

Colorectal Cancer™

U P D A T E

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

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SPECIAL ISSUE

Proceedings from a
Clinical Investigator
“Think Tank”

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Norman Wolmark, MD

POWERPOINT PRESENTATIONS

James Cassidy, MD

Lee M Ellis, MD

Norman Wolmark, MD

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Colorectal Cancer Update

A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 6 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of colorectal cancer research leaders present at a Think Tank meeting on the integration of emerging clinical research data into the management of colorectal cancer.

ACCREDITATION STATEMENT

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

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 4.25 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. www.ColorectalCancerUpdate.com includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **blue underlined text**. This monograph also contains clinical investigator PowerPoint presentations.

POWERPOINT STATEMENT

For this issue of our series, we are pleased to feature PowerPoint files from research leader presentations conducted during our recent *Colorectal Cancer Update* Think Tank meeting. These presentation slides are designed for individual and group use. We would appreciate feedback on this new education strategy.

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FACULTY AFFILIATIONS AND DISCLOSURES

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In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

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Join us for an upcoming live, interactive CME program.

Controversies in Systemic Therapy of Breast Cancer

October 29, 2005, 8:30 AM – 3:30 PM, The Westin Diplomat Resort & Spa, Hollywood, Florida

This program will focus on key management options for early and metastatic breast cancer and recent, relevant research results from the 2005 ASCO meeting.

For more information, log onto www.BreastCancerUpdate.com/CMEmeetings or email us at Meetings@ResearchToPractice.net. To register, call (800) 233-6153.

UPCOMING EDUCATIONAL EVENTS

European Cancer Conference

October 30-November 3, 2005

Paris, France

Event website: www.fecs.be

Chemotherapy Foundation Symposium: Innovative Cancer Therapy for Tomorrow

November 2-5, 2005

New York, New York

Event website: www.mssm.edu/tcf

Oncology World Congress

November 16-19, 2005

New York, New York

Event website: www.oncologycongress.com

28th Annual San Antonio Breast Cancer Symposium

December 8-11, 2005

San Antonio, Texas

Event website: www.sabcs.org

2006 ASCO Gastrointestinal Cancers Symposium

January 26-28, 2006

San Francisco, California

Event website: www.asco.org/gi2006

Miami Breast Cancer Conference

February 22-25, 2006

Miami Beach, Florida

Event website: www.cancerconf.com

2006 ASCO Annual Meeting

June 2-6, 2006

Atlanta, Georgia

Event website: www.asco.org



EDITOR'S EXECUTIVE SUMMARY

Neil Love, MD

Dinosaurs, European dosing and other assorted treats on the Think Tank tasting menu

Moderating a CME Think Tank like the enclosed second annual *Colorectal Cancer Update* event can feel a bit like being a traffic cop during rush hour in Times Square. The challenge of keeping up with 13 of the sharpest minds in the field is increased considerably because not only can all these people attempt to speak simultaneously, but they also continuously pound the keyboards in our wireless oncology “chat room,” making additional comments.

Having led a number of these intellectual adventures over the last few years, I have learned that it's best just to sit back, let people have their say and watch the fireworks erupt. Here are a few of the most memorable moments, listed in no particular order, from this most recent voyage into the heart of colorectal cancer research.



Richard M Goldberg, MD

A. Norman Wolmark is peeved at the FDA (again).

In 15 years of working with this legendary clinical investigator, I have never known him to mince words. Last year at ASCO, Norm expressed his displeasure with the FDA during a plenary presentation on an adjuvant NSABP trial that demonstrated the value of an agent (UFT) that was previously denied FDA approval.

This year, Norm again verbalized displeasure with the regulatory gods, this time because the adjuvant indication for oxaliplatin is for Stage III patients only, in spite of the fact that about 40 percent of patients in the MOSAIC trial had Stage II disease.

The initial MOSAIC data presented at ASCO 2003 by Aimery de Gramont demonstrated a disease-free survival advantage for the total trial population, but a secondary subset analysis revealed this to be statistically significant only in patients with Stage III disease, perhaps because more events occur in

that population. This led to the FDA’s action, which made Norm (and Axel Grothey and Dan Sargent in a *JCO* editorial) apoplectic.

