New Directions in Colorectal Cancer Clinical Research

Proceedings and Interviews from a CME Symposium at the NSABP 2006 Group Meeting

from the publishers of

Colorectal Cancer™ UPDATE

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Colorectal Cancer Update — NSABP CME Symposium

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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. The purpose of this special issue of *Colorectal Cancer Update* is to present the most current research developments in targeted and systemic therapies for the treatment of colon and rectal cancers.

GLOBAL LEARNING OBJECTIVES

- Discuss the absolute risks and benefits of adjuvant systemic therapy, including the use of oxaliplatin-containing regimens and the use of capecitabine or intravenous 5-FU in patients with Stage II and Stage III colon cancer.
- Describe the ongoing trials examining the safety and potential efficacy of various biologic therapies in patients with colon cancer.
- Explain the rationale for targeting the EGFR/VEGF pathways and the current and future roles of monoclonal antibodies and oral tyrosine kinase inhibitors in colorectal cancer.
- Describe the current understanding of predictors of response and toxicity and their application to patients with colorectal cancer contemplating anti-VEGF therapy.
- Describe clinical trials of emerging neoadjuvant radiation therapy/chemotherapy approaches to rectal cancer, including the absolute risks and benefits of these regimens.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of this special edition of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Hochster, Hurwitz, O'Connell, Marshall and Wolmark on the integration of emerging clinical research data into the management of colorectal cancer.

ACCREDITATION STATEMENT

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HOW TO USE THIS CME ACTIVITY

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. **ColorectalCancerUpdate.com/NSABP_Symposium** 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**.

TABLE OF CONTENTS

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UPCOMING EDUCATIONAL EVENTS

31st ESMO Congress
September 29-October 3, 2006
Istanbul, Turkey
Event website: **esmo.org**

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

The Chemotherapy Foundation Symposium Innovative Cancer Therapy for Tomorrow
November 8-11, 2006
New York, New York
Event website: **mssm.edu/tcf/**

2007 ASCO 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**

EDITOR'S NOTE

Neil Love, MD

Way, way beyond 5-FU

The colorectal cancer plenary session at the 2003 American Society of Clinical Oncology annual meeting was a milestone in oncologic research. For the first time, a major randomized adjuvant clinical trial (MOSAIC) demonstrated a significant advantage in disease-free survival with the addition of a second systemic agent (oxaliplatin) to a fluoropyrimidine.

Shortly after Aimery de Gramont presented these fascinating results, Herb Hurwitz reviewed the findings from another study that set the stage for what has quickly become the fourth strategy in systemic cancer therapy. In a stunning confirmation of the hypotheses posed by Judah Folkman and others, the anti-VEGF monoclonal antibody bevacizumab was found to significantly prolong progression-free and overall survival when added to IFL in the first-line metastatic setting. Now, in addition to cytotoxic treatment, endocrine therapy and agents such as trastuzumab that target growth-factor receptors on and in cancer cells, we had anti-angiogenesis as part of our treatment armamentarium.

Several weeks after that ASCO meeting, Dr Norman Wolmark quipped during the NSABP group meeting in Orlando that, for the first time, more people attended the ASCO colorectal cancer presentations than the breast cancer sessions. The most discussed future clinical trial at that NSABP meeting was C-08, which started out as a three-by-two factorial design comparing FLOX to FOLFOX to CAPOX with or without bevacizumab. This landmark trial eventually morphed into its current, more focused form comparing FOLFOX with or without bevacizumab — a study design few of us would have anticipated several years earlier.

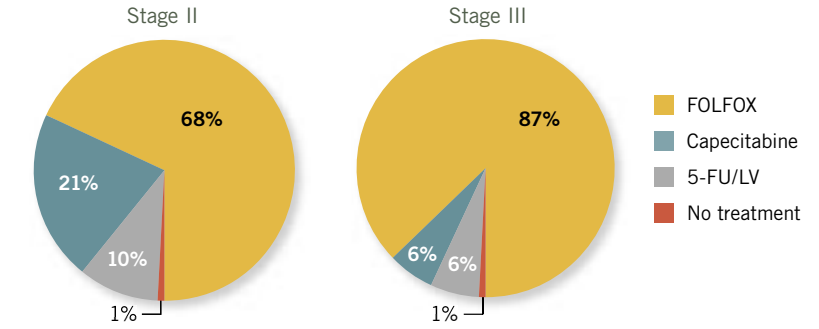
At the most recent NSABP group meeting in Denver on May 1, our education group had the honor of conducting a CME symposium during the scientific session to review recent important and related colorectal cancer clinical research developments since that historic 2003 ASCO meeting. The enclosed audio program includes highlights of that meeting and individual interviews with the speakers. The following issues are addressed:

1. Adjuvant systemic therapy for Stage II colon cancer
Dr Wolmark reviewed this controversy, which was fueled by a much-discussed ASCO position paper and the FDA approval of oxaliplatin, which

was restricted to Stage III disease despite the fact that 40 percent of patients in the MOSAIC trial had Stage II tumors. A related survey of 150 people with colorectal cancer that our CME group reported at the 2006 ASCO GI meeting demonstrated that, after listening to a 50-minute audio CD of Dr John Marshall describing in detail the risks and benefits of various adjuvant systemic therapies, patients preferred systemic therapies in a manner similar to other prior surveys of breast cancer patients (Figure 1). Of great interest is a recent related national Patterns of Care study of medical oncologists suggesting that the recurrence bar to trigger adjuvant therapy is significantly lower in breast cancer than in colon cancer (Figure 2).

1

What Would You Recommend to a Loved One in Their 60s?*

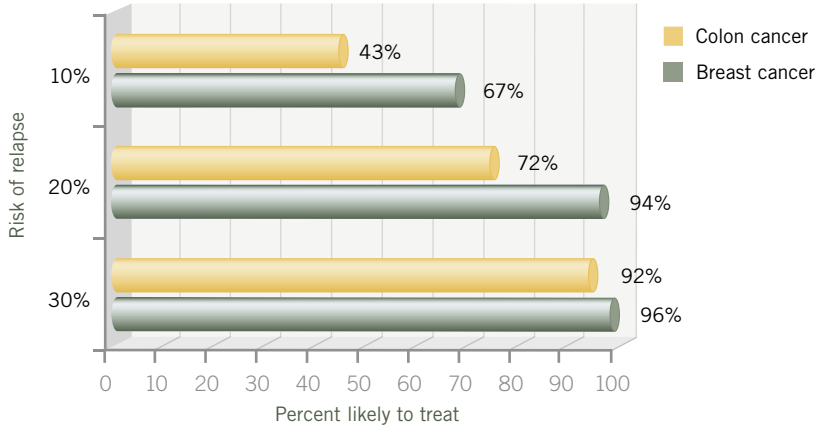


* Survey of 150 patients with colorectal cancer

SOURCE: Love N et al. ASCO GI 2006;**Abstract 373**.

2

Survey: N = 100 Medical Oncologists
Percent Recommending Chemotherapy



SOURCE: *Patterns of Care* in Colorectal Cancer 2005 (1).

2. What is the current optimal method to deliver oxaliplatin and a fluoropyrimidine in the adjuvant and metastatic settings?
Dr Wolmark presented results from NSABP-C-07 for the first time at the 2005 ASCO meeting, suggesting that FLOX, which uses bolus 5-FU, is an alternative to FOLFOX, which includes continuous infusion 5-FU. However, our CME group's Patterns of Care research demonstrates that adjuvant FOLFOX is currently prescribed much more commonly than FLOX.

A related issue is whether capecitabine can be substituted for 5-FU. The three-arm AVANT study is addressing that issue. During the symposium, Dr Howard Hochster discussed the TREE studies, which have resulted in encouraging data on the use of capecitabine/oxaliplatin combined with bevacizumab in the first-line metastatic setting.

3. What is the optimal fluoropyrimidine monotherapy in the adjuvant setting?
This issue seemed to be resolved with the 2004 ASCO presentation of the X-ACT trial, demonstrating an advantage in safety and relapse-free survival with capecitabine compared to the Mayo Clinic regimen of 5-FU/leucovorin. Our Patterns of Care work demonstrates a rapid uptake in the use of adjuvant capecitabine as monotherapy. It is interesting that in breast cancer, CALGB trial 49907 — comparing capecitabine to AC or CMF in patients older than age 65 — is limping along in accrual, whereas colorectal cancer has at least moved beyond the important question of whether orally administered chemotherapy can be substituted for intravenous treatment.

4. What is the current research database on the safety of bevacizumab?
The NSABP-C-08 research question of chemotherapy with or without bevacizumab is clearly the dominant issue in the current adjuvant colorectal trials, including AVANT, ECOG-E5202 in patients with high-risk Stage II disease and ECOG-E5204 in patients with rectal cancer. The Hurwitz IFL/bevacizumab trial heightened our awareness of the unusual complications of bowel perforation and hypertension associated with bevacizumab. Dr Hurwitz will update us on further work in this critical area, including the increased risk of arterial events. While the recent spectacular results from the adjuvant trastuzumab trials in breast cancer have resulted in optimism that monoclonal antibody therapy in the adjuvant setting might yield positive outcomes in colorectal cancer, to date there are minimal long-term toxicity data with bevacizumab. On this program, Herb Hurwitz updates what we do know currently.

5. What is the current and future role of anti-EGFR therapy in the adjuvant and metastatic settings?
Dr John Marshall provided an update on trials of monoclonal antibodies, cetuximab and panitumumab. A presentation at the April AACR meeting in Washington, DC of a trial in the metastatic setting comparing panitumumab with best supportive care to best supportive care with an optional crossover to panitumumab demonstrated, for the first time, a progression-free survival advantage to anti-EGFR monotherapy. Combined targeted biologic therapy

is another promising treatment strategy, and Dr Hochster reviewed findings from the BOND-2 study, which combined an EGFR antagonist (cetuximab) with bevacizumab.

These recent research advances leave oncology healthcare professionals and their patients optimistic that the management of this disease has moved past the days of 5-FU, 5-FU and 5-FU into new and very exciting territory. ■

— Neil Love, MD
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SELECT PUBLICATIONS

André 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**

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**

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**

Gordon MS, Cunningham D. **Managing patients treated with bevacizumab combination therapy.** *Oncology* 2005;69(Suppl 3):25-33. **Abstract**

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**.

Hurwitz H, Kabbinavar F. **Bevacizumab combined with standard fluoropyrimidine-based chemotherapy regimens to treat colorectal cancer.** *Oncology* 2005;69(Suppl 3):17-24. **Abstract**

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Jubb AM et al. **Impact of vascular endothelial growth factor-A expression, thrombospondin-2 expression, and microvessel density on the treatment effect of bevacizumab in metastatic colorectal cancer.** *J Clin Oncol* 2006;24(2):217-27. **Abstract**

Love N et al. **Patient perspectives on trade-offs of adjuvant systemic therapy for stage II and III colon cancer: A survey of 150 people with colorectal cancer.** Poster. ASCO GI Cancers Symposium 2006;**Abstract 373**.

Peeters M et al. **A phase 3, multicenter, randomized controlled trial (RCT) of panitumumab plus best supportive care (BSC) vs BSC alone in patients (pts) with metastatic colorectal cancer (mCRC).** *Proc AACR* 2006;**Abstract CP-1**.

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

Twelves C et al. **Capecitabine as adjuvant treatment for stage III colon cancer.** *N Engl J Med* 2005;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.** *Proc 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.** *Proc ASCO* 2005;**Abstract 3500**.

INTERVIEW

Norman Wolmark, MD

Dr Wolmark is Professor and Chairman in the Department of Human Oncology at Allegheny General Hospital, Professor at Drexel University College of Medicine and Chairman of the NSABP in Pittsburgh, Pennsylvania.

Tracks 1-11

Select Excerpts from the Interview and the CME Symposium

Tracks 2-3

DR LOVE: Can you discuss current controversies in the treatment of patients with Stage II colon cancer?

