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Colorectal Cancer™ UPDATE

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

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STATEMENT OF NEED/TARGET AUDIENCE

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

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 4 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Rothenberg, Petrelli, Hoff and Alberts on the integration of emerging clinical research data into the management of colorectal cancer.

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UPCOMING EDUCATIONAL EVENTS

NSABP Fall Meeting
October 13-16, 2006
Baltimore, Maryland
Event website: **nsabp.pitt.edu**

2nd Annual Oncology Congress
October 19-21, 2006
New York, New York
Event website: **oncologycongress.com**

4th Annual West Coast Colorectal Cancer Symposium: A Case-Based Approach
November 3, 2006
Seattle, Washington
Event website: **Swedish.org/cme**

ECOG Group Meeting
November 3-5, 2006
Ft Lauderdale, Florida
Event website: **ecog.org**

48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology
November 5-9, 2006
Philadelphia, Pennsylvania
Event website: **astro.org**

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

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

ASCO 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Event website: **asco.org**

INTERVIEW

Mace Rothenberg, MD

Dr Rothenberg is Ingram Professor of Cancer Research and Director of Phase One Drug Development at the Vanderbilt Ingram Cancer Center at Vanderbilt University in Nashville, Tennessee.

Tracks 1-15

Select Excerpts from the Interview

Track 6

DR LOVE: Let's talk about adjuvant therapy of colon cancer. Can you discuss your approach to off-protocol treatment and where you think we're heading in terms of the next generation of clinical trials?

DR ROTHENBERG: The MOSAIC trial from Europe (André 2004) and the C-07 trial from the NSABP (Wolmark 2005) both demonstrated that the addition of oxaliplatin to 5-FU/leucovorin improved three-year progression-free survival by approximately four to five percentage points, which was significant in both trials (1.1).

1.1 **Three-Year Disease-Free Survival (DFS) in NSABP-C-07 and MOSAIC**

	Three-year DFS (oxaliplatin arm)	Benefit from oxaliplatin	Hazard ratio (95% CI)
NSABP-C-07	76.5%	4.9%	0.79 (0.67-0.93)
MOSAIC	78.2%	5.3%	0.77 (0.65-0.91)

SOURCES: Wolmark N et al. Presentation. ASCO 2005;**Abstract 3500**; André T et al. *N Engl J Med* 2004;350(23):2343-51. **Abstract**

We have to be concerned about long-term toxicity with these kinds of regimens. If we counsel patients about potential permanent but mild neuropathy and they're accepting of this, then we have no reason not to administer oxaliplatin/5-FU/leucovorin — whether we use the schedule that the NSABP used, on which a lower total dose of oxaliplatin was administered, or the every two-week infusional 5-FU regimen from the MOSAIC trial.

An important clinical trial is being performed in ECOG and through the cooperative groups that's evaluating risk assessment of Stage II patients based on 18q deletion and microsatellite instability (MSI; [1.2]).

If patients have favorable characteristics for microsatellite instability — basically, MSI high and no 18q deletion — they are assigned to observation only.

If patients have one or two bad characteristics from this molecular analysis, they will be randomly assigned to either six months of FOLFOX or six months of FOLFOX and bevacizumab.

DR LOVE: How do you approach the treatment of Stage II disease off protocol?

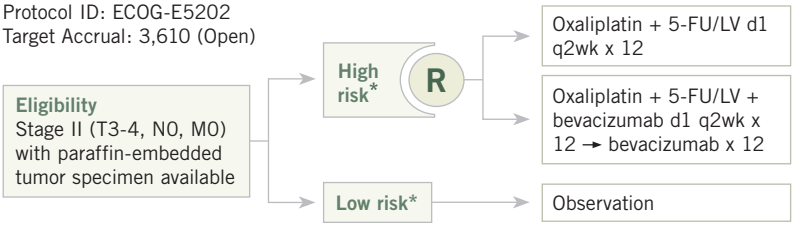
DR ROTHENBERG: I would probably look at these characteristics, although I have been in situations in which test results have come back conflicting — one criterion suggesting a good-prognosis tumor and another suggesting a poor-prognosis tumor. So it has ended up being rather puzzling and confusing to me.

