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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- and capecitabine-containing regimens, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients.
- Integrate emerging data on biologic therapies into management strategies for patients with advanced colorectal cancer.

### PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 3 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Saltz, Hoff and O'Connell on the integration of emerging clinical research data into the management of colorectal cancer.

### ACCREDITATION STATEMENT

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### HOW TO USE THIS MONOGRAPH

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**Dr Saltz** – **Grants/Research Support:** Bristol-Myers Squibb Company, ImClone Systems, Pfizer Inc, Roche Laboratories Inc **Consultant:** Genentech BioOncology, Pfizer Inc, Sanofi-Aventis. **Dr Hoff** – **Grants/Research Support:** Daiichi Pharmaceutical Co Ltd, Genentech BioOncology, Novartis Pharmaceuticals, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis. **Dr O'Connell** – No financial interests or affiliations to disclose.

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## UPCOMING EDUCATIONAL EVENTS

2005 ASCO Annual Meeting
May 14-17, 2005
Orlando, Florida
Event website: **www.asco.org**

American Association for Cancer Research Annual Meeting
April 16-20, 2005
Anaheim, California
Event website: **www.aacr.org**

Best of ASCO — San Francisco
June 17-18, 2005
San Francisco, California
Event website: **www.asco.org/meetings**

Multidisciplinary Treatment of Pancreas, Liver and Biliary Tract Cancer
June 17-18, 2005
Hyannis, Massachusetts
Event website: **www.mdanderson.org/prof_education/cmecs**

Best of ASCO — Dallas
June 25-26, 2005
Dallas, Texas
Event website: **www.asco.org/meetings**

International Society of Gastrointestinal Oncology 2nd Annual Conference
July 14-16, 2005
Arlington, Virginia
Event website: **www.isgio.org**

2005 ASCO/AACR Workshop — Methods in Clinical Cancer Research
July 30-August 5, 2005
Vail, Colorado
Event website: **www.vailworkshop.org**

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

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

## Editor's Note

### Is capecitabine the "AC" of adjuvant therapy for colorectal cancer?

*(And other related analogies to breast cancer as discussed by the faculty for this program)*

**DR LOVE:** Do you think that basic models used in breast cancer — such as relative and absolute risk reduction in adjuvant therapy — also apply to colorectal cancer?

**DR SALTZ:** I think the comparison of colorectal cancer to breast cancer is correct, and what I anticipated about a decade ago really is happening in our practices. What I said then was that we were GI doctors, but we wanted to be germ cell doctors. We wanted to cure 95 plus percent of our patients, and attempt to decrease the toxicity of curative regimens to figure out how to move the bar up and save those people with rare refractory disease.

We're not there yet, but along the way, we've become like breast cancer doctors. If you think about it, in 1990 it was absurd to talk about second-line chemotherapy for colorectal cancer. Now, with a straight face, we talk about, "What's your fourth-line treatment? What's your fifth going to be? You have six drugs. How are you going to use them? How are you going to sequence them?"

We now talk about expecting median survivals of two years for metastatic disease — and that's median survival, which means a fair number of people being treated with systemic chemotherapy will live three, four or five years with metastatic disease.

This is a huge paradigm shift in colorectal cancer and in GI oncology in general, which has really taken place fairly quickly over the past decade. I said that we were going to become more like breast cancer doctors as an interim step, and I think that's happened. Breast cancer care has continued to move forward, but we had a lot of ground to make up, and we've caught up some of the way.

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**DR LOVE:** In breast cancer, we often use less intense or less toxic chemotherapy for patients with lower risk, node-negative tumors — for example, AC — whereas a patient with a higher-risk, node-positive tumor might receive a more toxic therapy with a greater antitumor effect, which might include a taxane. Do you think that same approach applies in colorectal cancer in terms of using, for example, capecitabine alone in patients with lower-risk, Stage II disease?

**DR O'CONNELL:** I think so. It's a matter of looking at the risk-benefit ratio. The risk of treatment is going to be the same regardless of the risk posed by

the tumor, but the amount of absolute benefit with chemotherapy is going to be smaller in patients with good prognosis tumors.

So the incremental benefit of adding oxaliplatin along with 5-FU/leucovorin, although real and important, would result in a very small incremental gain for a favorable risk patient with Stage II disease. Therefore, I think it would be reasonable to treat those patients with a less toxic regimen, such as oral capecitabine.

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**DR HOFF:** It's very interesting how differently people who treat breast cancer and people who treat colon cancer approach the problem. In colorectal cancer, we tend to look at absolute benefit, while in breast cancer, relative risk reduction is taken much more seriously. If you were to look at the relative risk reduction, for example, of FOLFOX over 5-FU/leucovorin for Stage II disease, it's over 20 percent. Based on that, you might say that FOLFOX should be used for everyone with Stage II disease, which is not the case.

Perhaps because we have not had effective chemotherapy in the past, we have developed a nihilistic approach to colorectal cancer treatment. Although this takes a long time to change, I think it will happen. I think we'll be using more chemotherapy as our chemotherapy improves.