DR WOLMARK: When all is said and done, the Stage II controversy entails no basic disagreement. It's a matter of degree and of perspective (1.1). We don't advocate that all patients with Stage II disease be treated — we advocate that patients with Stage II disease be included in the discussion.

DR LOVE: Similarly in breast cancer, not all node-negative patients receive chemotherapy.

DR WOLMARK: Precisely. Just don't be authoritarian. Enter the patients into clinical trials, talk to them about the risks and benefits and make the decisions.

DR LOVE: I think the heterogeneity that I've seen is in the clinical investigator communities. Some are really on board with the relative risk concept in colon cancer, but others are not.

DR WOLMARK: It's a completely different mindset, and I believe a lot of it has been due to the higher level of advocacy in other cancers. In breast cancer, if you don't treat for a three percent survival difference, you'll have outrage.

DR LOVE: Can you talk about your take on the new data by the NSABP and Genomic Health that identified genes associated with prognosis in patients with colon cancer?

DR WOLMARK: Out of approximately 700 candidate genes, 140 genes, more or less, had independent prognostic significance in univariate analysis. If one performed multivariate analysis, controlling for the number of nodes and other variables, they remained significant.

I believe that's good news. I certainly consider it feasible to work out an Onco*type* DX™-like assay for colon cancer. The challenge will be validating it in a pristine subset, for which the tumor tissue bank is intact. That's something that can and will be done.

1.1

"Folklore, Fables and Myths" and the Adjuvant Treatment of Stage II Colon Cancer

"In the NSABP, we focus on both adjuvant breast and adjuvant colon cancer. I am surprised, amazed and perplexed at the frequency of education programs, which continue to debate the utility and propriety of treating patients with Stage II lesions. Is there a biologic difference?

We see a disparity in the threshold that it would take to initiate treatment for breast cancer and colon cancer. Withholding treatment for a three-percent difference in breast cancer leads to outrage. Withholding treatment for the same three-percent survival difference in colon cancer leads to a debate.

So, I ask you a question: Wherein lies the heterogeneity? Does it lie in the tumor or in the individuals treating the tumor? Is this a real biologic phenomenon or is it a matter of bias?"

SOURCE: Wolmark N. CME Symposium at the NSABP 2006 Group Meeting. May 1, 2006, Denver, Colorado.

Track 5

DR LOVE: Let's talk about some of the NSABP trials that are going on right now, starting with C-08 (1.2), evaluating the modified FOLFOX-6 regimen with or without bevacizumab. Where are we in terms of accrual, and how are physicians responding to that study?

DR WOLMARK: It's accruing very well. It started in September of 2004, and we've passed the 2,000 mark. The required sample size is 2,632. So we've had as good a response from the membership as we can possibly get. People are enthusiastic about using bevacizumab or assessing bevacizumab in the adjuvant setting.

DR LOVE: The adjuvant trastuzumab studies (Piccart-Gebhart 2005; Romond 2005) seem to have increased enthusiasm about the colon adjuvant bevacizumab studies because they use a similar model. Patients may be treated with a promising therapy that they wouldn't otherwise receive.

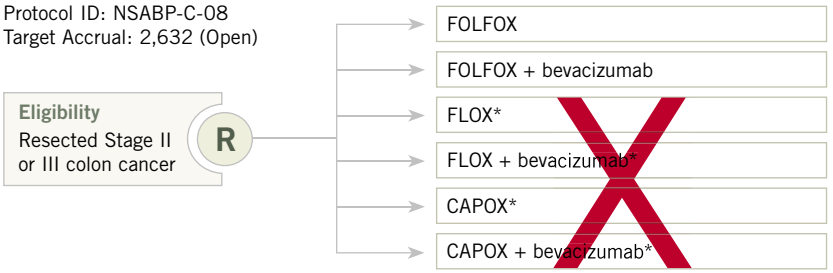
DR WOLMARK: I don't disagree. What further stimulated interest is that the results with trastuzumab were so spectacular. In some ways, it raises enormous expectations for what bevacizumab will do in the adjuvant setting.

I certainly don't expect it will do what trastuzumab did in breast cancer. We had a targeted subset of women whose tumors were HER2-positive. We don't have the same kind of population in the adjuvant setting in C-08.

On the other hand, "hope springs eternal," and I hope to see robust differences. The level of efficacy of trastuzumab in the adjuvant setting was a once-in-a-lifetime observation for some of us. Perhaps we'll be lucky and see it twice.

1.2

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



* Arms three through six were initially proposed in June 2003 but later deleted

SOURCES: NSABP-C-08 Protocol, May 2006; NCI Physician Data Query, July 2006.

Track 6

DR LOVE: In terms of the issue of safety with bevacizumab — particularly as it relates to patients being treated in the adjuvant setting — what's your take right now on where we are regarding arterial events — in particular, among patients with prior arterial events or older patients?

DR WOLMARK: We've restricted trial entry relative to prior events and prior myocardial infarctions. We hope to have a population that will not be at increased risk. This trial is being monitored very carefully and, to date, we haven't seen anything untoward or unexpected.

DR LOVE: With the idea that the accrual for the trial will be complete amazingly soon, can you talk about the discussions that are going on about a replacement study?

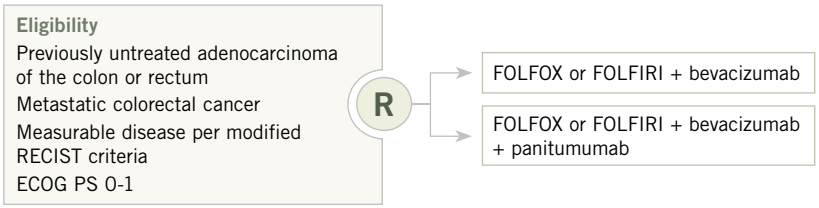
DR WOLMARK: The most enthusiasm for replacing C-08 would be in studying a double antibody regimen. Of course, the candidates would be bevacizumab with panitumumab, or bevacizumab with cetuximab, compared to bevacizumab alone, together with chemotherapy in both arms.

From what we have heard to date, the preference would be to use bevacizumab with panitumumab, seeking both an efficacy signal and a safety signal, provided we have supporting data from the PACCE trial (Panitumumab Advanced Colorectal Cancer Evaluation; [1.3]).

1.3

Phase III Randomized Trial of Bevacizumab with or without Panitumumab as First-Line Treatment of Metastatic Colorectal Cancer: The Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) Study

Protocol IDs: 200402-49; NCT00115765
Target accrual: approximately 1,000 (Open)



SOURCES: NCI Physician Data Query, July 2006; Amgen Press Release, April 26, 2005.

Track 7

DR LOVE: Why the focus on panitumumab as opposed to cetuximab?

DR WOLMARK: A general level of interest emerges when you have a fully human monoclonal antibody. It acquires some "designer cachet." It's certainly not based on a greater repository of data or any head-on comparisons. It's a matter of preference, and it's a matter of who is an active proponent of it.

DR LOVE: How do you think the panitumumab-associated rash will play out in the adjuvant setting? We're starting to consider this in the adjuvant lung cancer setting, with the tyrosine kinase inhibitors.

DR WOLMARK: Patients, particularly in the adjuvant setting, if given an opportunity to increase their survival, will be compliant. In the adjuvant setting, of course, it will be temporary, which is different from what you would have in other settings. So given the opportunity to increase cure rates, I believe the patients will be compliant if they know that the rash will occur and then resolve.

We went through issues of total alopecia in breast cancer, and we were told that nobody would tolerate it. Predictions were totally incorrect in the adjuvant setting, and it was not an insurmountable problem.

Track 8

DR LOVE: What are your thoughts about the new NSABP-C-09 trial of hepatic resection or ablation followed by CAPOX chemotherapy with or without intrahepatic FUDR (1.4)?

DR WOLMARK: The response we've received to date has been one that would perhaps engender cautious optimism as to the likelihood of our being able to carry out this trial. We need 400 patients, and we need those 400 patients referred by individuals who have experience in that area.

DR LOVE: My sense — and we've seen this in our Patterns of Care studies — is that there's a lot more sensitivity and activity among medical oncologists looking for curative situations in metastatic disease. So hopefully it will increase the denominator you might have available.

DR WOLMARK: We've gotten a good response from the CTSU as far as IRB approval. We see no reason to believe that this trial will not be successful at this point, but after one patient's been randomly assigned, I can say whatever I like. We'll revisit this issue in six to eight months, and then we'll have a much better idea.

DR LOVE: The NSABP has always attempted trials that have difficult randomizations, and this one's not easy.

DR WOLMARK: I certainly agree with you on both those issues; we've attempted difficult trials, and this is one of the more difficult ones.

Track 9

DR LOVE: Can you talk about the NSABP-C-10 study of FOLFOX with bevacizumab for patients with synchronous metastases?

DR WOLMARK: The C-10 study addresses a practical question: When you have a synchronous presentation of a primary lesion with metastatic disease, the standard has been to resect the primary lesion because you want to prevent the subsequent complications of bleeding, fistula formation, erosion into other organs and so on. Is that necessary, particularly when you have promising new agents such as oxaliplatin and bevacizumab?

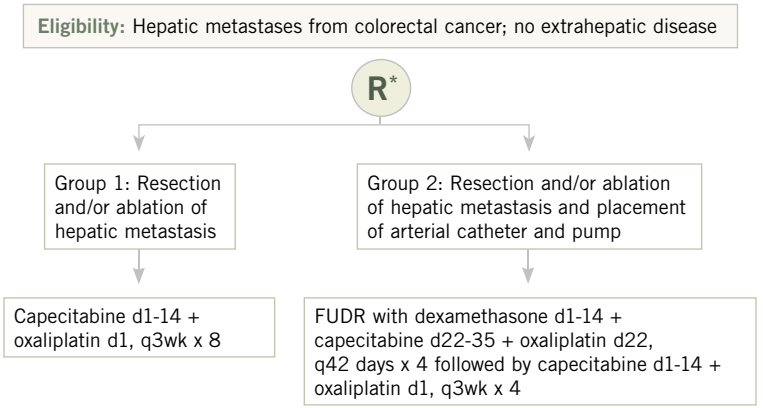
This is a Phase II trial with a sample size of 90 and complications of obstruction, bleeding and fistula formation and so on as the primary endpoints. So it's a feasibility trial. The intervention is FOLFOX with bevacizumab.

DR LOVE: Obviously, some selection will be involved in terms of patients with critical local problems who need surgery and who probably aren't going to be enrolled into this study. But, assuming the more typical situation, in which a patient's primary lesion is stable, one of the issues is that if they do develop some kind of problem that requires surgery, you're going to have bevacizumab on board, which may be an issue.

1.4

Phase III Study Comparing CAPOX and Hepatic Arterial Infusion of FUDR to CAPOX Alone in Patients with Resected or Ablated Liver Metastases from Colorectal Cancer

Protocol IDs: NSABP-C-09; NCT00268463
Target Accrual: 400 (Open)



* Stratified by (1) intended method for removal of hepatic metastases (surgical resection alone, cryoablation or radiofrequency ablation alone, or combination of resection and ablation); (2) adjuvant chemotherapy for colorectal cancer (chemotherapy regimen with oxaliplatin; chemotherapy regimen without oxaliplatin; no chemotherapy)

SOURCES: NCI Physician Data Query, July 2006; NSABP website, July 2006.

DR WOLMARK: Yes. It may be, but there's one way to find out. And, again, I don't say that flippantly. If we can demonstrate that you're going to get response in the primary site and elsewhere and that the rate of complications will be kept within the protocol limits, it should be a step forward.

DR LOVE: What do we know about the response of primary tumors to our current systemic therapies, particularly those that include bevacizumab?

DR WOLMARK: I don't know a great deal. We have the Willett data (Willett 2004), for example, for rectal tumors. I'm not sure we know a whole lot using bevacizumab. Regarding what it does to the primary tumors in colorectal cancer, I'm not sure there's much out there to allow us to make reasonable estimates. ■

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André 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**

Berry SR et al. **Preliminary safety of bevacizumab with first-line Folfox, Capox, Folfiri and capecitabine for mCRC — First BEA trial.** *Proc ASCO* 2006;**Abstract 3534**.