I hope the results of the clinical trial that I just described will help. Often, the situation is resolved by talking to the patients and finding out whether they are most concerned about side effects from treatment and inconvenience, whether they feel comfortable in a watch-and-wait mode or whether they want to go to great lengths to try and eradicate every last cancer cell that might be lying dormant and are willing to withstand four to six months of adjuvant treatment along with the potential risks and side effects.

I try to use what patients tell me to determine the recommendation for whether they receive treatment or not. I can't say that I follow a "one-size-fits-all" approach when it comes to Stage II colon cancer.

1.2

Phase III Randomized Study of Oxaliplatin, Leucovorin Calcium and Fluorouracil with or without Bevacizumab in Patients with Resected Stage II Colon Cancer



* Patients are stratified according to disease stage (IIA versus IIB) and microsatellite stability (stable versus low-grade instability [MSI-L]). Patients at high risk for microsatellite instability (MSI) and loss of heterozygosity (LOH) at chromosome 18q are randomly assigned to one of two treatment arms (arms I and II), whereas patients at low risk for MSI and 18q LOH are assigned to arm III.

SOURCE: NCI Physician Data Query, May 2006.

Track 7

DR LOVE: Can you discuss the X-ACT trial (Twelves 2005)?

DR ROTHENBERG: This study compared single-agent capecitabine to the Mayo Clinic regimen of 5-FU/leucovorin for patients with locally advanced colon cancer. It was conducted as a noninferiority trial to find out whether 5-FU and leucovorin could be replaced by an oral agent. The bottom line was that it could.

In some measures of activity, capecitabine was trending toward being a little bit better than 5-FU/leucovorin (1.3).

I believe this is a very important trial — it's been published in *The New England Journal of Medicine* (Twelves 2005) — and it showed that we have an option for individuals who may not want to come into a clinic on a weekly basis because of their work or travel schedules and are willing and able to comply with an oral dosing regimen of capecitabine.

The side effects associated with capecitabine are different from those of the bolus 5-FU. You have a little bit less mucositis and myelosuppression, but you have a little bit more in the way of hand-foot syndrome.

It is important to note that both regimens can result in diarrhea. So patients must understand which side effects they're most likely to encounter, whom to contact and what to do about those side effects.

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

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

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

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

Track 8

DR LOVE: How do you approach the dosing of capecitabine in the adjuvant setting?

DR ROTHENBERG: That's a tough question because I'm always concerned about citing statistics from a trial and then not giving the same doses that were given in the trial. I would probably not start at 2,500 mg/m^2* but at 2,000 mg/m^2 and then monitor the patient very closely. If the patient tolerated the drug well, I would escalate the dose to 2,500 mg/m^2 by the second cycle. If he or she were having some side effects of concern but they were manageable, I'd stay at 2,000 mg/m^2.

The key is to dose at the optimum or maximum-tolerated dose for each patient. If the patient is experiencing tolerable Grade II toxicities, he or she is receiving enough of the drug. ■

* Two divided doses for 14 of 21 days

SELECT PUBLICATIONS

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

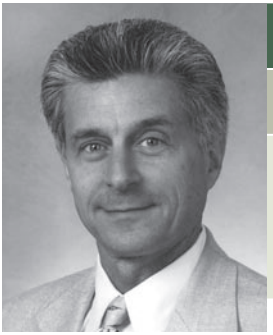
Cassidy J et al. **First-line oral capecitabine therapy in metastatic colorectal cancer: A favorable safety profile compared with intravenous 5-fluorouracil/leucovorin.** *Ann Oncol* 2002;13:566-75. **Abstract**

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

Hoff PM et al. **Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study.** *J Clin Oncol* 2001;19:2282-92. **Abstract**

Twelves C et al. **Capecitabine as adjuvant treatment for stage III colon cancer.** *N Engl J Med* 2005;352:2696-704. **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 the NSABP protocol C-07.** *Proc ASCO* 2005;**Abstract 3500**.