**DR LOVE:** If you have a patient who has an 80 percent chance of remaining disease free and that patient turns to you and says, "Could I further improve my odds by taking capecitabine," what would you say?

**DR HOFF:** Usually I tell my patients that this is a point of intense controversy, and depending on what study you believe, the absolute benefit in five years will be between two and five percent. I also tell them that there is a cost for that benefit — six months of therapy with some toxicity. Some patients opt to have treatment even for a one percent benefit, and I have had patients who look at me and say, "For five percent? Forget it." So I let my patients with Stage II disease help with the decision, unless they have strong risk factors. But I discuss it with all of them.

**DR LOVE:** The approach you just described is exactly what happens in breast cancer, where oncologists are now routinely offering statistics on expected absolute benefits to patients; however, I'm not sure that has occurred in terms of how people generally approach Stage II colorectal cancer.

**DR HOFF:** I hope we follow that path, because I really think that is the way to go. We should provide information and some direction to patients, but ultimately they have to decide what is acceptable.

**— Neil Love, MD**
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## BOND-2 study: Cetuximab/ bevacizumab plus or minus irinotecan in patients with metastatic colorectal cancer

### *Rationale and design*

In the BOND-1 trial, patients with irinotecan-refractory metastatic colorectal cancer were treated with cetuximab alone or in combination with irinotecan (Cunningham 2003). In the BOND-2 trial, we added bevacizumab to both arms (Saltz 2005). We wanted to know whether adding bevacizumab improved efficacy and whether it was safe and tolerable to give both monoclonal antibodies at the same time.

We had planned to accrue 75 patients in each arm; however, shortly after opening the study in December 2003, both agents became commercially available and within a month or so, the rapid rate of accrual slowed considerably. By the end of 2004, the number of eligible patients — patients who were bevacizumab naïve — was virtually nil, and we revised the statistical goals. The current data set is 39 patients who received irinotecan, cetuximab and bevacizumab and 35 patients who received cetuximab and bevacizumab. We anticipate that will be close to the final accrual total.

### *Efficacy data*

The combination of cetuximab, bevacizumab and irinotecan resulted in a response rate of 38 percent, and the time to progression was 8.5 months. The historical reference points in two previous trials of cetuximab and irinotecan without bevacizumab was a response rate of 23 percent and a time to progression of approximately four months (Saltz 2001, Cunningham 2004; [1.1]).

What I found even more interesting is the response rate with the two antibodies. In the BOND-2 trial, the response rate was 23 percent, and in the three historical references for cetuximab alone, the response rates ranged from nine to 12 percent (Saltz 2002, Cunningham 2004, Lenz 2004). In the prior studies, the time to tumor progression for single-agent cetuximab averaged 1.5 months, whereas in the

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BOND-2 trial the median time to tumor progression with the two antibodies at this analysis was 6.9 months.

This was a randomized Phase II study, and the comparison of the two arms was not the primary statistical hypothesis. We have to be very careful about interpreting a small study with a historical control; however, it's intriguing that the three-drug combination seems to show a significant increase in both response rate and time to tumor progression.

**1.1** Efficacy Data from BOND-2 Trial of Cetuximab/Bevacizumab with or without Irinotecan in Irinotecan-Refractory Colorectal Cancer and Historical Controls

| Efficacy parameter | Cetuximab/irinotecan + bevacizumab[1] (n=39) | Cetuximab/irinotecan[2] | *p*-value |
|---|---|---|---|
| Response rate | 38% | 23% (n=218) | 0.03 |
| Time to tumor progression | 8.5 months | 4 months | >0.01 |
| **Efficacy parameter** | **Cetuximab/bevacizumab[1] (n=35)** | **Cetuximab alone[2]** | ***p*-value** |
| Response rate | 23% | 11% (n=111) | 0.05 |
| Time to tumor progression | 6.9 months | 1.5 months | >0.01 |

[1] BOND-2 trial
[2] BOND-1 trial

SOURCES: [1] Saltz L et al. **Randomized Phase II trial of cetuximab/bevacizumab/irinotecan versus cetuximab/bevacizumab in irinotecan-refractory colorectal cancer.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 169b**.

[2] 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**

### *Toxicity data*

We saw no clear evidence of synergistic toxicity in the BOND-2 trial. The toxicities seen were essentially those of single-agent cetuximab or bevacizumab, such as skin rash and hypertension. We did see some instances in which it was difficult to discern whether we were seeing side effects or simply advancing cancer.

The incidence of these events was consistent with what has been reported in previous trials, so I don't believe they indicate a synergism of toxicities. However, we have less than 80 patients, and, as we gain more experience with the combination, we may begin to see some emerging toxicities.

### *Implications of the BOND-2 study in clinical practice and future research*

Data from the BOND-2 trial raise some interesting questions: What do we do with an interesting study that treats a population that no longer exists, and how do we extrapolate the data to clinical practice today?