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**.

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Hochster HS et al. **Results of the TREE-2 cohort: Safety, tolerability, and efficacy of bevacizumab added to three oxaliplatin/fluoropyrimidine regimens as first-line treatment of metastatic colorectal cancer.** *Proc ASCO GI Cancers Symposium* 2006;**Abstract 244**.

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**.

Land SR et al. **Patient-reported neurotoxicity with FULV versus FLOX in patients with stage II or III carcinoma of the colon: Results of NSABP Protocol C-07.** *Proc ASCO* 2006;**Abstract 3564**.

Lembersky BC et al. **Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: Results from the National Surgical Adjuvant Breast and Bowel Project Protocol C-06.** *J Clin Oncol* 2006;24:2059-64. **Abstract**

O'Connell MJ et al. **Relationship between tumor gene expression and recurrence in stage II/III colon cancer: Quantitative RT-PCR assay of 757 genes in fixed paraffin-embedded (FPE) tissue.** *Proc ASCO* 2006;**Abstract 3518**.

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

Paik S et al. **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *J Clin Oncol* 2006;[Epub ahead of print]. **Abstract**

Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. **Abstract**

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. **Abstract**

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

Wedam SB et al. **Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer.** *J Clin Oncol* 2006;24:769-77. **Abstract**

Willett CG et al. **Surrogate markers for antiangiogenic therapy and dose-limiting toxicities for bevacizumab with radiation and chemotherapy: Continued experience of a phase I trial in rectal cancer patients.** *J Clin Oncol* 2005;23(31):8136-9. No abstract available

Willett CG et al. **Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.** *Nat Med* 2004;10(2):145-7. **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.** *Proc ASCO* 2005;**Abstract 3500**.

INTERVIEW

John L Marshall, MD

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

Tracks 1-11

Select Excerpts from the Interview and the CME Symposium

Track 3

DR LOVE: Can you briefly describe what we know about cetuximab?

DR MARSHALL: Cetuximab arrived on the scene in a very dramatic fashion. Leonard Saltz conducted the first trial that showed us the strength and power of this drug in the United States (Saltz 2001). This was a fairly simple Phase II clinical trial in which patients who were refractory to everything that we had at the time were given cetuximab in combination with irinotecan, even though patients had already experienced progression on irinotecan.

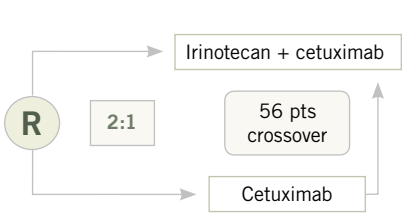
That was clever and insightful to have done at the time because there was a 23 percent response rate in the third-line setting. That kind of response rate is unheard of — second-line FOLFOX has a 10 percent response rate. They submitted the data to the FDA, and the FDA rejected the data, so they were forced to repeat that study.

The second study was a slightly larger version of the first and included about 300 refractory colon cancer patients given cetuximab. It was led by David

Cunningham and is known as the BOND-1 study. It was a Phase II randomized trial in which all of the patients had experienced progression on irinotecan, and about 60 percent had also experienced progression on oxaliplatin (Cunningham 2004; [2.1]). So the study included patients in the second- and third-line settings.

This study also found a 23 percent response rate among the patients treated with cetuximab and irinotecan and, interestingly, a 10 to 11 percent response rate with cetuximab alone. This trial dramatically demonstrated the efficacy of cetuximab in a refractory patient population, which led to its approval by the FDA in the United States.

2.1 **BOND-1 Study: Cetuximab with or without Irinotecan**



	RR	TTP	OS
Irinotecan + cetuximab	22.9%	4.1 mo	8.6 mo
Cetuximab	10.8%	1.5 mo	6.9 mo

"...Cetuximab alone or in combination with irinotecan had clinical activity in irinotecan-refractory colorectal cancer, confirming the results of phase 2 studies. The combination therapy group had a significantly higher response rate and a significantly longer time to progression than the monotherapy group, suggesting that the combination of irinotecan and cetuximab should be preferred for patients with irinotecan-refractory cancer.

Moreover, the number of previous treatment regimens and previous use or nonuse of oxaliplatin did not affect the efficacy of the cetuximab and irinotecan combination. Cetuximab monotherapy also had activity and only mild toxic effects and thus may be an option for patients who are not considered candidates for further treatment with irinotecan-based chemotherapy or who choose not to receive such treatment."

SOURCE: Cunningham D et al. *N Engl J Med* 2004;351(4):337-45. **Abstract**

Track 5

DR LOVE: Can you discuss what we know about panitumumab?

DR MARSHALL: Panitumumab is another antibody that targets the epidermal growth factor receptor (EGFR), and yet it has some important differences from cetuximab. It is a fully humanized antibody, which one would assume would have the advantage of reduced reactivity and therefore a reduced need for premedication and fewer infusion reactions.

This assumption has been borne out in the clinic. People are tolerating this medicine from a reactivity perspective better than patients treated with cetuximab in the past.

Although we don't have direct trials to compare panitumumab and cetuximab, panitumumab does look like an active drug in colorectal cancer. It has produced a very impressive set of data among end-stage colon cancer patients.

A large randomized trial comparing panitumumab to best supportive care demonstrated approximately a 10 percent response rate as well as a significant improvement in progression-free survival with panitumumab (Peeters 2006; [2.2, 2.3]).

2.2

Multicenter Phase III Trial of Best Supportive Care (BSC) with or without Panitumumab

Accrual: 463 (Closed)

Eligibility
Metastatic colorectal cancer, ECOG 0-2, radiologic documentation of progression after fluoropyrimidine, irinotecan and oxaliplatin, EGFR staining ≥ 1% of tumor cells

R

- Panitumumab 6.0 mg/kg q2wk + BSC → PD → follow-up
- BSC → PD → optional panitumumab crossover study → follow-up

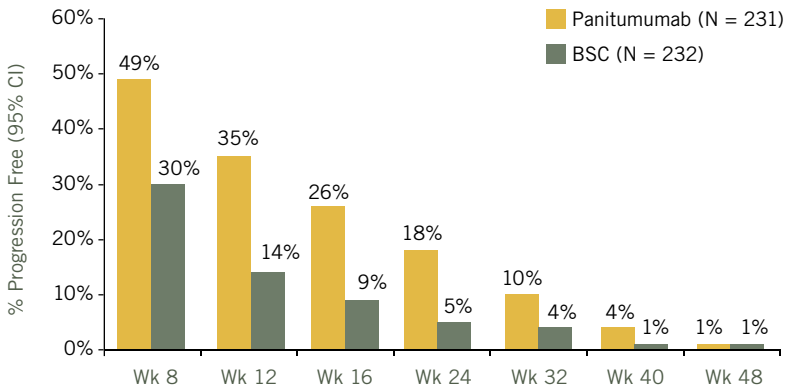
- Primary endpoint: Progression-free survival
- Secondary endpoints: Overall survival, best overall objective response, duration of and time to response

PD = progressive disease

SOURCE: Peeters M et al. Presentation. AACR 2006;**Abstract CP-1**.

2.3

Progression-Free Survival Rates at Prespecified Time Points in a Study of Best Supportive Care with or without Panitumumab in Metastatic Colorectal Cancer



Primary Analysis, All Randomized Analysis Set, Central Radiology

SOURCE: With permission. Peeters M et al. Presentation. AACR 2006;**Abstract CP-1**.

Whether this drug will play out as well in combination with chemotherapy as cetuximab has done is yet to be seen. Some small Phase I and Phase II trials of panitumumab in combination with chemotherapy look promising and consistent (Arends 2005; Roskos 2002; Weiner 2005).

The most important study for panitumumab right now is known as the PACCE study, in which patients with colorectal cancer are treated with frontline FOLFIRI or FOLFOX with bevacizumab and then randomly assigned to panitumumab or not (Wainberg 2006; [1.3]). If that study tells us that administering all the agents up front offers a significant advantage, then I expect we will see widespread use of that approach among patients with colon cancer.

DR LOVE: Putting aside cost and reimbursement issues, would you use panitumumab if it were available, and, if so, how would you integrate it into your algorithm as it relates to cetuximab?

DR MARSHALL: It's hard to know whether we need two of these agents on the market and whether one will offer advantages over the other from a clinical perspective. Right now the two agents look very similar, but one potential difference involves the mechanism of monoclonal antibodies.

Before I replace cetuximab with panitumumab, it is important to at least show equivalence in terms of efficacy between these two agents in a clinical setting.

Panitumumab offers some clear clinical advantages — it is administered every other week as opposed to weekly, it doesn't cause infusion reactions or require premedication, and its pharmacokinetics are a little better than those of cetuximab, but it must at least show equivalent efficacy before I would use it in place of cetuximab.

Track 6

DR LOVE: Do you believe there is a potential clinical role for panitumumab monotherapy?

DR MARSHALL: Yes, I believe EGFR blockade could serve as a maintenance-type therapy. We have considered bevacizumab in that role extensively — that is, using it to prevent progression. If it weren't for the rash associated with the EGFR agents, I believe we'd also be considering cetuximab and panitumumab in this setting.

Certainly, panitumumab will likely receive its indication as monotherapy for refractory disease. Unlike cetuximab, its indication will not likely be in combination with irinotecan. Do we make the leap of faith and say it probably works just as well? I imagine we probably can, but it would be nice to have some clinical research to support that.

The question is whether panitumumab is a replacement for cetuximab and whether you'd use the panitumumab any time you would have used cetuximab.

Initially, panitumumab's only strict indication will likely be by itself. The

PACCE study will help inform us whether we can use it in other scenarios (Wainberg 2006). That raises the bigger question of when to include an EGFR blocker as a treatment option.

Right now, the indications for cetuximab and the likely indication for panitumumab are as last therapy or, at best, second-line therapy. Agents such as bevacizumab are leading the way as front-line treatments (Hochster 2006a, 2006b).

Should we be using these agents earlier? We still don't have an answer for that, but the major pushback is the visible toxicity. The rash that one gets from this class of agents is a public display — and not a very attractive one — that one is on cancer therapy.

The "slippery slope" of using these agents earlier and earlier, therefore, is the rash, unless clear evidence indicates an advantage to using them early. We need efficacy data before we make that decision.

Track 7

DR LOVE: What has your experience been with the rash and does anything help ameliorate it?

DR MARSHALL: We are teaching patients to expect it and in some crazy way to want it, because the more rash experienced, the greater the likelihood that they are benefiting from the therapy. Some patients come back excited because they've developed some rash, but it is a problem. It can be very itchy, and it can be temporarily disfiguring. It would be hard to hide it in public.

Many people are getting dermatologists involved early in the management of the rash. I personally find that dose adjustments and modifications are the best way to manage the rash and help patients not to give up on the drug too early. The rash tends to be quite intense in the first month or two and then tends to fade and look more like a dark set of freckles.

The patients who are responding to the treatment are benefiting, and their rash tends to quiet over time and become a lot less angry looking and a lot less visible from a distance. My general recommendation is to stick it out.

DR LOVE: How long does it take to go away, or does it go away when you stop therapy?

DR MARSHALL: It goes away fairly quickly once you stop treatment — within a week or two. That is why even a week off therapy can be enough to quiet the rash.

DR LOVE: What's the difference between the rash with these agents compared to what you see with the tyrosine kinase inhibitors (TKIs) like erlotinib?

DR MARSHALL: It's a little different. These rashes are more pustular and more diffuse. I have seen cases in which the rash marches from head to foot — starting on the face and chest, moving to the body and arms, and then ultimately moving all the way down to the feet and toes. So it is an angrier

rash, a little itchier and a little more persistent.

Track 8

DR LOVE: What do you consider to be the potential role of panitumumab in clinical practice?

DR MARSHALL: The weekly schedule required for cetuximab is a burden, as is the need to premedicate the patient with Benadryl®. Panitumumab is administered every two weeks, which is similar to our other regimens, and requires no loading dose and no premedication.