INTERVIEW

Nicholas J Petrelli, MD

Dr Petrelli is Professor of Surgery at Thomas Jefferson University in Philadelphia, Pennsylvania and Medical Director at the Helen F Graham Cancer Center in Newark, Delaware.

Tracks 1-14

Select Excerpts from the Interview

Track 2

DR LOVE: For patients with liver-only metastases, how do you determine whether the disease is resectable, possibly resectable in the future or never resectable?

DR PETRELLI: When patients come to me for a possible liver resection, I'm looking for a reason not to operate. You need to ascertain whether the disease in their liver looks like resectable disease, which depends on the size and number of lesions. But the most important question is, does the patient have any evidence of extrahepatic disease?

In my mind and I think most of my colleagues' minds — although a shift is occurring — extrahepatic disease is a contraindication to resection outside any type of protocol. I know an undercurrent exists, because of the new agents, to take patients with extrahepatic disease and resect their primary tumor along with their liver disease, but I believe that should be done as part of a clinical trial.

DR LOVE: Can you talk about those patients with disease you consider unresectable at the moment but that has the potential for resectability?

DR PETRELLI: Those patients need a true multidisciplinary approach to their disease. They must have input from the surgeon and the medical oncologist. Those individuals will likely be treated up front with FOLFOX and bevacizumab. They have to be followed closely because a window of opportunity will arise when those cases are converted from unresectable to resectable. Constant communication is necessary between the medical and surgical oncologists. After the first two cycles, the patient should be reevaluated to determine if the disease has become resectable.

Track 9

DR LOVE: NSABP-R-04 originally compared neoadjuvant radiation therapy in combination with continuous infusion 5-FU or capecitabine, and a second question concerning the role of oxaliplatin has been added. What are your thoughts about this trial?

DR PETRELLI: I believe NSABP-R-04 is a very important study. It goes back to the issue of a prospective, randomized, multicenter trial. I've been in this business long enough to know that data from a single-institution trial have to be reproduced.

I believe the addition of oxaliplatin is important, and it didn't increase the target accrual because we're talking about a noninferiority trial for the capecitabine versus continuous infusion 5-FU comparison. The accrual has been going very well for NSABP-R-04, even before oxaliplatin was added.

DR LOVE: If capecitabine is equivalent to infusional 5-FU, it will be a big boost to the patient in terms of avoiding the pump, et cetera.

DR PETRELLI: Sure. It's a good quality-of-life question.

Track 13

DR LOVE: Can you talk about the NSABP-C-10 trial?

DR PETRELLI: NSABP-C-10 is a Phase II trial for patients who present with endoscopically detected, asymptomatic primary colon cancer and unresectable distant metastases (2.1). This trial evaluates the hypothesis that by treating those patients with chemotherapy and bevacizumab, you don't have to remove

the primary tumor. I believe that's a very provocative and practical question because about 60 percent of these patients, according to SEER data, are having their primary tumors removed (Cook 2005).

The primary aim of the study is to observe the incidence of obstruction, perforation, fistula formation and hemorrhage that requires surgery. The secondary aim is to assess those potential complications with which the patient may not require surgery but needs hospitalization.

DR LOVE: If you see that the patients respond well with very low rates of local complications, what do you think will be the next step?

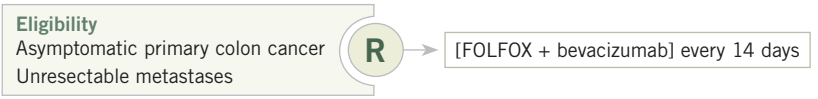
DR PETRELLI: If we see what you describe, I don't believe we'll have to do a Phase III trial. I believe we could probably state that if a patient presents with an asymptomatic primary tumor in the colon, not the rectum, you don't have to worry about removing the primary tumor.