This trial doesn't tells us whether to add bevacizumab to cetuximab-based therapy in patients who have already received bevacizumab, but our next study will basically repeat this trial in patients who have failed bevacizumab.

Until we have that data, I do not advocate routinely adding bevacizumab to cetuximab in patients who have previously received bevacizumab. However, if a patient is bevacizumab naïve, I believe these data support adding bevacizumab to cetuximab in a salvage setting.

While very few circumstances exist where the BOND-2 trial should change routine practice, it does provide important safety and pilot data for moving these two antibodies to front-line trials.

In a proposed design for a new Intergroup study, patients will be allowed to receive either FOLFOX or FOLFIRI at the physician's discretion. They will then be randomly assigned to receive bevacizumab, cetuximab or both in addition to the chemotherapy. In addition, we are considering several other constructs to evaluate the double-antibody approach as front-line therapy.

## EGFR staining and response to cetuximab

We just published an article in the *Journal of Clinical Oncology* that reports activity with cetuximab in colorectal cancer in tumors that do not express the EGFR by immunohistochemistry (IHC; [Chung 2005]). We reviewed charts of patients treated for colorectal cancer with cetuximab at Memorial Sloan-Kettering in a nonprotocol setting and found 16 patients with documented EGFR-negative tumors.

A reference pathologist confirmed that these tumors were negative, and then a reference radiologist reviewed the patients' scans prior to and during cetuximab treatment. It was confirmed that four patients had major objective responses and two had minor regressions on cetuximab, so a fair amount of antitumor activity was confirmed in these EGFR-negative tumors.

These are very compelling data. We all wanted to believe that EGFR would be an important prognostic indicator, but our technology for assessing EGFR expression is flawed. We generally use the primary tumor as the basis for the EGFR status of the metastasis, but that appears to be inaccurate. Data shows that EGFR degrades over time.

In addition, EGFR staining is very sensitive to the type of fixative used on the tissue. It appears that EGFR exists in two conformations — tethered and untethered. The antibodies we use do not discriminate between these conformations, but only the untethered has biologic activity in terms of signal transduction, and it represents a very small percentage of the total.

We know that blocking the EGFR alters regulation of VEGF expression, so scientific reasons exist to combine bevacizumab and cetuximab. However, EGFR staining has no prognostic significance, so the BOND-2 study did not require staining for entry. When we examined the original ImClone and BOND study, we saw exactly the same activity level regardless of whether the staining was very weak or very strong.

Putting all this together, I believe EGFR staining should not be permitted in standard practice. I find it a waste of money, and it's worrisome that physi-

cians might rebiopsy a patient just to obtain this material. At this time, no clinical decision should be made on the basis of EGFR staining. Specifically, no patient should be excluded from a therapy — cetuximab or otherwise — simply because their IHC staining for EGFR is negative and, just as importantly, no patient should be treated with these agents simply because the tumor is strongly EGFR positive.

This doesn't mean cetuximab isn't an EGFR-specific targeted agent — it almost certainly is. The fact is that cetuximab does bind to the epidermal growth factor receptor. The question is whether quantitating EGFR by IHC can give us any handle on cetuximab activity, and the answer is no.

These EGFR-negative data are very fresh and have enormous implications. They confirm what virtually every GI academic oncologist has known for a long time, which is that EGFR staining is a sham. It is wrong to use it for decision-making, and it is unethical to exclude patients from treatment on the basis of it.

## Impact of BOND-2 and ECOG-E3200 data on clinical practice

When Hurwitz presented the data on front-line IFL plus bevacizumab, I chose a fairly broad interpretation, as did many other oncologists, and decided it indicated that bevacizumab contributed to the activity of front-line chemotherapy (Hurwitz 2004). I extrapolated that to second-line therapy in my practice in bevacizumab naïve patients. Indeed, E3200 data confirmed that adding bevacizumab to FOLFOX in this patient population was beneficial (Mitchell 2005). The BOND-2 data builds on that and showed that adding bevacizumab to cetuximab-based therapy improves activity.

The E3200 study and BOND-2 study both show the utility of adding bevacizumab to a standard therapy and, at the same time, they're both treating a population that no longer exists — bevacizumab naïve patients. We need to investigate what will happen in patients who have been exposed to one of the drugs in advance, because one of the major questions regarding bevacizumab is whether it should be continued forever. Some very intelligent thought leaders feel that bevacizumab should be continued with sequential regimens in colorectal cancer. While I believe that's an interesting hypothesis, until it's tested it remains a hypothesis.

I am concerned that physicians will extrapolate the E3200 data to justify continuing bevacizumab after progression. They may think, "I used bevacizumab at 5 mg/kg front line, so now I'll continue it and maybe double the dose to 10 mg/kg as second-line therapy because that's what they did in E3200." That may be the right thing to do, but we don't have the data. Bevacizumab is expensive and while the subjective toxicity is minimal, it has some very rare but very serious potential toxicities.