It causes no infusion reaction. If a clinician doesn't have to worry about an allergic-type reaction or about reimbursement issues, he or she is likely to switch to panitumumab.

DR LOVE: Are there patients for whom you might not want to combine these agents with irinotecan?

DR MARSHALL: Sure, some patients really do not want to try irinotecan again, but even in my practice, I'd rather administer a little irinotecan with the cetuximab or panitumumab than not use it, because the response rate is so much greater.

I can't anticipate what the FDA will say, but I believe panitumumab has some advantages over the existing label for cetuximab because of toxicity. I believe it will have the same indication that cetuximab currently has, but perhaps with a slightly better safety profile.

Unlike cetuximab, panitumumab also has large-scale randomized data against best supportive care, so you could argue that this provides a little more proof. In addition, the results of the PACCE trial (1.3) are expected to be positive.

However, the question then arises about cost and about how you manage the disease. If the response rate is 80 to 90 percent in the front-line setting, you might be able to perform curative resections in some patients, but then what do you do with the patients?

I also believe that the combination of EGFR-VEGF blockade with no chemotherapy might be the way to go. Patients would come in every couple of weeks and receive their antibody load.

Track 9

DR LOVE: Can you discuss your approach to patients with Stage II disease?

DR MARSHALL: I begin by asking why I wouldn't administer FOLFOX chemotherapy to a patient with Stage II disease when 5-FU has shown efficacy in three percent of patients treated. I believe that adding oxaliplatin might increase efficacy by another two to three percent.

So if I believe that I can help six out of every 100 patients treated, and I

present that to a patient from a risk/benefit perspective, very few patients will turn down that chemotherapy (2.4).

This is similar to breast cancer patients, who also accept chemotherapy despite its efficacy in only one percent of patients treated. I don't need a 9,000-patient clinical trial to prove that the three to six percent is real. I am in the camp of "Why not give a patient chemotherapy?"

However, I have to recognize that I am greatly overtreating patients. I am treating 70 to 80 out of 100 patients who can't benefit from chemotherapy because they don't have cancer. Instead of an excuse to administer chemotherapy, I am looking for a good excuse to say, "You don't need it."

That's why I like the current ECOG clinical trial for patients who are of average risk — those who have had enough nodes sampled and who are not found to have "bad things" under the microscope.

For these patients, we can then use further genetic markers to try to confirm that. It's a difficult trial to explain to patients and get them to enroll in, but it is an important study.

If we can demonstrate that patients with those genetic characteristics do not have an increased risk of recurrence, then we can save all of those people from having to receive chemotherapy. That, to me, is the most important piece. ■

SELECT PUBLICATIONS

2.4

FOLFOX for Stage II Colon Cancer? A Commentary on the Recent FDA Approval of Oxaliplatin for Adjuvant Therapy of Stage III Colon Cancer

"It must be made clear that we are not calling for the use of adjuvant chemotherapy in general, or FOLFOX in particular, in all patients with stage II colon cancer. But by not approving FOLFOX as an option for the treatment of stage II colon cancer, the US Food and Drug Administration has limited the treatment options for oncologists who, according to recently published American Society of Clinical Oncology guidelines, should discuss the risk:benefit ratio of adjuvant chemotherapy in patients with stage II disease with the individual patient. In view of the restrictive US Food and Drug Administration approval, for patients for whom reimbursement is a factor, this discussion between patient and physician will have to exclude the currently most effective adjuvant chemotherapy for colon cancer."

SOURCE: Grothey A et al. *J Clin Oncol* 2005;23(15):3311-3. No abstract available

Arends R et al. **Flexible dosing schedules of panitumumab (ABX-EGF) in cancer patients.** *Proc ASCO* 2005;**Abstract 3089**.

Chu E. **Panitumumab: A new anti-EGFR antibody for the treatment of advanced colorectal cancer.** *Clin Colorectal Cancer* 2006;6(1):13. No abstract available

Ciardiello F, Tortora G. **A novel approach in the treatment of cancer: Targeting the epidermal growth factor receptor.** *Clin Cancer Res* 2001;7(10):2958-70. **Abstract**

Cunningham D et al. **Cetuximab monotherapy and cetuximab plus irinotecan in irino-**

tecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351(4):337-45. **Abstract**

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

Gibson TB et al. **Randomized phase III trial results of panitumumab, a fully human anti-epidermal growth factor receptor monoclonal antibody, in metastatic colorectal cancer.** *Clin Colorectal Cancer* 2006;6(1):29-31. **Abstract**

Gould P. **Monoclonal antibody aids colorectal-cancer treatment.** *Lancet Oncol* 2006;7(5):370. No abstract available

Grothey A, Sargent DJ. **FOLFOX for stage II colon cancer? A commentary on the recent FDA approval of oxaliplatin for adjuvant therapy of stage III colon cancer.** *J Clin Oncol* 2005;23(15):3311-3. **Abstract**

Hochster HS et al. **Results of the TREE-2 cohort: Safety, tolerability, and efficacy of bevacizumab added to three oxaliplatin/fluoropyrimidine regimens as first-line treatment of metastatic colorectal cancer.** *Proc ASCO GI Cancers Symposium* 2006a;**Abstract 244**.

Hochster HS et al. **Safety and efficacy of oxaliplatin/fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): Final analysis of the TREE-study.** *Proc ASCO* 2006b;**Abstract 3510**.

Malik I et al. **Safety and efficacy of panitumumab monotherapy in patients with metastatic colorectal cancer (mCRC).** *Proc ASCO* 2005;**Abstract 3520**.

Peeters M et al. **A Phase 3, Multicenter, Randomized Controlled Trial (RCT) of panitumumab plus Best Supportive Care (BSC) vs BSC alone in patients (pts) with Metastatic Colorectal Cancer (mCRC).** *Proc AACR* 2006;**Abstract CP-1**.

Roskos L et al. **Low pharmacokinetic variability facilitates optimal dosing of ABX-EGF in cancer patients.** *Proc ASCO* 2002;**Abstract 362**.

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 Cancers 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**.

Snyder LC et al. **Overview of monoclonal antibodies and small molecules targeting the epidermal growth factor receptor pathway in colorectal cancer.** *Clin Colorectal Cancer* 2005;(5 Suppl 2):71-80. **Abstract**

Terstriep S, Grothey A. **First- and second-line therapy of metastatic colorectal cancer.** *Expert Rev Anticancer Ther* 2006;6(6):921-30. **Abstract**

Thomas SM, Gandis JR. **Pharmacokinetic and pharmacodynamic properties of EGFR inhibitors under clinical investigation.** *Cancer Treat Rev* 2004;30(3):255-68. **Abstract**

Vallbohmer D, Lenz HJ. **Epidermal growth factor receptor as a target for chemotherapy.** *Clin Colorectal Cancer* 2005;(5 Suppl 1):19-27. **Abstract**

Venook A et al. **Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) ± cetuximab for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): CALGB 80203 preliminary results.** *Proc ASCO* 2006;**Abstract 3509**.

Wainberg Z, Hecht JR. **A phase III randomized, open-label, controlled trial of chemotherapy and bevacizumab with or without panitumumab in the first-line treatment of patients with metastatic colorectal cancer.** *Clin Colorectal Cancer* 2006;5(5):363-7. **Abstract**

Weiner LM et al. **Updated results from a dose and schedule study of panitumumab (ABX-EGF) monotherapy, in patients with advanced solid malignancies.** *Proc ASCO* 2005;**Abstract 3059**.

INTERVIEW

Howard S Hochster, MD

Dr Hochster is Professor of Medicine and Clinical Pharmacology at the New York University Cancer Institute in New York, New York.

Tracks 1-9

Track 1	Introduction
Track 2	Background, design and results of TREE-1 and TREE-2 trials
Track 3	Efficacy of bFOL regimen in TREE-1 and TREE-2
Track 4	Selection of first-line therapy for metastatic disease
Track 5	Management of patients with neurotoxicity who progress on FOLFOX with bevacizumab
Track 6	Management of oxaliplatin-associated neurotoxicity
Track 7	Selection of first-line therapy for patients who have received adjuvant FOLFOX
Track 8	Potential benefits of panitumumab versus cetuximab
Track 9	Future directions in the management of colon cancer

Select Excerpts from the Interview and the CME Symposium

Tracks 2-4

DR LOVE: What was the rationale for the TREE trials?

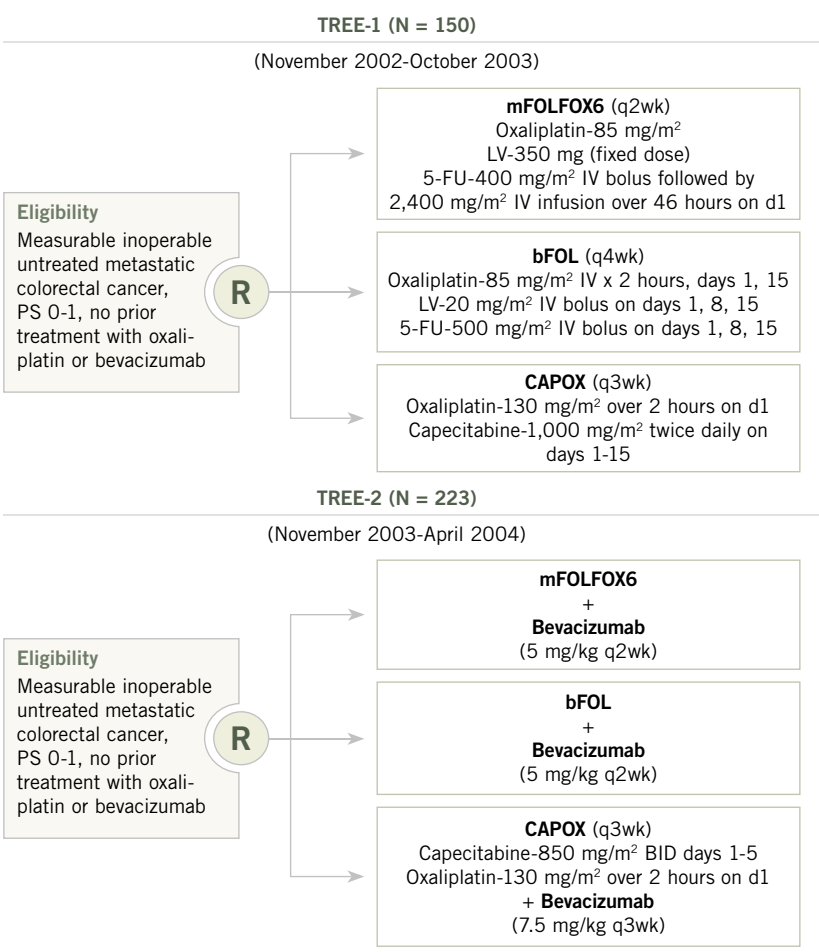
DR HOCHSTER: I proposed the TREE study around the time that oxaliplatin was approved. The real issue at that time was whether it was necessary to administer 5-fluorouracil (5-FU) by infusion or if it could be administered on a bolus schedule, which we piloted at NYU, or the schedule used with capecitabine reported in the European literature.

We didn't want to mount a huge study that would look for outcome differences, because frankly, we didn't expect a large difference in terms of response rate or survival between the three arms: infusional 5-FU (modified FOLFOX6), bolus 5-FU (bFOL) and capecitabine (CAPOX). We did predict, however, that a significant difference in toxicity might appear among the arms, and we definitely anticipated differences in convenience.

So we designed a randomized trial to compare toxicity among the three arms over the first 12 weeks. Although this trial is referred to as a Phase II trial, it really is a Phase III trial in how it is designed and the endpoint it evaluates (Hochster 2005; [3.1]).

3.1

TREE-1 and TREE-2: Treatment Schemas



SOURCE: Hochster HS et al. *Proc ASCO* 2006;**Abstract 3510**.