The NSABP decided a long time ago that in both breast and colon cancer there is a continuum between node-negative and node-positive disease and that trials should focus on hazard rates in patients with varying absolute risks. Nodal status as a qualitative entity was thought to be well on its way to becoming a historical oncologic footnote.

Thus, at the most recent ASCO meeting, perhaps because of concerns that the FDA might misapply any stage subset data, Norm presented the NSABP-C-07 data in toto only — not broken down by stage — and concluded, “The addition of oxaliplatin to weekly bolus FU/leucovorin significantly improves three-year disease-free survival in patients with Stage II and III colon cancer. The data confirm and extend the results of the MOSAIC trial (Figure 1). The benefit of oxaliplatin does not appear to be dependent on the schedule of FU/leucovorin. The data support the use of weekly bolus FU/leucovorin in combination with oxaliplatin in adjuvant therapy of colon cancer.”

We need more people like Norm.

1 Three-Year Disease-Free Survival in NSABP-C-07 and MOSAIC			
	3y DFS	Benefit from Oxaliplatin	HR
NSABP-C-07	76.5%	4.9%	0.79
MOSAIC	77.9%	5.1%	0.77

SOURCES: Wolmark N et al. Presentation. ASCO 2005. [Abstract 3500](#); de Gramont A et al. Presentation. ASCO 2003; [Abstract 1015](#).

B. Oxaliplatin adds significant adjuvant benefit to fluoropyrimidines. Irinotecan does not.

The tepid results of the PETACC trial presented at ASCO 2005 further reinforce the lack of adjuvant benefit for irinotecan, and it is unclear if there is any current clinical role for this agent in the adjuvant setting. As noted above, continued follow-up of the MOSAIC trial and the spectacular new NSABP-C-07 data set showing a similar benefit when bolus 5-FU (a la Roswell Park) was added to oxaliplatin further reinforce the role of this agent in the adjuvant setting.

C. Clinical investigators now generally prefer capecitabine over intravenous 5-FU/leucovorin as adjuvant therapy when oxaliplatin is not being utilized.

Another ASCO update of the X-ACT trial continues to demonstrate that the adjuvant antitumor effect of capecitabine is at least equivalent and possibly

superior to intravenous 5-FU/leucovorin and that it produces fewer adverse events (see page 37, Cassidy Figures 9, 10). The Think Tank faculty seem to have fully accepted the X-ACT premise, and these clinical investigators have switched their practices accordingly, generally offering capecitabine rather than 5-FU to patients who are not receiving oxaliplatin.

However, based on the initial results from an ongoing patterns of care study conducted by our CME group (Figure 2), it seems that a not-inconsequential number of community-based oncologists continue to prefer 5-FU monotherapy over capecitabine in the adjuvant colorectal cancer setting. We hope to determine the rationale for this finding, which is likely to be the result of a combination of reimbursement issues and a lack of information.

2 Adjuvant Therapy in Patients with Stage III Colon Cancer

- Woman in average health
- T2 tumor in the left descending colon
- 1/25 lymph nodes positive

Which adjuvant systemic therapy regimen, if any, would you most likely recommend?

	Age 38	Age 65	Age 75	Age 85
5-FU/LV (bolus Roswell Park)	—	—	20%	22%
5-FU/LV (bolus Mayo Clinic)	—	—	2%	4%
5-FU/LV (infusion)	—	4%	6%	4%
FOLFOX	90%	82%	38%	2%
FOLFOX + bevacizumab	6%	6%	4%	2%
Capecitabine	—	2%	22%	22%
CAPOX	2%	2%	2%	2%
FLOX	2%	4%	2%	2%
Observation	—	—	4%	40%

SOURCE: 2005 Research To Practice National Patterns of Care Survey.

D. Is the package insert dose of capecitabine (2,500 mg/m² for 14 of 21 days) really a “European dose,” and is the appropriate “American dose” much lower because of differences in dietary and nutritional supplement patterns?