## Adjuvant therapy for patients with Stage III disease

I'm pretty comfortable with the MOSAIC data (de Gramont 2005), so I generally use FOLFOX in the adjuvant setting for patients with Stage III disease. When I have a patient who is particularly dependent on their fine-motor skills, I discuss

with them whether we want to include oxaliplatin in their treatment because the neurotoxicity might compromise their quality of life. If I'm concerned about a patient's ability to tolerate combination chemotherapy, I might consider using one of several schedules of 5-FU/leucovorin or capecitabine.

We don't know the efficacy of FOLFIRI in the adjuvant setting, but if the PETACC-3 and ACCORD-2 studies are positive, then we would have an interesting alternative to FOLFOX for combination therapy without long-term neurotoxicity. We do know that IFL was not effective in the adjuvant setting, so that's not an option that should be considered.

## Capecitabine as adjuvant therapy: The X-ACT trial

In a reliable patient, capecitabine is a reasonable alternative when we don't want to use oxaliplatin, bearing in mind that the capecitabine data were generated in Europe (Cassidy 2004) and, for reasons that are not completely clear, European patients tolerate capecitabine better than American patients. In the X-ACT trial, the European adjuvant trial comparing capecitabine to Mayo Clinic 5-FU/leucovorin, the results for patients with Stage III disease who received capecitabine looked remarkably good. The study was designed as a non-inferiority study, but in a number of parameters capecitabine actually appears to be modestly superior.

## 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.** *Proc ASCO* 2004;**Abstract 3509**.

Chung KY et al. **Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry.** *J Clin Oncol* 2005;23(9):1803-10. **Abstract**

Cunningham D et al. **Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.** *N Engl J Med* 2004;351(4):337-45. **Abstract**

de Gramont A et al. **Oxaliplatin/5FU/LV in the adjuvant treatment of stage II and stage III colon cancer: Efficacy results with a median follow-up of 4 years.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 167**.

Giantonio B et al. **High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 169a**.

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

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

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

Saltz LB et al. **Interim report of randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 169b**.

Saltz L et al. **Cetuximab (IMC-C225) plus irinotecan (CPT-11) is active in CPT-11-refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR).** *Proc ASCO* 2001;**Abstract 7**.

Paulo M Hoff, MD

EDITED COMMENTS

## AVANT adjuvant trial: FOLFOX versus FOLFOX plus bevacizumab versus CAPOX plus bevacizumab

This very large multinational trial will attempt to accrue 3,450 patients (2.1). The study utilizes two dosing levels for bevacizumab. Since the CAPOX (capecitabine and oxaliplatin) regimen uses an every three-week infusion of oxaliplatin, those patients will receive 7.5 mg/kg of bevacizumab every three weeks for six months.

The patients treated with FOLFOX will receive five mg/kg of bevacizumab every two weeks for six months. Hence, the dose intensity is the same. Once the patients finish their chemotherapy, they will receive 7.5 mg/kg of bevacizumab every three weeks.

A lot went into the discussions for this trial. One issue was the choice of a control arm. While some discussion remains, we ultimately opted for FOLFOX. The next discussion was about patient selection. We decided to conduct the trial in patients with Stage III and high-risk Stage II disease, although the patients with high-risk Stage II disease will be part of an exploratory analysis.

The final and perhaps greatest discussion we had was about the length of treatment. Right now, the majority of adjuvant trials incorporate six months of chemotherapy and one year of molecularly targeted agents. We followed the same lead.

The rationale for using bevacizumab alone for six additional months after chemotherapy comes from the thought that bevacizumab has enough activity by itself to suppress the formation of new blood vessels and inhibit tumor growth.

Of course, it is possible that most of the benefit from bevacizumab comes from its association with chemotherapy. ECOG-E3200 demonstrated that bevacizumab alone was inferior to FOLFOX with or without bevacizumab (Giantonio 2005). Since this is a question without a good answer, the feeling was that it was justified to use the molecularly targeted agents longer than the chemotherapy. I see this as a proof-of-concept trial, and the length of treatment will have to be further refined in future trials.

*Dr Hoff is an Associate Professor of Medicine at The University of Texas MD Anderson Cancer Center in Houston, Texas.*

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


*SOURCE:* Cancer Care Nova Scotia. Clinical Trials — Cape Breton Cancer Centre. Available at: **www.cancercare.ns.ca/inside.asp?cmPageID=231**. Accessed February 24, 2005.

## Role of adjuvant CAPOX in the nonprotocol setting

There is great interest, especially in the community, in having an oral chemotherapy-based regimen, and the CAPOX regimen is very attractive in that regard. Given the opportunity, patients will tend to choose oral agents. We have the X-ACT adjuvant study showing that capecitabine was equivalent and had a hint of being better than bolus 5-FU/leucovorin (Cassidy 2004). I think the data from the Phase II CAPOX trials in the advanced setting are intriguing enough to say that it's at least equivalent to FOLFOX.