With 50 patients per arm, the study found about a 25 percent difference in the overall incidence of Grade III-IV toxicity between the 5-FU infusion arm and the 5-FU bolus arm (3.2).

The study was interesting because it showed that initially the worst-tolerated regimen was CAPOX when administered according to the European schedule at 1,000 mg/m^2 twice a day. This group experienced a lot more diarrhea, leukopenia and hospitalizations, and 50 percent of the patients required dose reduction within the first 12 weeks. Based on that finding, the Data Safety Monitoring Board (DSMB), which independently reviewed the toxicity data, suggested that further trials should use the reduced dose of capecitabine of 850 mg/m^2 twice per day.

3.2 **Grade III/IV Adverse Events Occuring in TREE-1 and TREE-2**

	TREE-1 (percent patients)			TREE-2 (percent patients)		
	mFOLFOX (n = 49)	bFOL (n = 50)	CAPOX (n = 48)	mFOLFOX + bev (n = 71)	bFOL + bev (n = 70)	CAPOX + bev (n = 72)
Related events during first 12 weeks*	59%	36%	67%	59%	51%	56%
Grade III/IV adverse events occuring in ≥ 5 percent of patients						
Neutropenia	53%	18%	15%	49%	19%	10%
Dehydration*	8%	12%	27%	6%	14%	8%
Diarrhea†	33%	26%	31%	13%	26%	19%
Hypertension	0%	0%	2%	7%	13%	15%
TE, arterial TE, other	2% 10%	0% 4%	0% 2%	0% 10%	0% 10%	3% 4%
Nausea	16%	14%	19%	6%	11%	11%
Vomiting	14%	10%	19%	1%	13%	10%
Neurotoxicity	18%	10%	23%	14%	11%	15%
Hand-foot	8%	2%	19%	0%	0%	10%
Any Grade III/IV	**96%**	**76%**	**85%**	**85%**	**74%**	**76%**

* Determined by the investigators to be related (possibly or probably) to study drug; primary endpoint.

† The high incidence of dehydration and diarrhea in the CAPOX arm in TREE-1 was effectively reduced by capecitabine dose reduction in TREE-2.

TE = thromboembolic events

SOURCE: Hochester HS et al. *Proc ASCO* 2006;**Abstract 3510**.

During this time in 2004, the data were just being reported on the efficacy of bevacizumab with bolus IFL (Hurwitz 2004), and FOLFOX was beginning to be used as the first-line regimen of choice based on the Intergroup NCCTG-N9741 study (Grothey 2004).

Based on this, we decided to amend the TREE protocol by adding bevacizumab to each arm so that we could quickly obtain toxicity data on each of these oxaliplatin-fluoropyrimidine combinations together with the anti-VEGF antibody.

The study was amended and opened in essentially the same institutions, with the addition of a couple more, and we then treated 70 patients per arm, so we had about 220 patients in the TREE-2 cohort (Hochster 2006a; [3.3]). So we had two cohorts within the TREE protocol that were sequential in time, which is a historical comparison but a very good historical comparison given that the studies included virtually the same investigators and the same protocol.

When assessing overall toxicity among the regimens, we found that CAPOX with bevacizumab was now tolerated well with the reduced capecitabine dose as well as the FOLFOX with bevacizumab regimen (3.2). The response rates were higher with the addition of bevacizumab (3.3, 3.4, 3.5).

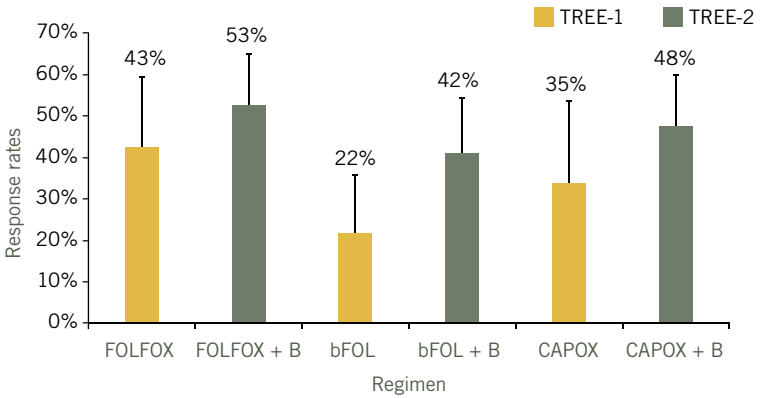
DR LOVE: Can you discuss the update of the data reported at ASCO?

DR HOCHSTER: With bevacizumab, the time to progression was approximately two to three months longer for each of the arms, especially for the CAPOX arm (Hochster 2006).

Survival is more difficult to comment on because we still haven't had 50 percent deaths in each of the arms in the TREE-2 cohort after well over two years. It's fair to say that the median overall survival will be greater than two years in the TREE-2 trial, with the addition of bevacizumab to the treatment regimens.

3.3

Comparative Response Rates for TREE-1 and TREE-2



FOLFOX = infusional 5-FU/leucovorin and oxaliplatin; bFOL = bolus 5-FU/leucovorin and oxaliplatin; CAPOX = capecitabine and oxaliplatin; B = bevacizumab

SOURCE: Hochster HS et al. *Proc ASCO* 2006;**Abstract 3510**.

3.4

Efficacy Summary in TREE-1 and TREE-2

Parameter	TREE-1	TREE-2
Overall response rate*	22-43%	41-53%
Time to progression†	6.1-8.7 months	8.3-10.3 months
Time to treatment failure	4.4-6.5 months	5.5-5.8 months
Median survival‡	18.2 months	24.4 months

* Per-protocol population; † censored for second-line therapy
‡ All three treatment arms combined

SOURCE: Hochster HS et al. *Proc ASCO* 2006;**Abstract 3510**.

Comparison of these regimens shows that the bevacizumab-specific toxicities were no different — that is, the incidences of hemorrhagic and thrombotic complications were similar to those reported previously. By and large, the data are comparable to what would have been expected based on first- and second-line data from ECOG-E3200 (Giantonio 2005).

I don't see that any surprises have come out of the TREE-2 study. It simply shows that all of these regimens are well tolerated in the first-line setting and that you can add bevacizumab without significantly changing the toxicity of the chemotherapy. The anti-angiogenesis type toxicity is pretty much the same across regimens.

3.5

Conclusions from the Final Analysis of the TREE Study

"Oxaliplatin in combination with bolus, infusional or oral fluoropyrimidine regimens is active and well tolerated in previously untreated metastatic colorectal cancer. No major differences in activity were observed between the three fluoropyrimidine regimens, but the bFOL regimen may be the least efficacious in terms of response and time to progression in both cohorts. With the dose reduction of capecitabine, as performed with going from 1,000 mg/m^2 to 850 mg/m^2 BID, CAPOX plus bevacizumab was tolerated much better compared with CAPOX in TREE-1 and then had equivalent activity to FOLFOX with bevacizumab in terms of response rate, time to progression and survival.

Bevacizumab, when added to oxaliplatin-fluoropyrimidine regimens, resulted in increased efficacy with the expected toxicity profile. The addition of bevacizumab did not result in a change in time to treatment failure but did result in an improval in time to progression. Overall survival was improved with the addition of bevacizumab. The median survival was 18.2 months in TREE-1 and 24.4 months in the TREE-2 cohort."

SOURCE: Hochster HS et al. *Proc ASCO* 2006;**Abstract 3510**.

DR LOVE: What about the combination of CAPOX with bevacizumab?

DR HOCHSTER: The CAPOX regimen is based on these data using the lowest doses of capecitabine, so CAPOX combined with bevacizumab is an equally good regimen as far as we can see in terms of toxicity and activity. I believe this regimen is a reasonable choice.

Approval for the use of bevacizumab with 5-FU-based therapy that doesn't incorporate capecitabine may be the one issue with using this regimen, but if it's not a reimbursement issue, then I believe that's a reasonable option as well. I'm not sure that this regimen is a big favor for a lot of patients because it requires them to take the pills twice a day for 14 days compared to simply being on a pump for 48 hours.

DR LOVE: Why do you use FOLFOX with bevacizumab rather than irinotecan or FOLFIRI with bevacizumab?

DR HOCHSTER: The oxaliplatin-based chemotherapy is tolerated pretty well by most patients. Patients experience some fatigue, but we can easily control

the nausea. Hair loss is minimal, and we see much less diarrhea than with irinotecan.

I've personally been impressed with the responses I've seen with oxaliplatin compared to irinotecan, so I tend to use oxaliplatin-based therapy, but it's hard to be dogmatic about that. If a patient has issues with neuropathy or some other difficulty that makes them not want oxaliplatin, then irinotecan-based therapy is a perfectly reasonable option.

Track 5

DR LOVE: How do you treat a patient who has a good response to FOLFOX with bevacizumab but then develops neuropathy and has to discontinue the oxaliplatin?

DR HOCHSTER: At the time that the patient develops the neurotoxicity, I stop the oxaliplatin and continue the 5-FU and leucovorin regimen with bevacizumab. On average, these patients will go another four to six months before they eventually have disease progression. At that point, I hope a study will be open that I can recommend to them.

Outside of a study, however, the number of choices one has is pretty large. You can give irinotecan alone, administer FOLFIRI or continue bevacizumab at that point. You can give cetuximab, which would be outside the labeled indication for this drug, or you can administer the chemotherapy first followed by irinotecan and cetuximab.

A lot of options are available. In general, it depends on the patient. For a very robust, younger patient whom I'm trying to treat with everything possible, I'd probably continue with FOLFIRI and bevacizumab and then go to cetuximab as third-line treatment.

I believe this treatment approach provides patients an extra opportunity for response. If their disease progresses, then I'll give bevacizumab and cetuximab together, based on the data from the BOND study (Cunningham 2004; Saltz 2005).

DR LOVE: If the neuropathy is starting to resolve, will you reintroduce oxaliplatin?

DR HOCHSTER: I do try to go back to oxaliplatin down the line. Many times we can get people out to maybe a two-year interval by using irinotecan followed by irinotecan and cetuximab, and patients can go on for a couple of years. At that point, I normally go back to oxaliplatin.

Sometimes we have to deal with hypersensitivity reactions to oxaliplatin, especially on the second dose, but by and large patients seem to benefit again from going back on oxaliplatin. Their disease is at least stabilized, and some patients have nice responses the second time on oxaliplatin. ■

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Terstriep S, Grothey A. **First- and second-line therapy of metastatic colorectal cancer.** *Expert Rev Anticancer Ther* 2006;6(6):921-30. **Abstract**

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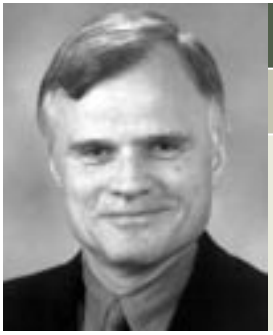


INTERVIEW

Michael J O'Connell, MD

Dr O'Connell is Professor of Human Oncology at Drexel University College of Medicine, Director of the Allegheny Cancer Center, Director of the Division of Medical Oncology at Allegheny General Hospital and Associate Chairman of the NSABP in Pittsburgh, Pennsylvania.

Tracks 1-12

Select Excerpts from the Interview and the CME Symposium

Track 2

DR LOVE: Can you comment on your recent work with Genomic Health in colon cancer?

DR O'CONNELL: We've gone back and looked at fixed paraffin-embedded tissue from 270 patients participating in NSABP-C-01 and NSABP-C-02, and another 300 patients participating in NSABP-C-04 (O'Connell 2006; [4.1]).

The intention regarding prognostic markers in colon cancer is to provide a scientific rationale for the selection of patients with Stage II colon cancer who might benefit from adjuvant chemotherapy. We're looking to develop a prognostic signature that would identify patients at very high risk following surgery alone, for whom you might consider adjuvant treatment, and another group who might have very low risk and would be appropriately treated with surgery alone.

DR LOVE: Which genes were examined?

DR O'CONNELL: Genomic Health identified 757 genes, based on review of the medical literature, various microarray studies and consideration of molecular pathways.