I had heard this concept bantered about for the last few years, but our Think Tank revealed an unexpected twist to the story. Jim Cassidy and Axel Grothey had been part of a group of European-based and European-trained investigators who had blamed United States oncologists for the increased level of capecitabine-related toxicity that seems to occur in patients treated on this

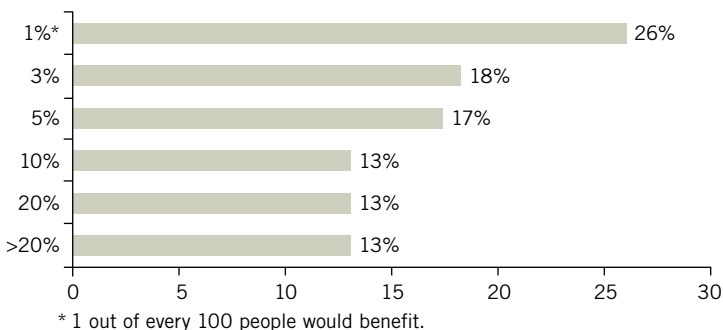
continent. It was stated that US docs needed to pay more attention to patient education to prepare patients to identify early signs of toxicity.

However, Axel recently moved to the New World (Mayo Clinic, Minnesota) and suddenly found that his patients in the frozen tundra were having more toxicity with the same capecitabine doses compared with those he treated in Germany. He and Jim now both believe that dietary and nutritional supplement differences across the pond may explain why patients in North America should be started on a lower dose of capecitabine, which should lessen toxicity, hopefully without compromising efficacy. This requires further definition in clinical trials.

E. Should all patients with Stage II colon cancer be presented with the option of adjuvant chemotherapy?

3

How much of a reduction in the chance that your cancer would come back in five years would you require to undergo therapy with FOLFOX?



SOURCE: Survey of 137 patients with colorectal cancer. Research To Practice 2005.

With great humility and a touch of anxiety, I asked Peter Ravdin of Adjuvant! Online fame to join me in presenting information to our learned faculty on current patterns of care in breast cancer. We challenged the group to explain why women with node-negative breast cancer are routinely presented with the option of chemotherapy, while patients with similar risks and potential benefits with Stage II colon cancer may not be offered a discussion of this option.

Most importantly, we shared with the group initial data from a survey that our CME group is conducting of 129 patients with colorectal cancer, demonstrating that they are at least as proactive as breast cancer patients in wishing to receive adjuvant chemotherapy (Figure 3).

F. There is consensus that FOLFOX plus bevacizumab is the optimal first-line therapy for metastatic disease.

The sudden emergence of the fascinating anti-VEGF agent bevacizumab requires considerable reflection. This agent clearly does not follow the model of cytotoxic treatment, and optimal strategies to use bevacizumab in the clinic are controversial.

On our lung cancer audio series, Eric Rowinsky made a bold prediction that is gaining support among clinical investigators: “In five years, I think we’re going to use VEGF inhibitors with chemotherapy across the board, and all chemo regimens will include anti-VEGF agents.”

What is interesting in that regard is that all anti-VEGF agents do not seem to be created equally, and a major plenary paper at ASCO 2005 by Hecht et al revealed absolutely no benefit for the combination of PTK787/ZK (vatalanib) when added to FOLFOX as first-line therapy for metastatic disease. PTK/ZK is an orally administered VEGF tyrosine kinase inhibitor.

On the other hand, bevacizumab continues to spin out encouraging trial data. Also at ASCO, Bruce Giantonio presented the results from ECOG-E3200 demonstrating a significant improvement in response rate, progression-free and overall survival with the addition of bevacizumab to FOLFOX as second-line therapy (Figure 4).

Several other trials have also demonstrated the benefit of combining bevacizumab with chemotherapy in patients with metastatic colorectal cancer, including encouraging results from the TREE-2 study of capecitabine, oxaliplatin and bevacizumab (Figure 5).