I wouldn't recommend CAPOX as my first option in the adjuvant setting, because obviously we prefer to use evidence-based medicine. However, I would not necessarily find it incorrect to use CAPOX in the adjuvant setting. Scientifically, it makes sense. Depending on individual patient issues (eg, dealing with access lines, etcetera), it might make sense.

## Nonprotocol adjuvant therapy for patients with colon cancer

If a patient has Stage III colon cancer, I tend to offer adjuvant FOLFOX first, unless they have a contraindication such as pre-existing peripheral neuropathy from other causes or a dependence on fine motor skills to earn a living. For example, I had a patient who worked with small watches who opted to receive capecitabine alone. I still tend to discuss adjuvant FOLFOX with patients who have contraindications, and if they want it, I will still use it.

Once I explain all the options, even some patients in whom I would prefer to use FOLFOX surprisingly ask to receive capecitabine. They feel attracted to the oral agent. Also, in patients with severe comorbid conditions or the very frail elderly patients, I tend to use adjuvant capecitabine instead of FOLFOX.

For those patients who present with Stage II disease, the decision about the use of adjuvant chemotherapy is much more complicated. Obviously, we have to discuss the potential benefits and toxicities of chemotherapy. I tend to offer adjuvant chemotherapy more strongly if their disease has a high-risk feature (eg, obstruction, perforation or lymphovascular invasion).

## Adjuvant therapy for elderly patients with colon cancer

I don't consider age, per se, a contraindication to chemotherapy. I think that's a problem these days; patients are sometimes denied chemotherapy when it could be beneficial. We have to remember that if a patient is an 82-year-old now and in good shape, they still have a life expectancy of several years.

I think adjuvant chemotherapy will be beneficial for those patients, and I don't necessarily approach them differently than a younger patient. However, I tend to be more conservative with the choice of chemotherapy. I tend to discuss the options, and I'm more inclined to use a fluoropyrimidine alone in the adjuvant setting.

Quite frankly, even before the X-ACT trial results, I was already inclined to use adjuvant capecitabine on occasion in elderly patients. That was not necessarily evidence-based medicine, but we had data from the metastatic setting showing it was equivalent to 5-FU. Capecitabine makes a huge difference for the patients' convenience and ability to receive the treatment at home.

## E3200: FOLFOX with or without bevacizumab

E3200 randomly assigned patients who had failed front-line treatment with IFL (irinotecan/bolus 5-FU/leucovorin) to one of three treatment arms: FOLFOX, FOLFOX plus bevacizumab or bevacizumab alone.

In the first interim analysis, bevacizumab alone was inferior to the other two treatments, and accrual to that arm was suspended. As you would imagine, the results have been eagerly awaited, because this is the first trial that we investigated the combination of bevacizumab and FOLFOX — a main first-line regimen used in the United States.

When the initial toxicity results were reported, we were impressed that patients receiving FOLFOX plus bevacizumab had a higher incidence of Grade III peripheral neuropathy (Mitchell 2005). There were two possibilities: (1) bevacizumab when added to FOLFOX caused peripheral neuropathy or (2) patients were staying on treatment longer.

Of course, we all wanted the second possibility to be the true reason. That was confirmed at the end of 2004 when an NCI news release reported approximately two months of benefit in the overall survival for those patients who had received bevacizumab plus FOLFOX. Median overall survival was about 10.5 months with FOLFOX alone, and around 12.7 months with FOLFOX plus bevacizumab (Mitchell 2005; [2.2]).

## Continuation of bevacizumab as part of second-line therapy

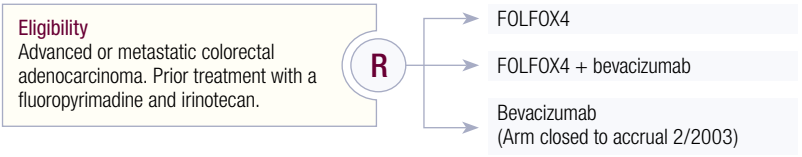
One big question arising from E3200 to which we do not have an answer is: If you treat a patient with an irinotecan-based regimen and bevacizumab as front-line therapy and the patient responds, but eventually progresses, do you treat with FOLFOX alone or FOLFOX plus bevacizumab as second-line therapy? Does it help to maintain the patient on bevacizumab? We do not know, and I would

be sad if we did not conduct a trial to find out. I think its time to back off and perform a trial evaluating the continuation of bevacizumab.

If you assume that the main mechanism of bevacizumab is a decrease in intratumoral pressure and that when the tumor progresses it is because of resistance to chemotherapy and not to bevacizumab, then bevacizumab should help again if combined with effective second-line therapy. If that is incorrect and bevacizumab has direct activity and the tumors are resistant to that direct activity, then the trial would be negative, but I believe the trial will most likely be positive.