It's interesting that a number of clusters of highly interrelated genes were identified and shown to be significantly related to outcome as measured by recurrence-free interval in NSABP-C-01 and NSABP-C-02 (O'Connell 2006; [4.2]). These clusters of genes were quite different from the ones we saw previously in breast cancer with the Onco*type* DX assay; hence, different molecular pathways are involved.

The second part of our project was looking for specific predictive markers that will indicate which patients would benefit from adjuvant 5-FU/leucovorin. We chose 300 patients from NSABP-C-04 who received 5-FU/leucovorin and looked at the same 757 genes. The analysis is not complete, and we have not yet identified a potential predictive signature. However, 42 or 43 genes that showed significant correlation with outcome in NSABP-C-01 and NSABP-C-02 also showed significant correlation with outcome in NSABP-C-04 (O'Connell 2006).

The hazard ratios in each of these two studies were very similar, suggesting that a cluster of genes were prognostic in both studies. A few outlying genes showed up in NSABP-C-04 (O'Connell 2006) but didn't show up in NSABP-C-01/C-02, and these would be potential candidates as predictive markers, but those analyses are ongoing.

4.1

Early NSABP Adjuvant Clinical Trials in Colon Cancer

Protocol	N	Randomization	Dates of accrual
NSABP-C-01	1817	Bacillus Calmette-Guerin MeCCNU/5-FU/vincristine	11/77 – 2/84
NSABP-C-02	1158	Surgery Surgery + 5-FU + heparin	3/84 – 7/88
NSABP-C-04	2151	5-FU + leucovorin 5-FU + leucovorin + levamisole 5-FU + levamisole	7/89 – 12/90

SOURCE: NSABP.pitt.edu

4.2

Relationship Between Tumor Gene Expression and Recurrence among Patients with Stage II/III Colon Cancer

"Quantitative RT-PCR assay of FPE [fixed paraffin-embedded] colon cancer tissue can be used to identify large numbers of genes associated with RFI [recurrence-free interval] in patients with Stage II and III colon cancer. If these results are confirmed by additional studies in progress, this technique has promise to improve selection of colon cancer patients for adjuvant chemotherapy."

SOURCE: O'Connell MJ et al. Presentation. ASCO 2006;**Abstract 3518**.

Track 3

DR LOVE: Were you able to categorize the patients into lower and higher risk groups?

DR O'CONNELL: In an exploratory sense, we found, in the NSABP-C-01/C-02 data sets, that we were able to identify one third of the Stage II patients who had a recurrence rate greater than 40 percent (O'Connell 2006). If that holds up in future studies as we go through the validation process, it will be useful in clinical management.

DR LOVE: What about the other two thirds of the patients?

DR O'CONNELL: One subset of patients was identified as having a greater than 90 percent disease-free survival rate following surgery alone, and an intermediate group was identified. The hazard ratios for the genes identified are as robust for colon cancer as they were for breast cancer. We've actually identified more genes associated with outcome in colon cancer than we previously did in breast cancer.

Track 6

DR LOVE: Let's discuss the clinical management of Stage II disease. What do you consider a rational approach to those patients?

DR O'CONNELL: It's a matter of looking at the risk-to-benefit ratio. If you have a patient with T3N0 disease who had an adequate number of lymph nodes resected — say more than 10 or 12 lymph nodes — who does not have a poorly differentiated tumor and who has no evidence of high-grade obstruction or lymphatic or vascular invasion, the risk of relapse with surgery alone is quite low.

DR LOVE: What number would you present to that type of patient?

DR O'CONNELL: The patient I'm talking about would be at an 85 percent five-year disease-free survival rate, maybe even a little higher. I would tell the patient that we have an excellent chance — eight or nine chances out of 10 — that surgery cured the cancer and that the incremental benefit of the treatments we have available, in absolute terms, would be quite small, maybe adding one or two percent to the five-year disease-free survival.

Even in this situation you need to engage the patient, because I've had individual patients say, "If there's a one or a two percent potential benefit, I would like to take the treatment." In general, however, most of the patients I talk with in this situation would choose observation.

On the other hand, if a patient has a high-grade T4 lesion with obstruction, lymphatic or vascular invasion and only five or six lymph nodes were removed, then I would say that the risk of relapse would be closer to 30 or 35 percent. In this situation, without medical contraindication, the benefit associ-

ated with adjuvant therapy would outweigh the risk for many patients.

DR LOVE: What type of chemotherapy would you offer to a younger patient with Stage II disease who is in good condition and had some type of adverse prognostic factor?

DR O'CONNELL: For a younger patient with adverse factors, high-risk tumor and no comorbid conditions, I would strongly advocate using the most effective regimens available, which in my view are oxaliplatin combined with 5-FU/leucovorin — either the FOLFOX regimen used in the MOSAIC study (de Gramont 2005) or the FLOX regimen used in NSABP-C-07 (Wolmark 2005). Each of those regimens showed very similar improvements in outcome (4.3).

DR LOVE: Are you using FLOX off protocol?

DR O'CONNELL: I would consider it. One has to consider the overall context of the patient. The FLOX regimen has more gastrointestinal toxicities, such as diarrhea. The FOLFOX regimen carries a higher risk of neurotoxicity and requires a central venous catheter and a portable ambulatory infusion pump.

If I had a patient with ulcerative colitis or some kind of inflammatory bowel disease, I would not want to treat that patient with FLOX because of the higher risk of aggravating the condition and causing severe diarrhea. If I had a patient who was a violin player or had an underlying neuropathy, I would stay away from the FOLFOX regimen because it includes a higher cumulative dose of oxaliplatin.

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

	Three-year DFS (oxaliplatin arm)	Benefit from oxaliplatin	Hazard ratio
NSABP-C-07	76.5%	4.9%	0.79
MOSAIC	78.2%	5.3%	0.77

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

Track 8

DR LOVE: Would you discuss the current NSABP-C-08 adjuvant trial for colorectal cancer, which evaluates FOLFOX with or without bevacizumab?

DR O'CONNELL: We are pleased that our study of the use of bevacizumab in the adjuvant setting has not shown a significant increase in toxicity. Specifically, we have not seen any increase in wound complications or in arterial thrombotic emboli. In fact, the only toxicity we've seen with significantly increased frequency is hypertension. I'm not aware of any patients who have

had to stop bevacizumab because of this, and it's been medically manageable.

One issue that was of significant potential concern was the problem of GI perforation in patients who had recently undergone a bowel resection. At this time, we've seen a total of five perforations in the trial, three in the bevacizumab arm and two in the control arm — obviously no significant difference.

DR LOVE: How long after surgery is bevacizumab started?

DR O'CONNELL: Bevacizumab is initiated within six weeks of surgery.

DR LOVE: In this trial design, as in the adjuvant trastuzumab studies, bevacizumab is continued for a total duration of one year.

DR O'CONNELL: Correct. Nobody knows the optimal duration of therapy with bevacizumab in the adjuvant setting. Our rationale in choosing one year was that we wanted to be certain bevacizumab was given the full opportunity to show a benefit, if in fact a benefit existed. If we see a significant improvement in disease-free survival, which is our primary endpoint in this trial, then it would be very appropriate to look at alternative treatment durations in the future.

Track 9

DR LOVE: Can you talk about the potential replacement trial for NSABP-C-08?

DR O'CONNELL: We haven't made any decisions, but I can certainly talk about some of the concepts we believe are interesting and quite promising. One idea is to study FOLFOX, bevacizumab and either panitumumab or cetuximab (4.4). In the past, NSABP has not studied anti-EGFR therapy, and we believe that emerging data for both cetuximab and panitumumab indicate these monoclonal antibodies may be ready for use in the adjuvant setting.

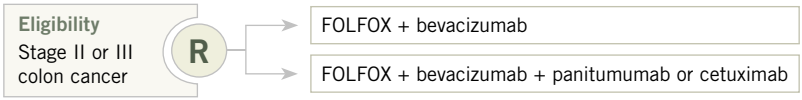
The Intergroup is looking at FOLFOX with or without cetuximab (N0147), which I think is a very rational study. In fact, in the interval between our current study and our next study, we plan to support the Intergroup trial.

Panitumumab is interesting for a number of reasons. Because it's a fully human monoclonal antibody and doesn't have any murine components, no antimouse

4.4

Proposed Phase III Randomized Study of FOLFOX and Bevacizumab with or without Panitumumab or Cetuximab in Patients with Resected Stage II or III Colon Cancer

Protocol ID: NSABP-C-11



SOURCE: NSABP group meeting, April 2006.

antibodies are produced by the patients. It also is associated with lower rates of infusion reactions, and this molecule has some theoretical advantages, although its mechanism of action is apparently very similar to cetuximab.

We also found the data presented by Len Saltz from the BOND-2 trial, combining cetuximab with bevacizumab, very intriguing (Saltz 2005; [4.5]). His preliminary data, although from relatively small numbers and a nonrandomized sequential study, were still very intriguing in that the response rates were significantly higher when cetuximab and bevacizumab were administered together to irinotecan-refractory patients with metastatic colon cancer — about twice as high — compared to when cetuximab was used by itself in previous studies (Cunningham 2004; Saltz 2004).

Obviously this doesn't establish that combined monoclonal therapy is superior, but it hints that this may be a productive strategy to pursue. Some of the patients also received irinotecan, and some received cetuximab and bevacizumab alone.

Of the patients who were resistant to irinotecan and then received further irinotecan with cetuximab and bevacizumab, 37 percent responded. Of the patients who received only the antibodies without irinotecan, the response rate was about 20 percent (Saltz 2005; [4.5]), which is still substantial activity.

4.5

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. Presentation. ASCO 2005;**Abstract 3508**.

DR LOVE: Can you also talk about the data that were recently presented comparing panitumumab to best supportive care?

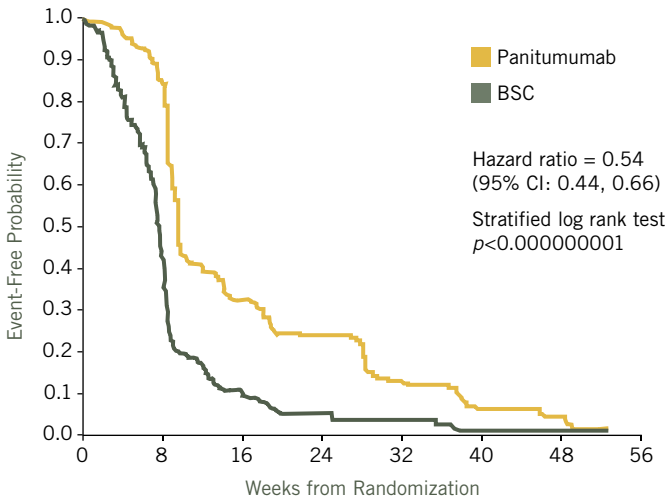
DR O'CONNELL: This was the study where more than 300 patients who had received two or three previous chemotherapy regimens for metastatic colorectal cancer were randomly assigned to either best supportive care or best supportive care and panitumumab.

There was a marked improvement in progression-free survival, the primary endpoint, among the patients receiving panitumumab. In fact, the progression-free survival hazard ratio was decreased by about 46 percent for patients receiving panitumumab, and these results were highly statistically significant (Peeters 2006; [4.6]).

We have a randomized study, looking not at tumor response rates but progression-free survival, which showed a definite biological effect. As a single agent, panitumumab also produces objective responses in about 10 percent of patients

4.6

Phase III Randomized Trial Comparing Best Supportive Care (BSC) with or without Panitumumab in Patients with Previously Treated Metastatic Colorectal Cancer



Primary Analysis, All Randomized Analysis Set, Central Radiology

SOURCE: With permission. Peeters M et al. Presentation. AACR 2006;**Abstract CP-1**.

previously treated with chemotherapy, which is very similar to what we're seeing with cetuximab.

DR LOVE: What has been seen in terms of side effects and toxicity?