In this Phase II trial, a small number of patients will probably receive chemotherapy and their liver disease will become resectable. I wouldn't be surprised if we saw some of those patients undergoing a resection of both their primary and distant disease. ■

2.1

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

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



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

SOURCE: NCI Physician Data Query, July 2006.

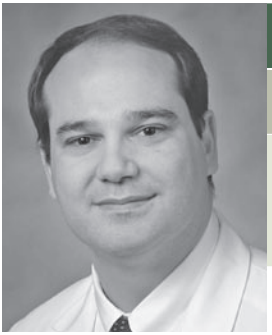
SELECT PUBLICATIONS

Benson AB III 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**

Clinical Outcomes of Surgical Therapy (COST) Study Group. **A comparison of laparoscopically assisted and open colectomy for colon cancer.** *N Engl J Med* 2004;350(20):2050-9. **Abstract**

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

Degiuli M et al. **Outcome of laparoscopic colorectal resection.** *Surg Endosc* 2004;18(3):427-32. **Abstract**



INTERVIEW

Paulo M Hoff, MD

Dr Hoff is Executive Director at Hospital Sirio Libanes in São Paulo, Brazil.

Tracks 1-11

Select Excerpts from the Interview

Track 2

DR LOVE: Can you discuss your FOLFIRI/bevacizumab study (3.1)?

DR HOFF: We now know that IFL with bevacizumab is better than IFL alone (Hurwitz 2004) and that FOLFIRI is less toxic and more efficacious than IFL, but we do not have any trial data on the efficacy of adding bevacizumab to FOLFIRI.

So we decided to conduct a Phase II trial evaluating the combination of FOLFIRI and bevacizumab (Hoff 2006). We are also collecting blood from the study participants for proteomic analysis and are doing DC MRIs to look at blood flow and changes in blood flow with bevacizumab alone or bevacizumab with FOLFIRI.

The trial has an interesting design. To conduct these correlative studies, patients receive only bevacizumab in the first cycle of treatment. We call that day minus 14 when they receive bevacizumab alone. After two weeks, the patients

begin treatment with FOLFIRI and bevacizumab. This allows us to have information from blood and imaging of the use of bevacizumab alone and in combination with FOLFIRI. It's something that I believe will allow us to learn a lot about the interaction of the drugs and what happens within the tumor when the drugs are taken. Among the first 20 patients we have evaluated so far, we have reached a response rate of 70 percent. For us, this is very good.

Although patients have diarrhea because of the use of irinotecan, it has been relatively straightforward to control. We have seen the expected incidence of neutropenia, but the percentages of Grade III and IV toxicities have been in line with those previously reported with FOLFIRI. It seems that adding bevacizumab has not increased toxicity tremendously but has increased the efficacy of the regimen.

The primary endpoint for the trial is progression-free survival, although we are following the response rate. This trial has been open for more than one year now and we still do not yet have median progression-free survival data, but we hope to achieve a progression-free survival that will be significantly longer than what we used to see with FOLFIRI alone.

3.1

Phase II Study of Bevacizumab with FOLFIRI

Protocol IDs: 2004-0614, NTC00354978
Targeted Accrual: 43 (Open)

Eligibility

- Confirmed colorectal adenocarcinoma with metastatic disease
- Measurable lesions as defined by modified RECIST
- No previous treatment with chemotherapy for metastatic disease
- Well-controlled hypertension exists

Treatment regimen → Bevacizumab day 1 → FOLFIRI/bevacizumab q2wk

Study Contacts:
Katrina Y Glover
MD Anderson Cancer Center
Tel: 800-392-1611 (in US), tel: 713-792-6161 (outside US)

SOURCE: http://utm-ext01a.mdacc.tmc.edu/dept/prot/clinicaltrialswp.nsf/index/2004-0614; http://ClinicalTrials.gov/show/NCT00354978

Track 4

DR LOVE: What are the practical clinical implications of this study?

DR HOFF: If our results are maintained with this high response rate and prolonged progression-free survival with acceptable toxicity, it will be an indication that the use of FOLFIRI with bevacizumab is a very good option in front-line treatment for metastatic colorectal cancer.