### 2.2 Phase III Randomized Study of Oxaliplatin, Fluorouracil and Leucovorin Calcium (FOLFOX4) with or without Bevacizumab versus Bevacizumab Only in Patients with Previously Treated Advanced or Metastatic Colorectal Adenocarcinoma

Protocol IDs: E-3200, CTSU, NCT00025337
Accrual: 579 (Closed)




| Efficacy data | FOLFOX4 + bevacizumab (n=290) | | FOLFOX4 (n=289) | | HR | *p*-value |
|---|---|---|---|---|---|---|
| Median overall survival | 12.5 months | | 10.7 months | | 0.74 | 0.0024 |
| | FOLFOX4 + bevacizumab (n=286) | | FOLFOX4 (n=282) | | | |
| Toxicity data | Grade III | Grade IV | Grade III | Grade IV | | |
| Hypertension | 5% | 1% | 2% | <1% | | 0.018 |
| Sensory neuropathy | 15% | <1% | 9% | <1% | | 0.027 |

SOURCE: Giantonio BJ. *Proc ASCO GI Cancer Symposium*;**Abstract 169a**.

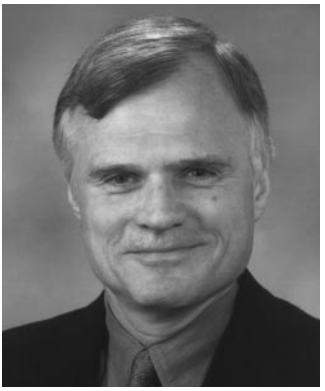
## Select publications


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.** *Proc ASCO* 2004;**Abstract 3509**.

Giantonio BJ. **High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO GI Cancer Symposium*;**Abstract 169a**.

Mitchell EP et al. **High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** ASCO Gastrointestinal Cancer Symposium 2005;**Abstract 169a**.

## NSABP colorectal trials in the adjuvant and metastatic settings



NSABP trial C-08 is an adjuvant therapy study for patients with Stage II and III colon cancer. It uses the modified FOLFOX6 regimen as the chemotherapy platform and asks whether or not the addition of bevacizumab will increase the possibility of long-term, disease-free survival and cure. The study opened in October 2004.

NSABP-R-04 is a preoperative study for patients with clinical Stage II or III rectal cancer, which randomly assigns patients to continuous infusion 5-FU using an ambulatory infusion pump and central venous catheter or oral treatment with capecitabine. We're currently in the process of amending that protocol to include a second question; namely, whether the addition of oxaliplatin along with either continuous infusion 5-FU or capecitabine could further increase the pathologic complete response rate and improve local control.

Another important trial is NSABP-C-09, which will focus on colorectal cancer that has metastasized to the liver. It's being submitted to the National Cancer Institute for final approval, and we anticipate it will be open soon. The primary question is whether, following hepatic metastasectomy, we can improve the outcome by administering intra-arterial FUDR in addition to systemic treatment with capecitabine and oxaliplatin compared to the capecitabine and oxaliplatin combination alone.

We're basically trying to confirm, in a multi-institutional setting, the data that Nancy Kemeny from Memorial Sloan-Kettering published some years ago in the *New England Journal of Medicine*, where the addition of intrahepatic FUDR seemed to decrease hepatic recurrences and improve two-year disease-free survival (Kemeny 1999a).

We have another study that has been approved by the National Cancer Institute, which will move forward in the first half of 2005 and which will evaluate the need for resection of an asymptomatic primary colon cancer in patients who present

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with metastatic disease. There's been a lot of controversy about this in the literature. Approximately 25 percent of patients with metastatic colorectal cancer who have an unresected primary will develop a complication — primarily, obstruction — if that tumor isn't resected.

Now that we have more effective systemic chemotherapy, our goal is to determine whether we can avoid the need for resection in patients who don't have any symptoms related to the primary tumor but who have distant, unresectable metastatic disease. We'll treat them all with the modified FOLFOX6 regimen plus bevacizumab. Our endpoint of this Phase II trial is to determine the local complication rates.

We will also be conducting a Phase II trial in patients with metastatic disease, where we will be evaluating capecitabine combined with oxaliplatin or capecitabine plus irinotecan, and adding bevacizumab to both of those oral combinations. Our rationale for this study is to obtain additional clinical evidence of activity and tolerability data in consideration of the next generation of adjuvant colon studies, because we have an interest in oral chemotherapy in the adjuvant setting.

NSABP trial C-06 compared oral UFT plus leucovorin versus intravenous 5-FU/leucovorin and was presented at ASCO last year (Wolmark 2004). The oral regimen was as effective as the intravenous, and there were improvements in quality of life. Unfortunately, that compound is not available in the US, so we will focus on capecitabine.

## ASCO guidelines for treating Stage II disease

I believe the ASCO guidelines for adjuvant treatment of colorectal disease were reasonable (Benson 2004). They certainly recommended adjuvant therapy for patients with Stage III disease. For Stage II disease, they didn't recommend it on a routine basis but did express that it would be a reasonable option to consider for high-risk patients. I think that's fair. In my own practice, I certainly offer adjuvant therapy to patients with Stage II disease. I try to provide them with an assessment of the absolute magnitude of benefit from therapy. If they understand those numbers and prefer to undergo the therapy, then I do it.