DR O'CONNELL: The toxicity associated with panitumumab, like cetuximab, is a cutaneous eruption — acneiform skin rash. Nearly 100 percent of the patients receiving panitumumab are reported to have some degree of skin rash. Infusion reactions have been very uncommon with panitumumab.

A variety of other side effects are seen infrequently — diarrhea, fatigue — but the major dose-limiting side effect has been skin rash.

DR LOVE: To what extent, if any, has panitumumab been studied in combination with chemotherapy?

DR O'CONNELL: A large randomized trial is currently being conducted that's called the PACCE trial (1.3). It's a trial of first-line therapy for patients with metastatic colorectal cancer. All patients receive chemotherapy, either FOLFOX or FOLFIRI (but most of the patients receive FOLFOX in this particular study design).

All patients also receive bevacizumab. The experimental group also receives panitumumab, so they receive dual monoclonal antibody inhibition — anti-

EGFR and anti-angiogenesis therapy — with chemotherapy.

Track 11

DR LOVE: Can you talk about where we are with the NSABP-R-04 trial?

DR O'CONNELL: NSABP-R-04 is a neoadjuvant study for patients with potentially operable carcinoma of the rectum. We offer patients neoadjuvant chemotherapy and radiation therapy, and then they go to definitive surgery. NSABP-R-04 started out comparing the standard approach of continuous infusion 5-FU during radiation therapy to a new and possibly more effective and convenient approach using capecitabine with radiation therapy.

The study has now accrued over 300 patients to examine the efficacy and toxicity profiles of capecitabine versus continuous infusion 5-FU with radiation therapy. However, about a year ago we were also very interested in the results from a number of pilot studies that also incorporated oxaliplatin into the neoadjuvant setting.

CALGB showed a pathologic complete response rate of about 25 percent in their pilot study (Ryan 2006). Another smaller study, conducted earlier by ECOG, also showed preliminary but interesting results (Rosenthal 2003).

Therefore, we've modified NSABP-R-04 to make it a factorial design. In addition to receiving either capecitabine or continuous infusion 5-FU, half of the patients also receive oxaliplatin. The study has four individual treatments in a two-by-two factorial design (4.7). That addendum has been sent out to our membership recently; it has been activated and should be coming on line very soon.

DR LOVE: What do we know about the side effects and tolerability of the fluoropyrimidines with oxaliplatin and radiation therapy for rectal cancer?

DR O'CONNELL: What we know comes from these pilot studies (Ryan 2006; Rosenthal 2003). Severe diarrhea is a potential side effect when we administer high-dose pelvic irradiation combined with a fluorinated pyrimidine and oxaliplatin. In fact, problems with severe diarrhea in the pilot studies required some modification in our Phase III trial.

We decreased the number of doses of oxaliplatin in the Phase III trial by one dose because of this increase in toxicity. Also, we advocate careful monitoring and, if the patient develops diarrhea during treatment, interrupting the weekly doses of oxaliplatin and the fluorinated pyrimidine. So the major side effect we're concerned about is diarrhea with dehydration, which will require very careful monitoring.

DR LOVE: Do you think oxaliplatin has a role in the neoadjuvant setting off protocol right now?

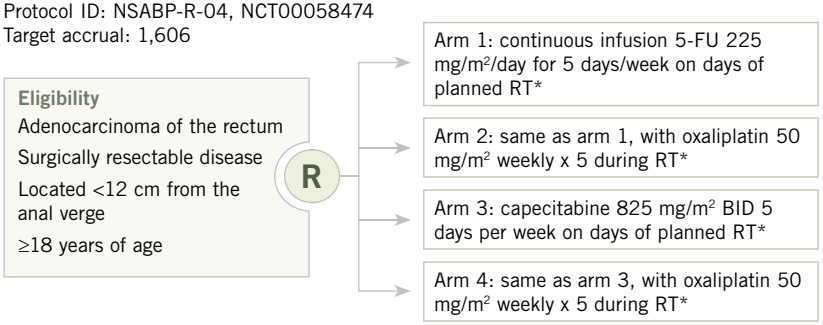
DR O'CONNELL: One could make that argument. It's an active drug in this disease. We haven't proven that it will add to the treatment benefit, but we

know oxaliplatin-containing regimens for patients with metastatic disease have definitely increased response rates and improved survival. So I believe one could make a rationale for doing that. If the clinician decides to do that, great caution should be exercised because of the potential for greater toxicities. ■

4.7

Preoperative Radiation Therapy (RT) Combined with Capecitabine and Oxaliplatin versus Radiation Therapy Combined with 5-FU and Oxaliplatin in Patients with Resectable Rectal Cancer

Protocol ID: NSABP-R-04, NCT00058474
Target accrual: 1,606



* 4,500 cGy in 25 fractions over five weeks with a 540 cGy boost in three fractions for nonfixed tumors or a 1,080 cGy boost in six fractions for fixed tumors

SOURCE: NSABP-R-04 Protocol, October 27, 2005.

SELECT PUBLICATIONS

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* 2005;**Abstract 3501**.

O'Connell MJ et al. **Relationship between tumor gene expression and recurrence in stage II/III colon cancer: Quantitative RT-PCR assay of 757 genes in fixed paraffin-embedded (FPE) tissue.** *Proc ASCO* 2006;**Abstract 3518**.

Peeters M et al. **A phase 3, multicenter, randomized controlled trial (RCT) of panitumumab plus best supportive care (BSC) vs BSC alone in patients (pts) with metastatic colorectal cancer (mCRC).** *Proc AACR* 2006;**Abstract CP-1**.

Rosenthal DI et al. **ECOG 1297: A phase I study of preoperative radiation therapy (RT) with concurrent protracted continuous infusion 5-FU and dose escalating oxaliplatin followed by surgery, adjuvant 5-FU, and leucovorin for locally advanced (T3/4) rectal adenocarcinoma.** *Proc ASCO* 2003;**Abstract 1094**.

Ryan DP et al. **Phase I/II study of preoperative oxaliplatin, fluorouracil, and external-beam radiation therapy in patients with locally advanced rectal cancer: Cancer and Leukemia Group B 89901.** *J Clin Oncol* 2006;24(16):2557-62. Abstract

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

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.** *Proc ASCO* 2005;**Abstract 3500**.

INTERVIEW

Herbert Hurwitz, MD

Dr Hurwitz is Associate Professor of Medicine in the Division of Hematology/Oncology, Clinical Director of the Phase I Program and Co-leader of the GI Oncology Program at the Duke University Medical Center in Durham, North Carolina.

Tracks 1-13

Select Excerpts from the Interview and the CME Symposium

Track 2

DR LOVE: Would you comment on the side effects associated with bevacizumab and their implications for the adjuvant setting?

DR HURWITZ: The side-effect profile for bevacizumab is best established from the large Phase III studies in advanced disease with the IFL regimen (Hurwitz 2004; [5.1]) and also the FOLFOX4 regimen (Giantonio 2005; [5.2]). In general, several themes to the toxicity profile in those settings may be informative about what to expect in the adjuvant setting.

The first is that no increase occurred in the chemotherapy-related side effects. The only exception was an increase in neuropathy, which was related to a greater time on oxaliplatin because patients were deriving more benefit and staying on treatment longer (Giantonio 2005; [5.2]). This should not be an increased risk in the adjuvant setting, because the duration of treatment is mandated by the standards of adjuvant therapy, not by continued benefit as in

the advanced disease setting.

Aside from the chemotherapy-related side effects, which are not increased, a few bevacizumab-specific side effects may be relevant in the adjuvant setting. Most notably, these are going to be issues like hypertension. In general, however, this is probably reversible over time for most patients.

A small increase appears in the risk of an arterial thromboembolic event, such as a heart attack, stroke, transient ischemic attack or unstable angina. While there are many ways to look at this in aggregate, the best way is probably to assume that the risk is increased about twofold (Skillings 2005). The vast majority of such events are not fatal, although even nonfatal events can carry significant morbidity.

When the background rate is one percent, which is the risk for most patients with advanced colorectal cancer, doubling that risk goes to about two percent or so. If the background risk is one to two percent, the risk with bevacizumab is around three to four percent.

In the adjuvant setting, this may be an issue for patients who would potentially be cured, if a small increased risk of morbidity were related to these arterial thromboembolic events. In general for advanced disease, the greatest risk to the patient in terms of both mortality and morbidity is the cancer. In the adjuvant setting, the risk associated with arterial thromboembolic events is likely to be low.

However, we don't know the true risk-to-benefit ratio until we know the impact of adjuvant bevacizumab in terms of improvement in disease-free and overall survival, the incidence of specific side effects — such as arterial thromboembolic events — and the implications of those side effects on mortality or morbidity.

Track 3

DR LOVE: What's the incidence of bowel perforation associated with bevacizumab?

DR HURWITZ: Bowel perforation occurs in about one to two percent of patients treated with bevacizumab, particularly in settings that include a risk of some inflammatory condition or injury to the bowel. For example, patients with colorectal cancer have a risk of perforation around one to 1.5 percent (Hurwitz 2004; [5.1]; Giantonio 2005; [5.2]).

It's not clear if these events are tied to any one special phenomenon. For example, they do not always occur in the setting of chemotherapy enteritis. Sometimes they're associated with a procedure; sometimes the inciting event is not clear. This risk also does not appear to be related to having cancer in situ. The bigger risk, in terms of perforation, is wound healing in general. It's hard to predict exactly what the event rate will be in the adjuvant setting, although we do have some guidance from patients with more advanced disease.

5.1

Phase III Trial Comparing IFL and IFL/Bevacizumab: Selected Adverse Events*

Adverse event	IFL/placebo (n = 397)	IFL/bevacizumab (n = 393)
Any Grade III/IV event	294 (74.0%)	334 (84.9%†)
Grade III/IV leukopenia	123 (31.1%)	145 (37.0%)
Grade III/IV diarrhea	98 (24.7%)	127 (32.4%)
Grade III/IV bleeding	10 (2.5%)	12 (3.1%)
Grade III hypertension	9 (2.3%)	43 (11.0%†)
Grade III proteinuria	3 (0.8%)	3 (0.8%)
Any thrombotic event	64 (16.2%)	76 (19.4%)
Deep thrombophlebitis	25 (6.3%)	35 (8.9%)
Pulmonary embolus	20 (5.1%)	14 (3.6%)
Adverse event requiring hospitalization	157 (39.6%)	177 (44.9%)
Adverse event leading to death	11 (2.8%)	10 (2.6%)
60-day all-cause mortality	19 (4.9%)	12 (3.0%)
Gastrointestinal perforation	0 (0.0%)	6 (1.5%)

* Not adjusted for differences in the median duration of therapy between IFL and IFL/bevacizumab groups (27.6 weeks versus 40.4 weeks)

† $p < 0.01$

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

5.2

Phase III Trial Comparing FOLFOX4/Bevacizumab, FOLFOX4 and Bevacizumab: Grade III/IV Toxicity

	Study arm A FOLFOX4 + bevacizumab (n = 287)		Study arm B FOLFOX4 (n = 284)		Study arm C Bevacizumab (n = 234)		*p*
	GIII	GIV	GIII	GIV	GIII	GIV	A vs B
Hypertension	5%	1%	2%	<1%	7%	0%	0.018
Bleeding	3%	<1%	<1%	0%	2%	0%	0.011
Neuropathy	16%	<1%	9%	<1%	<1%	<1%	0.016
Vomiting	9%	1%	3%	<1%	5%	0%	0.010
Bowel perforation	1%		0%		1.3%		

SOURCE: Giantonio BJ et al. Presentation. ASCO 2005;Abstract 2.

If one looks at patients with advanced or metastatic disease who were treated after they healed from surgery and waited at least four weeks, one sees no increased risk in wound healing complications if they were on bevacizumab

as compared to chemotherapy alone. By extrapolation, in the adjuvant setting, most patients will probably not see any increased risk of wound healing.

In addition, because patients are, in general, a little healthier in the adjuvant than in the metastatic setting, it is plausible that the overall risk profile may even be better in this group of patients. What we don't know is whether some long-term complications may be seen only after long surveillance in patients who are cured of their cancer. In all likelihood, such risks, if any, are likely to be small, but we can't speculate at this point what they may actually be.