One important point in favor of FOLFIRI with bevacizumab is that we do not encounter a cumulative toxicity that will necessitate patients changing therapy after a set number of cycles. Of course, we do see fatigue and neutropenia with FOLFIRI, but once the patients reach a dose that their organs are used to, I believe they can tolerate this regimen for quite some time.

An important point is that we have seen late responses with this combination. We are used to seeing a maximal response around two months after we start chemotherapy. In our trial, many of the responses that reached RECIST were seen later. Our median time to response in this trial is 18 weeks. This is very encouraging because I believe it is due to the impact of bevacizumab, and perhaps long-term benefits will continue to be seen in patients who are on treatment.

Tracks 5-6

DR LOVE: What tends to be your first-line therapy for metastatic disease in a patient who is chemotherapy naïve?

DR HOFF: I'm increasingly tailoring therapy for individual patients. I discuss with my patients that the two regimens I most commonly use right now are FOLFIRI or FOLFOX with bevacizumab, provided patients have no contraindications to the use of the bevacizumab or any of the other agents.

If I have a patient who has a disease that may become operable within a relatively short period of time, I often use FOLFOX and bevacizumab. With patients for whom I expect the treatment to be necessary for longer periods of time, I often use FOLFIRI and bevacizumab. I believe the use of FOLFOX or FOLFIRI is a decision that must be made based on physician comfort with the regimens because the efficacy between the two combinations is very similar.

DR LOVE: What about CAPIRI or CAPOX?

DR HOFF: CAPIRI and CAPOX are very good options. We have less experience with the use of CAPIRI or CAPOX with bevacizumab here in the United States. I believe the way bevacizumab was approved in the United States directed us more to using combinations with infusional 5-FU than with capecitabine, which is an excellent agent.

Recently, we have had patients who were treated with CAPOX and bevacizumab. Although it's difficult to compare efficacy between these two regimens because we only have personal experience and no randomized trial experience, our results have been similar to what we would expect to see with FOLFOX and bevacizumab. I feel comfortable with these agents in combination with bevacizumab, particularly CAPOX, with which we have more experience from other centers.

DR LOVE: How do you treat a patient who has responded well to FOLFOX and bevacizumab, is eventually taken off oxaliplatin because of neurotoxicity, continues with 5-FU/bevacizumab, and then experiences disease progression at 18 months?

DR HOFF: This is an important question because FOLFOX or CAPOX with bevacizumab are probably the most commonly used regimens in the United States. We know that patients treated with these regimens do not progress within the first few months and that the majority will still derive benefit from the treatment when they develop too much neuropathy to be able to continue with oxaliplatin. We often stop oxaliplatin and continue with a fluoropyrimidine and bevacizumab.

Those patients eventually will progress, although some patients derive great benefit for long periods of time just from the fluoropyrimidine and bevacizumab. We have two ways of approaching these patients at this point. Those patients who rapidly recover from the peripheral neuropathy from oxaliplatin could be reexposed to a combination with oxaliplatin, more or less following the OPTIMOX design that has been recently published by the group from Dr de Gramont (Tournigand 2006).

DR LOVE: Continuing the bevacizumab?

DR HOFF: If you're going to reintroduce the oxaliplatin, that's one option, although we do not know about the benefit of continuing bevacizumab, particularly in this situation. Since patients were previously responding to a combination with oxaliplatin and bevacizumab, however, it would be reasonable to continue in this particular situation.

However, for those patients who still have significant peripheral neuropathy and for whom reintroduction of oxaliplatin would not be reasonable, I tend to switch completely to an irinotecan-based regimen, and usually I do not continue bevacizumab in that situation.

Tracks 9-10

DR LOVE: Can you comment on the AVANT trial?

DR HOFF: The AVANT trial is one of the most important ongoing trials right now. It's for patients who have high-risk Stage II or Stage III colon cancer (3.2). After surgery, patients are randomly assigned to receive FOLFOX4 for six months, which is considered the standard of care for those patients right now. This trial has two experimental arms. In the first arm, patients receive FOLFOX4 and bevacizumab for six months and then six more months of bevacizumab alone. In the second arm, patients receive CAPOX with bevacizumab for six months followed by another six months of bevacizumab.