## X-ACT adjuvant trial: Capecitabine versus 5-FU/leucovorin

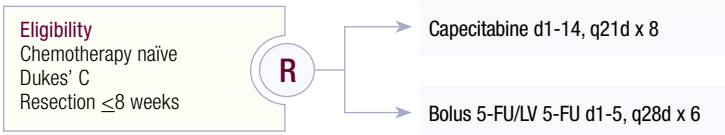
The X-ACT trial established the principle that oral chemotherapy could be effective in the adjuvant setting, compared to intravenous chemotherapy (Cassidy 2004; [3.1]). Capecitabine offers the patient the advantage of not requiring IV injections. The dosage level that was used is a bit higher than most oncologists in the United States have been able to administer to their patients, and it raises some interesting questions about possible pharmacogenetic differences between the populations in Europe and those in the United States.

I believe the data are very compelling and suggest that there might be an advantage for capecitabine over the Mayo Clinic method of administering 5-FU and leucovorin in the primary endpoint of disease-free survival, which practically reached statistical significance in favor of the capecitabine. The primary goal of

the study was to demonstrate noninferiority. They certainly accomplished that. I now believe that in clinical practice, for a patient in whom fluoropyrimidine therapy is considered appropriate, capecitabine is a viable option.

### 3.1 X-ACT Study: Randomized Phase III Adjuvant Trial Comparing Capecitabine to Bolus 5-FU/Leucovorin in Patients with Dukes' C Colon Cancer

Protocol IDs: X-ACT, ROCHE-M66001, NCT00009737
Accrual: 1,987 (Closed)




| Efficacy data | Capecitabine (n=1,004) | 5-FU/LV (n=983) | HR (95% CI) | *p*-value |
|---|---|---|---|---|
| Primary endpoint | | | | |
| 3-year DFS | 64.2% | 60.6% | 0.87 (0.75-1.00) | 0.0528 |
| Secondary endpoint | | | | |
| 3-year RFS | 65.5% | 61.9% | 0.86 (0.74-0.99) | 0.0407 |
| 3-year OS | 81.3% | 77.6% | 0.84 (0.69-1.01) | 0.0706 |

LV=leucovorin; HR=hazard ratio; CI=confidence interval; DFS=disease-free survival; RFS=relapse-free survival; OS=overall survival

SOURCES: Cassidy J et al. *Proc ASCO* 2004;**Abstract 3509**.
NCI Physician Data Query, March 2005.

## Management of metastatic colorectal cancer

Selection of therapy for first-, second- and third-line therapy is an evolving process. Presently, I utilize FOLFOX plus bevacizumab for first-line nonprotocol therapy. We're extending the survival times for our patients with this regimen, and they're receiving more and more treatment. However, the neurotoxicity is becoming increasingly problematic. We're approaching that problem in the same manner as in our Phase II trials of CAPOX or CAPIRI by administering a defined number of cycles of oxaliplatin or irinotecan with bevacizumab for approximately six months of therapy.

In those patients who are either responding or stable, we'll continue the capecitabine and bevacizumab as maintenance therapy until the time of progression. That's one way to provide the potential benefits of agents that do have cumulative toxicities — irinotecan and oxaliplatin — but then continue therapy with the agents that don't have significant cumulative toxicities. Another approach that's been utilized is the so-called "stop-and-go" technique of treating for several months to maximum response and perhaps a couple of additional cycles, and then simply stopping therapy and reinitiating treatment at a later time (3.2). I believe that is a reasonable alternative as well and I sometimes do that in my clinical practice.

Irinotecan and cetuximab would be very reasonable second-line options, whether it's with single-agent irinotecan and adding in cetuximab at the time of progression or, taking out the reimbursement issues, starting with both cetuximab and irinotecan together, which would make sense. The third-line setting is wide open, and clinical trials would definitely have a value in identifying new agents.

### 3.2 OPTIMOX Stop-and-Go Strategy to Limit Oxaliplatin-Induced Neurotoxicity

Stop

- After predefined cumulative oxaliplatin dose has been reached, or
- When sensory neurotoxicity of a certain grade has developed

Go

- When sensory neurotoxicity has regressed, or
- When oxaliplatin therapy is required to stop tumor progression

"Based on the observation of reversibility of the neurotoxic symptoms after discontinuation of oxaliplatin, de Gramont et al developed a Stop-and-Go strategy, the so-called OPTIMOX concept. This approach aims to increase the cumulative oxaliplatin dose that can be given to individual patients until the neurotoxic threshold is reached. This concept uses a dose-intensified treatment regimen with purely infusional 5-FU/LV over 46 hours (without bolus) plus oxaliplatin 130 mg/m$^2$ every 2 weeks (FOLFOX7) for six cycles until a cumulative oxaliplatin dose of 780 mg/m$^2$ has been administered. Subsequently, oxaliplatin is paused and treatment is continued with 5-FU/LV (sLV5FU2 [day 1: LV 200 mg/m$^2$ (2 hour), bolus 5-FU 400 mg/m$^2$, infusional 5-FU 2.4 to 3.0 mg/m$^2$ over 46 hours; every 2 weeks]) and oxaliplatin is reintroduced after 6 months."

