/LV as adjuvant therapy for patients (pts) with Dukes' C colon cancer.** Presentation. ASCO 2005b;**Abstract 3521**.

Wolmark N et al. **A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07.** Presentation. ASCO 2005;**Abstract LBA3500**.

Post-test:

Colorectal Cancer Update — Issue 5, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. NSABP trial C-07, which evaluated bolus 5-FU/leucovorin with or without oxaliplatin in the adjuvant setting, showed that the addition of oxaliplatin significantly _____ patients' three-year disease-free survival rate.
   a. Improved
   b. Reduced

2. ECOG-E5202, a Phase III study of adjuvant therapy, will assign treatment in patients with Stage II disease according to the patient's prognosis based on their tumor's molecular phenotype.
   a. True
   b. False

3. ECOG-E3200 initially compared three regimens in the second- or third-line setting in treating metastatic disease. Which arm significantly improved response rate, progression-free and overall survival?
   a. 5-FU/leucovorin
   b. 5-FU/leucovorin plus bevacizumab
   c. Bevacizumab alone

4. In a small, randomized Phase II study published by Kabbinavar in 2003, which dose of bevacizumab was superior when combined with front-line 5-FU/leucovorin in the treatment of metastatic colon cancer?
   a. 5 mg/kg
   b. 10 mg/kg
   c. 15 mg/kg

5. It is proposed that NSABP-R-04, a neoadjuvant trial comparing capecitabine/radiotherapy versus 5-FU/radiotherapy in patients with locally advanced rectal cancer, be amended to add _____ in a 2 x 2 factorial design.
   a. Irinotecan
   b. Oxaliplatin
   c. Bevacizumab

6. In a Phase I trial with capecitabine, radiation therapy and bevacizumab in the treatment of pancreatic cancer, the partial response rate was 50 percent and the tumors shrank by 50 percent in six of the 12 patients who received bevacizumab five mg/kg.
   a. True
   b. False

7. MD Anderson's Phase II neoadjuvant study, 2003-0832, is evaluating which regimen in the treatment of patients with locally advanced rectal cancer?
   a. Capecitabine, radiation therapy and bevacizumab
   b. 5-FU, radiation therapy and bevacizumab

8. In the four-year update of the MOSAIC adjuvant trial, the absolute difference in disease-free survival is 8.6 percent in patients with _____ who received FOLFOX4.
   a. Stage II disease
   b. High-risk Stage II disease
   c. Stage III disease
   d. All of the above

9. In a Phase III randomized trial with 476 patients, CAPOX was significantly better than FUFOX in terms of response rate and progression-free survival.
   a. True
   b. False

10. The TREE-1 and TREE-2 trials initially randomly assigned patients to receive a fluoropyrimidine-based regimen with or without _____ .
    a. Oxaliplatin
    b. Irinotecan
    c. Cetuximab
    d. None of the above

11. In the BOND-2 trial, the median time to progression for patients with irinotecan-refractory disease who received the combination of cetuximab/bevacizumab/irinotecan approached _____ .
    a. 20 months
    b. 15 months
    c. 8 months
    d. 1 month

Post-test Answer Key: 1a, 2a, 3b, 4a, 5b, 6a, 7a, 8c, 9b, 10a, 11c

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GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment and incorporate these data into management strategies in the local and advanced disease settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging 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
- 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
Neal J Meropol, MD	5 4 3 2 1	5 4 3 2 1
Christopher H Crane, MD	5 4 3 2 1	5 4 3 2 1
Axel Grothey, 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

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Colorectal Cancer™ UPDATE

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