The objective is to determine if the addition of bevacizumab adds to the benefit of an oxaliplatin and fluoropyrimidine regimen in this setting and whether we can use CAPOX instead of FOLFOX. CAPOX offers some significant advantages in convenience, but I remind you that if we use CAPOX, the cumulative dose of oxaliplatin may be slightly less than that from administering 12 cycles of FOLFOX because you only use eight cycles with CAPOX.

DR LOVE: Why was the decision made to administer eight cycles of CAPOX?

DR HOFF: That's six months of therapy, and the idea was to continue to use the same regimens with which we have experience. The X-ACT trial was eight cycles of capecitabine versus the Roswell Park regimen. The CAPOX trial in the adjuvant setting is eight cycles, which ended up being the six months that we have come to accept as necessary for those patients. One could argue that perhaps six months is too much. We do have the British trial in which three months of infusional 5-FU was similar to six months of 5-FU/leucovorin. But I think that right now, worldwide, the feeling is that until we have further data, six months should be considered our standard. ■

3.2

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

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

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

R

- FOLFOX x 6 months
- [FOLFOX + bevacizumab] x 6 months → bevacizumab x 6 months
- [CAPOX + bevacizumab] x 6 months → bevacizumab x 6 months

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

SOURCE: NCI Physician Data Query, May 2006.

SELECT PUBLICATIONS

Colucci G et al. **Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: A multicenter study of the Gruppo Oncologico Dell'Italia Meridionale.** *J Clin Oncol* 2005;23(22):4866-75. **Abstract**

Diaz-Rubio E, Schmoll HJ. **The future development of bevacizumab in colorectal cancer.** *Oncology* 2005;69(Suppl 3):34-45. **Abstract**

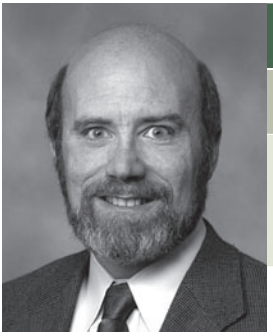
Ferrara N et al. **Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy.** *Biochem Biophys Res Commun* 2005;333(2):328-35. **Abstract**

Hoff PM et al. **Preliminary results of a phase II study of FOLFORI plus bevacizumab as first-line treatment for metastatic colorectal cancer (mCRC).** *Proc ASCO GI Cancers Symposium* 2006;**Abstract 252**.

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

Hurwitz H. **Integrating the anti-VEGF-A humanized monoclonal antibody bevacizumab with chemotherapy in advanced colorectal cancer.** *Clin Colorectal Cancer* 2004;4(Suppl 2):62-8. **Abstract**

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



INTERVIEW

Steven R Alberts, MD

Dr Alberts is Associate Professor of Oncology at the Mayo Clinic College of Medicine in Rochester, Minnesota.

Tracks 1-15

Select Excerpts from the Interview

Track 2

DR LOVE: How do you approach the treatment of patients with Stage II colon cancer?

DR ALBERTS: Generally, I tend to follow the Mayo Clinic approach of considering ploidy status, tumor size, angiolymphatic invasion and adequacy of node assessment as risk factors in deciding whether or not to treat a patient. If a patient has a diploid tumor and an adequate lymph node assessment, I often recommend observation.

DR LOVE: What is your specific choice of adjuvant therapy for patients with Stage II disease?

DR ALBERTS: If I were going to treat somebody, given the lack of information, I would certainly treat with FOLFOX. If you're going to make that commitment, it's hard to justify treating somebody with something that's potentially an inferior regimen.

DR LOVE: How do you approach the management of patients who have a suboptimal number of nodes identified?