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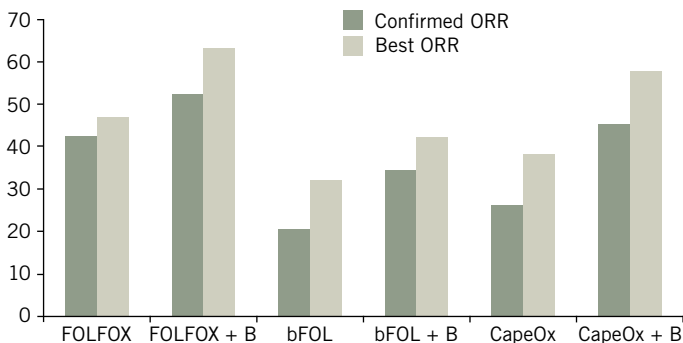
ECOG-E3200 FOLFOX Plus Bevacizumab versus FOLFOX: Clinical Endpoints

	FOLFOX + bevacizumab	FOLFOX	Hazard ratio, <i>p</i> -value
Median OS	12.9 months	10.8 months	HR = 0.76, <i>p</i> = 0.0018
Median PFS	7.2 months	4.8 months	HR = 0.64, <i>p</i> < 0.0001
Overall response	21.8%	9.2%	<i>p</i> < 0.0001

OS = overall survival; PFS = progression-free survival

SOURCE: Giantonio BJ et al. Presentation. ASCO 2005; [Abstract 2](#).

Comparative Response Rates for TREE-1 and TREE-2



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

SOURCE: Hochster HS et al. Poster 3515. ASCO 2005; [Abstract 3515](#).

G. Intrahepatic infusion of FUDR is considered by some to be a dinosaur that belongs in a museum rather than a treatment strategy that should be studied in a major randomized clinical trial (Figure 6).

Here again, Norm Wolmark was in the middle of a fray. He defends the NSABP-C-09 trial evaluating intrahepatic 5-FUDR, because an important secondary benefit will be the development of a national network of cancer hepatic surgeons who will be critical in future trials of curative interdisciplinary treatment. (Note to Norm: Please also do this with thoracic surgeons and adjuvant lung cancer trials and urologists for prostate cancer trials.)

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

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

Eligibility
Patients with colorectal cancer who have no more than six hepatic metastases and no extrahepatic disease

R

Capecitabine + oxaliplatin (CAPOX)

Capecitabine + oxaliplatin
+ intra-arterial floxuridine → CAPOX

SOURCE: www.nsabp.pitt.edu, June 2005.

The critical need for highly trained surgical oncology input in the next generation of colorectal cancer trials also relates to the next point.

H. With increasingly effective cytotoxic and biologically targeted regimens, it is time to rethink the concept of a cure for metastatic colorectal cancer.

Clinical colorectal cancer investigators like our Think Tank faculty have already changed their practices in this direction. Heinz-Josef Lenz notes that in Israel, approval for payment of higher-priced systemic regimens in metastatic disease takes into consideration whether the goal of treatment is cure or palliation.

All of the faculty members of the Think Tank agreed that medical oncologists in practice should identify patients with oligometastatic disease in either the liver or lung or some confined degree of tumor bulk that makes surgery an option if there is a good response to systemic treatment, which, in a sense, is neoadjuvant to surgery for metastatic disease.

Alan Venook notes that clinical trials are addressing these issues in a cohesive, prospective manner, and these studies are including in the data gathered when patients are registered for trials whether the intent of treatment is tumor debulking to prepare for curative surgery.

Len Saltz draws the analogy of using systemic therapy with the specific up-front intention of preparing a patient for curative surgery to Babe Ruth pointing to the bleachers to predict the trajectory of his next at bat. Cure of metastatic disease is certainly a grand slam.

I. The next key research frontier for rectal cancer is the addition in the neoadjuvant setting of new agents combined with a fluoropyrimidine and radiation therapy.

Oxaliplatin combined with either continuous-infusion 5-FU or capecitabine is now being studied by the NSABP and others (Figure 7).

The exciting work of Chris Willett evaluating the addition of bevacizumab combined with neoadjuvant 5-FU and radiation therapy has led to a great deal of enthusiasm for new studies evaluating bevacizumab as part of neoadjuvant therapy of rectal cancer combined with radiation therapy and chemotherapy (Figure 8).

The rationale for exploring new agents in the neoadjuvant rectal cancer setting is not only potential improvement in cancer-free and overall survival and greater rates of sphincter-sparing surgery but also more opportunities for crucial translational studies such as the remarkable work by Willett.