Track 4

DR LOVE: Does the hypertension usually reverse upon discontinuation of bevacizumab?

DR HURWITZ: Hypertension seems to be reversible in most patients. The reversal of hypertension after the discontinuation of bevacizumab, as one would expect, has not been well studied. This is in part because patients who have discontinued bevacizumab come off protocol, and their follow-up is obviously limited.

Anecdotally, it appears that most patients will have their hypertension reduced, if not completely normalized, over a period of several weeks to months — probably consistent with the half-life of the drug.

Track 5

DR LOVE: Do models exist to predict the baseline risk of arterial thromboembolic events?

DR HURWITZ: The considerations related to the risk of arterial thromboembolic events, in one part, should be seen as those that are standard risks for cardiovascular disease. Most cardiovascular studies, including intervention studies, have excluded patients with cancer, so we don't know whether typical risks in noncancer populations extrapolate to cancer populations. This becomes even more complicated because of all the other issues going on in cancer patients.

Within the study of irinotecan/5-FU/leucovorin with or without bevacizumab and several other studies, a model has been created to try to identify which risk factors may predict who is at higher risk of an arterial thromboembolic event (Skillings 2005; [5.3]). At this point, that appears to be patients who are older and those who have had a prior event.

Patients with an arterial thromboembolic event more than a year prior to enrollment were allowed to participate in the clinical studies. However, a prior event more than a year before and an age of 65 years or more do appear to increase the risk for an arterial thromboembolic event in general and in particular with bevacizumab (Skillings 2005).

5.3 **Incidence of Arterial Thromboembolic Events (ATEs) in a Pooled Analysis of Five Randomized Trials of Chemotherapy with or without Bevacizumab**

	Bevacizumab/chemotherapy	Chemotherapy alone
All patients	37/963 (3.8%)	13/782 (1.7%)
Age ≥ 65 years	24/339 (7.1%)	7/279 (2.5%)
History of ATEs	14/89 (15.7%)	2/59 (3.4%)
Age ≥ 65 years and history of ATEs	12/67 (17.9%)	1/46 (2.2%)

SOURCE: Skillings JR et al. *Proc ASCO* 2005;**Abstract 3019**.

Track 8

DR LOVE: Can you review your clinical algorithm for adjuvant therapy in patients with Stage II or Stage III disease?

DR HURWITZ: For Stage III disease, the two approaches that I believe are currently well supported are the adjuvant use of FOLFOX or, for patients who are not candidates for oxaliplatin, capecitabine alone. It is a logical interpolation to use capecitabine and oxaliplatin instead of FOLFOX, given the activity of capecitabine alone. However, that is an extrapolation that has not yet been validated.

In the adjuvant setting, with potential curative intent, I'm a bit more reluctant to treat patients outside a standard, well-proven algorithm. Therefore, I usually use FOLFOX for most robust patients. Since FOLFOX is tolerated fairly well by most patients, we usually start with this even for those who are older, unless they have a clear contraindication to oxaliplatin, such as a significant preexisting neuropathy.

For patients with Stage II disease, the discussion is much more complicated because it's not clear that any standard therapy exists. A benefit has been suggested but has not yet been proven. For those patients, the risk-to-benefit discussion can often take a considerable amount of time to put it in a frame of reference that's meaningful.

For example, the risk reduction for a patient with Stage II disease may be an absolute difference of one or two percent. Also, we're not sure whether that one or two percent benefit exists. It could be three to four percent, but it's not likely to be more than a five percent absolute difference.

I believe there can be room for discussion with patients about whether a few percent difference in overall survival is worth six months of therapy. I usually have that discussion with them, and then I take their lead on how they prioritize the risks and benefits in their individual setting.

We need to remember the adequacy of lymph node sampling in the discussion about Stage II versus Stage III disease. We know the data fairly well for

those with properly staged Stage II or Stage III disease. Those who are "stage ambiguous," with less than 11 lymph nodes, have a prognosis that sits between Stage II and Stage III disease.

While we don't know for sure that treatment will have a similar benefit in that population, it's a reasonable inference. Therefore, for patients who have inadequate lymph-node staging, the discussion about the benefits of adjuvant therapy is probably a little bit more favorable than for those who have true Stage II disease.

Track 9

DR LOVE: In breast cancer, a concept has evolved of using less toxic and probably slightly less effective chemotherapy for patients with node-negative tumors. Typically, those patients might receive an anthracycline without a taxane. Do you think the same approach would make sense in colon cancer, for example, using capecitabine for patients with Stage II disease?

DR HURWITZ: The approach makes sense in general but carries a few caveats. The first is that we need data to drive the discussion. One of the problems is that when we believe we should be able to extrapolate a result to a different setting, it doesn't always work.

Another issue is whether the substitution of capecitabine for FOLFOX is being made in a hybrid or a rational way. That is, if one believes that a benefit truly exists in the adjuvant setting with FOLFOX for patients with Stage II disease — and as we discussed, a small benefit might exist — it's not clear that a benefit exists with capecitabine.

It clearly will be a little better tolerated; however, if it's not active, the risk-to-benefit ratio may not be as favorable. Therefore, I tend not to do that.

Track 12

DR LOVE: Where do you believe panitumumab will fit into the treatment of colorectal cancer, and what is your opinion about the data that have been reported so far?

DR HURWITZ: Panitumumab showed benefit in the third-line setting compared to best supportive care (Peeters 2006; [2.3]). It causes tumor shrinkage that as monotherapy is in the same ballpark as cetuximab. The tumor control rate showed improvement. Evaluating the curves as a whole, the hazard ratio is favorable. No survival benefit emerged in that study (Peeters 2006).

The studies of panitumumab with chemotherapy are not as mature as those with cetuximab. While a strong likelihood exists that the two antibodies will perform similarly, we need the data to validate that. The monotherapy third-

line setting with panitumumab will be highly appropriate. Its use with chemotherapy earlier on must be driven by the data as they mature.

Track 13

DR LOVE: What are your thoughts about combining biologic therapies, specifically bevacizumab and an EGFR inhibitor?

DR HURWITZ: The combination of VEGF and EGF inhibition makes sense, particularly if you are a mouse. For patients, the data are unfortunately limited. In colorectal cancer, we do have the promising pilot study known as BOND-2, which is cetuximab/irinotecan/bevacizumab versus cetuximab/bevacizumab (Saltz 2005; [4.5]). The original BOND-1 study compared cetuximab alone or with irinotecan (Cunningham 2004).

There are many problems with cross-study comparisons. Also, disclaimers have been made for data from relatively small studies in which the therapeutic regimen was attractive, meaning that the potential exists for bias in the types of patients who were accrued.

Saltz reported the study combining cetuximab and bevacizumab, and in general, those patients seem to be similar to the types of patients accrued to previous studies, although other imbalances may not have been detected. The response rates and times to progression with the double biologics were impressive (Saltz 2005; [4.5]).

One pilot study and the wonderful mouse data we mentioned justify combining these drugs in clinical trials. That is why the GI Intergroup's first-line study (C80405) is chemotherapy (FOLFOX or FOLFIRI) with cetuximab or bevacizumab or both (5.4). It is also the reason for the first-line PACCE

5.4

Randomized Phase III Study of Bevacizumab and/or Cetuximab Plus FOLFOX or FOLFIRI in Untreated Advanced Colorectal Cancer

Protocol IDs: CALGB-C80405, NCT00265850, SWOG-C80405
Target Accrual: 2,300 (Open)

Eligibility
No CNS metastases or carcinomatous meningitis
No prior treatment with VEGF or EGF receptors
More than 12 months since adjuvant 5-FU with or without oxaliplatin or irinotecan

R

- FOLFOX or FOLFIRI + bevacizumab
- FOLFOX or FOLFIRI + cetuximab
- FOLFOX or FOLFIRI + bevacizumab + cetuximab

FOLFOX = 5-FU/leucovorin/oxaliplatin
FOLFIRI = 5-FU/leucovorin/irinotecan

SOURCE: NCI Physician Data Query, July 2006.

study, which compares FOLFOX/bevacizumab with or without panitumumab (1.3). A number of studies will be needed to address this question. ■

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which NSABP trial is analyzing the use of hepatic resection or ablation followed by CAPOX chemotherapy with or without intrahepatic FUDR in patients with resected or ablated liver metastases from colorectal cancer?**
   a. C-08
   b. C-09
   c. C-10
   d. R-04
2. **Which of the following is not true of panitumumab?**
   a. It is a fully humanized antibody that targets the epidermal growth factor receptor (EGFR).
   b. Randomized comparison with cetuximab shows comparable efficacy between the two agents.
   c. It is administered once every two weeks.
3. **The BOND-2 trial compared cetuximab/bevacizumab with or without oxaliplatin for patients who failed irinotecan.**
   a. True
   b. False
4. **In the TREE-2 study, the dose of capecitabine combined with oxaliplatin/bevacizumab utilized was _____.**
   a. 1,250 mg/m^2 days one through 14 every three weeks
   b. 1,000 mg/m^2 days one through 14 every three weeks
   c. 850 mg/m^2 days one through 14 every three weeks
5. **In the TREE-2 study, the addition of bevacizumab improved overall response rates for _____.**
   a. Bolus 5-FU/leucovorin/oxaliplatin
   b. FOLFOX
   c. CAPOX
   d. All of the above
6. **The CALGB-C80405 trial for patients with advanced colorectal cancer investigates FOLFOX or FOLFIRI (physician discretion) with which of the following agents?**
   a. Bevacizumab
   b. Cetuximab
   c. Panitumumab
   d. Both a and b
7. **In NSABP-C-10 evaluating FOLFOX plus bevacizumab in patients with a synchronous primary lesion and metastatic disease, the primary endpoint is:**
   a. Survival
   b. Disease-free survival
   c. Safety
8. **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
9. **Among patients with previously treated metastatic colorectal cancer, _____ plus best supportive care was associated with improved progression-free survival compared to best supportive care alone.**
   a. Cetuximab
   b. Bevacizumab
   c. Panitumumab
   d. All of the above
10. **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
11. **Which of the following may increase the risk of developing an arterial thromboembolic event while being treated with bevacizumab?**
    a. Age of 65 years or older
    b. History of a prior arterial thromboembolic event
    c. Concomitant treatment with aspirin
    d. Both a and b
    e. All of the above
12. **The PACCE trial is evaluating chemotherapy plus bevacizumab with or without _____ in the metastatic setting?**
    a. Erlotinib
    b. Panitumumab
    c. Cetuximab
    d. Both a and b
    e. All of the above

Post-test answer key: 1b, 2b, 3b, 4c, 5d, 6d, 7c, 8b, 9c, 10b, 11d, 12b

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- Discuss the absolute risks and benefits of adjuvant systemic therapy, including the use of oxaliplatin-containing regimens and the use of capecitabine or intravenous 5-FU in patients with Stage II and Stage III colon cancer. . . . . 5 4 3 2 1 N/A
- Describe the ongoing trials examining the safety and potential efficacy of various biologic therapies in patients with colon cancer. . . . . 5 4 3 2 1 N/A
- Explain the rationale for targeting the EGFR/VEGF pathways and the current and future roles of monoclonal antibodies and oral tyrosine kinase inhibitors in colorectal cancer. . . . . 5 4 3 2 1 N/A
- Describe the current understanding of predictors of response and toxicity and their application to patients with colorectal cancer contemplating anti-VEGF therapy. . . . . 5 4 3 2 1 N/A
- Describe clinical trials of emerging neoadjuvant radiation therapy/ chemotherapy approaches to rectal cancer, including the absolute risks and benefits of these regimens. . . . . 5 4 3 2 1 N/A

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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John L Marshall, MD	5 4 3 2 1	5 4 3 2 1
Howard S Hochster, 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
Herbert Hurwitz, MD	5 4 3 2 1	5 4 3 2 1

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Colorectal Cancer™

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