DR ALBERTS: For patients who may come in with 10 or fewer involved lymph nodes, I always explain that, given the few lymph nodes that were removed or assessed, it may be a little harder to determine whether they indeed have Stage II or, potentially, Stage III disease. In that setting, I may be more likely to advocate the use of adjuvant therapy.

Track 4

DR LOVE: In general, how do you decide between 5-FU and capecitabine if you're going to use fluoropyrimidine monotherapy?

DR ALBERTS: Part of the decision is related to convenience and the other is related to monitoring of therapy. At least in my experience, capecitabine has manageable side effects if the patient understands the need to hold the therapy if he or she develops hand-foot syndrome or other side effects.

Certainly, some patients do go on to develop significant side effects despite stopping the therapy, but capecitabine is convenient, and its efficacy is equivalent to 5-FU/leucovorin. Thus, the ability to take pills home and not have to come into the office for either the Mayo Clinic regimen or weekly 5-FU/leucovorin makes capecitabine a lot easier for the patients.

Track 10

DR LOVE: What is the rationale for using capecitabine with oxaliplatin in your pilot study of hepatic-only disease and in the subsequent NSABP-C-09 study?

DR ALBERTS: Several thoughts went into making this decision. One was the observation that through the three-step process of metabolizing capecitabine, you achieve higher hepatic levels of the active metabolite in tumor cells versus nontumor cells, and the hope was that this would enhance the response rate.

The other consideration was convenience for the patients. Compared to bolus 5-FU, capecitabine seemed to provide a more convenient method of administration, and it also simulated infusional 5-FU because it was being administered over two weeks.

At this point, it's still unclear whether capecitabine/oxaliplatin is equivalent to infusional 5-FU/oxaliplatin. A number of randomized Phase II trials, including the TREE-1 trial, suggest they're comparable (Hochster 2005, 2006).

Track 11

DR LOVE: In your Phase II trial, what did you see in terms of side effects and toxicity when you combined CAPOX and intrahepatic FUDR for patients with surgically resected liver metastases (4.1)?

DR ALBERTS: Primarily, as patients completed the FUDR infusion, had a one-week rest and then went on to receive capecitabine/oxaliplatin, a little bump in liver enzymes occurred (Alberts 2006). The thought was that because of the metabolism of the drug in the liver, some interaction with FUDR was causing mild but subclinical irritation of the liver. Adding the capecitabine enhanced that effect, and that was one reason we reduced the dose from 1,000 mg/m^2 twice to 850 mg/m^2 twice a day.

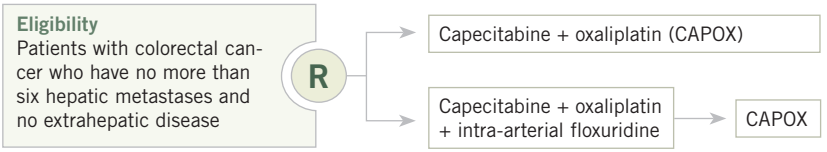
Beyond that, we didn't see an increase in events such as neutropenia, with the belief that very little of the FUDR gets out into the systemic circulation. Because we were administering a two-week infusion of FUDR followed by a one-week break and then the capecitabine/oxaliplatin for two weeks followed by a one-week break, a long lag existed between the systemic therapies.

Beyond some mild increase in liver enzymes, we didn't see any apparent synergistic toxicities between the two treatments. ■

4.1

Phase III Trial Comparing Intravenous Oxaliplatin and Oral Capecitabine and Hepatic Arterial Infusion of Floxuridine to Intravenous Oxaliplatin and Oral Capecitabine in Patients with Resected or Ablated Metastases to the Liver from Colorectal Cancer

Protocol ID: NSABP-C-09
Accrual: 400 patients (Open)



SOURCE: nsabp.pitt.edu, August 2006.

SELECT PUBLICATIONS

Alberts SR et al. **Systemic capecitabine and oxaliplatin administered with hepatic arterial infusion (HAI) of floxuridine (FUDR) following complete resection of colorectal metastases (M-CRC) confined to the liver: A North Central Cancer Treatment Group (NCCTG) phase II Intergroup trial.** *Proc ASCO* 2006;**Abstract 3525**.

De Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized mosaic trial.** *Proc ASCO* 2003;**Abstract 1015**.

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.** *Proc ASCO* 2005;**Abstract 3515**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The addition of oxaliplatin to 5-FU/leucovorin increased three-year progression-free survival among patients with Stage II or III colon cancer by approximately four to five percentage points in the _____ trial(s) of adjuvant therapy.**
   a. X-ACT
   b. BOND-2
   c. NSABP-C-07
   d. MOSAIC
   e. Both a and b
   f. Both c and d

2. **Which NSABP trial is analyzing the use of hepatic resection or ablation followed by CAPOX chemotherapy with or without intrahepatic FUDR for patients with resected or ablated liver metastases from colorectal cancer?**
   a. C-08
   b. C-09
   c. C-10
   d. R-04

3. **In the NSABP-C-10 trial evaluating FOLFOX with bevacizumab in patients with synchronous primary lesions and metastatic disease, the primary endpoint is _____.**
   a. Survival
   b. Disease-free survival
   c. Safety

4. **The NSABP adjuvant trial C-08 is evaluating _____ with or without bevacizumab.**
   a. FLOX
   b. FOLFOX
   c. FOLFIRI
   d. CAPOX
   e. All of the above

5. **NSABP-R-04 has been amended to evaluate the efficacy and toxicity of neoadjuvant _____, in combination with either continuous infusion 5-FU or capecitabine, and radiation therapy.**
   a. Irinotecan
   b. Oxaliplatin
   c. Cetuximab
   d. Bevacizumab
   e. None of the above

6. **NCCTG adjuvant trial N0147 is evaluating FOLFOX with or without _____.**
   a. Bevacizumab
   b. Cetuximab
   c. Panitumumab
   d. All of the above

7. **In the X-ACT adjuvant trial for patients with Stage III colon cancer, capecitabine was equivalent, if not superior, to bolus 5-FU/LV with regard to _____.**
   a. Disease-free survival
   b. Relapse-free survival
   c. Overall survival
   d. All of the above

8. **The randomized multicenter trial by the COST Study Group demonstrated the following advantage(s) for laparoscopic compared to open colectomy:**
   a. Decreased duration of hospitalization
   b. Decreased narcotic use
   c. Decreased operative time
   d. Both a and b
   e. a, b and c

9. **MD Anderson is conducting a Phase II trial evaluating _____ with bevacizumab as first-line therapy for patients with metastatic colon cancer.**
   a. FOLFOX
   b. CAPOX
   c. FOLFIRI

10. **Analysis of SEER data by Cook and colleagues demonstrated that approximately _____ percent of patients in the United States with synchronous primary and metastatic colorectal cancer have their primary tumors removed.**
    a. 27
    b. 48
    c. 60
    d. 79

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

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Colorectal Cancer Update — Issue 4, 2006

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GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *CCU* address the following 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. . . . . 5 4 3 2 1 N/A
- Counsel appropriate patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging research data on various adjuvant chemotherapy approaches, including the use of oxaliplatin-containing regimens and the use of capecitabine or intravenous 5-FU, and explain the absolute risks and benefits of these regimens to patients. . . . . 5 4 3 2 1 N/A
- Evaluate emerging research data on various neoadjuvant radiation therapy/chemotherapy approaches to rectal cancer and explain the absolute risks and benefits of these regimens to patients. . . . . 5 4 3 2 1 N/A
- Integrate emerging data on biologic therapies into management strategies for patients with advanced colorectal cancer. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Mace Rothenberg, MD	5 4 3 2 1	5 4 3 2 1
Nicholas J Petrelli, MD	5 4 3 2 1	5 4 3 2 1
Paulo M Hoff, MD	5 4 3 2 1	5 4 3 2 1
Steven R Alberts, 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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Signature: ..... Date: .....

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If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

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.....

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Additional comments about this activity:

.....

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CCU406

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Colorectal Cancer™

U P D A T E

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