SOURCE: Grothey A. *Semin Onc* 2003;30(4 Suppl 15):5-13. **Abstract**

## Select publications


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

Benson AB 3rd et al. **American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer.** *J Clin Oncol* 2004 22(16):3408-19. **Abstract**

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.** *Proc ASCO* 2004;**Abstract 3509**.

Kemeny N et al. **Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer.** *N Engl J Med* 1999;341(27):2039-48. **Abstract**

Kemeny MM et al. **Results of the Intergroup [Eastern Cooperative Oncology Group (ECOG) and Southwest Oncology Group (SWOG)] prospective randomized study of surgery alone versus continuous hepatic artery infusion of FUDR and continuous systemic infusion of 5FU after hepatic resection for colorectal liver metastases.** *Proc ASCO* 1999;**Abstract 1012**.

Wolmark N et al. **A phase III trial comparing oral UFT to FULV in stage II and III carcinoma of the colon: Results of NSABP Protocol C-06.** *Proc ASCO* 2004;**Abstract 3508**.

# Post-test:
## *Colorectal Cancer Update* — Issue 3, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. Data from the BOND-2 trial showed which of the following when comparing the combination of cetuximab/irinotecan/bevacizumab to historical controls with cetuximab/irinotecan only?
   a. Increased response rate
   b. Increased time to tumor progression
   c. Increased overall survival
   d. a and b

2. According to Chung et al, EGFR-staining by immunohistochemistry should always be used when determining which patients should be treated with cetuximab.
   a. True
   b. False

3. Based on a three-year, disease-free survival benefit demonstrated in the MOSAIC trial, FOLFOX has become a commonly used therapy for Stage III colorectal cancer in the adjuvant setting.
   a. True
   b. False

4. In the X-ACT adjuvant trial, which regimen was superior in efficacy?
   a. Capecitabine
   b. Mayo Clinic 5-FU/leucovorin regimen

5. The AVANT adjuvant trial will compare which of the following regimens:
   a. FOLFOX
   b. FOLFOX plus bevacizumab
   c. CAPOX plus bevacizumab
   d. Both b and c
   e. a, b and c

6. In the AVANT adjuvant trial, therapy with bevacizumab alone will continue for an additional six months following chemotherapy.
   a. True
   b. False

7. E3200 demonstrated that patients treated with bevacizumab plus FOLFOX had a better overall median survival than patients treated with _____ .
   a. Bevacizumab plus IFL
   b. FOLFOX alone
   c. Cetuximab plus FOLFOX
   d. Cetuximab plus IFL

8. The recently published ASCO recommendations concluded that the available evidence indicates it is inappropriate to administer adjuvant chemotherapy to patients with Stage II disease in a nonprotocol setting.
   a. True
   b. False

9. NSABP adjuvant trial C-08 will compare FOLFOX6 to FOLFOX6 plus:
   a. Cetuximab
   b. Bevacizumab
   c. Celecoxib
   d. None of the above

10. The pending NSABP trial C-09 will randomly assign patients with colorectal cancer metastasized to the liver to hepatic arterial FUDR with or without _____ following metastasectomy.
    a. FOLFOX-6
    b. Oxaliplatin
    c. Capecitabine and oxaliplatin (CAPOX)

11. The NSABP is in the process of amending preoperative trial R-04, which randomly assigns patients to continuous infusion 5-FU or capecitabine, by adding oxaliplatin to both arms of the study.
    a. True
    b. False

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

# Evaluation Form:

## *Colorectal Cancer Update* — Issue 3, 2005

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion will be issued upon receipt of your completed evaluation form.

**Please answer the following questions by circling the appropriate rating:**

| 5 = Outstanding | 4 = Good | 3 = Satisfactory | 2 = Fair | 1 = Poor | N/A = not applicable to this issue of *CCU* |
|---|---|---|---|---|---|

### GLOBAL LEARNING OBJECTIVES

**To what extent does this issue of *CCU* address the following 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-and capecitabine-containing regimens, and explain the absolute risks and benefits of adjuvant chemotherapy 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

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| Faculty | Knowledge of Subject Matter | Effectiveness as an Educator |
|---|---|---|
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| Paulo M Hoff, MD | 5 4 3 2 1 | 5 4 3 2 1 |
| Michael J O'Connell, 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
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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
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Overall, the activity met my expectations . . . . . 5 4 3 2 1 N/A
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**I certify my actual time spent to complete this educational activity to be _____ hour(s).**

Signature:..... Date:.....

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☐ Yes ☐ No

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.....

**What other faculty would you like to hear interviewed in future educational programs?**

.....

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**Additional comments about this activity:**

.....

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# Colorectal Cancer™
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# Colorectal Cancer™

## U P D A T E


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