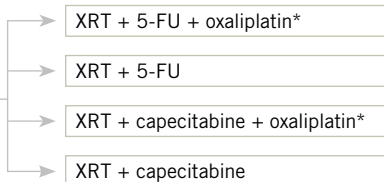
Preoperative Radiotherapy (XRT) Combined with Capecitabine and Oxaliplatin versus Radiotherapy Combined with 5-FU and Oxaliplatin in Patients with Resectable Rectal Cancer

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

Eligibility

Stage II or III invasive rectal adenocarcinoma diagnosed by incisional biopsy within 35 days; measurable disease amenable to curative resection; located <12 cm from anal verge

R



* Protocol amendment to add oxaliplatin is currently under review.

SOURCES: NSABP Protocol R-04, NSABP website.

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

Phase II Neoadjuvant Trial of Chemoradiation with Bevacizumab for Rectal Cancer

Protocol IDs: MDACC 2003-0832, NCT00113230 (Open)

Eligibility

T3, T4 or recurrent rectal cancer

Rectal tumor must be either palpable on DRE or the inferior edge of the tumor must be within 12 cm of the anal verge

Protocol

Bevacizumab 5 mg q2wk x 3 beginning on day 1 of radiotherapy

Radiotherapy: 45 Gy in 25 fractions to the pelvis followed by 5.4 Gy as a boost to the primary tumor with margin

Chemotherapy: Concurrent capecitabine 900 mg/m² BID during radiation x 5wk

Notes: Weekly dose adjustments of capecitabine as needed. Surgical resection will occur five to eight weeks after completion of chemoradiation therapy.

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SOURCE: NCI Physician Data Query, August 2005.

On the following pages, we capture some of the Think Tank discussion on these and other topics. To hear how it all unfolded that fascinating day, slap on some headphones, click “play” on your iPod and give it a whirl. ■

— Neil Love, MD
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Mechanism of action of bevacizumab

► **DR ELLIS:** It is important to state that this is all hypothesis; we really don't have any hard facts, but I look at four potential mechanisms of action of anti-VEGF therapy. The first is the obvious: anti-VEGF therapy is, indeed, anti-angiogenic. Progression-free survival and response rate are significantly greater when bevacizumab is added to chemotherapy.

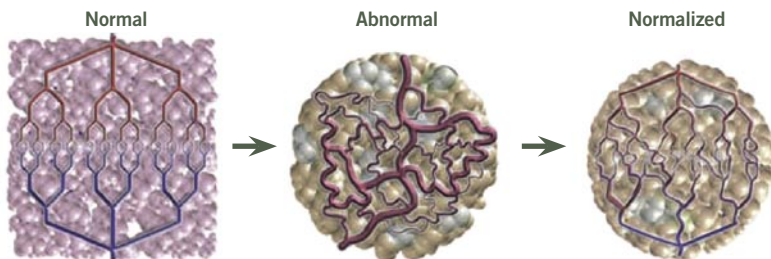
In addition, the hypothesis raised by Rakesh Jain is true — you can normalize the tumor vasculature and, for a short period of time, can actually improve tumor blood flow (Figure 1). This is based on the hypothesis that VEGF leads to bad blood vessels with inefficient blood flow. With anti-VEGF therapy, you may normalize the vasculature. But what Rakesh Jain has also recently shown is that this is a relatively short window of opportunity.

In other words, in preclinical models, about four or five days after giving anti-VEGF therapy, you have an increase in oxygen delivery, potential blood flow and potential chemotherapy delivery (Figure 2). But after that, you don't have an improvement in blood flow. So I think that the normalization hypothesis represents a transient effect on improving blood flow in tumors. That's the second possibility by which bevacizumab, or anti-VEGF therapy, works.

The third is work that's been of interest in our laboratory, which is that tumor cells themselves express VEGF receptors. We have found VEGF receptor-1 on colon cancer cells and pancreatic cancer cells, and this mediates migration, invasion and a relatively new process called epithelial-to-mesenchymal transition, which we're trying to work out right now. So VEGF receptors are present and functional on tumor cells. And by inhibiting VEGF activity, you can possibly inhibit activation of tumor cells.

1

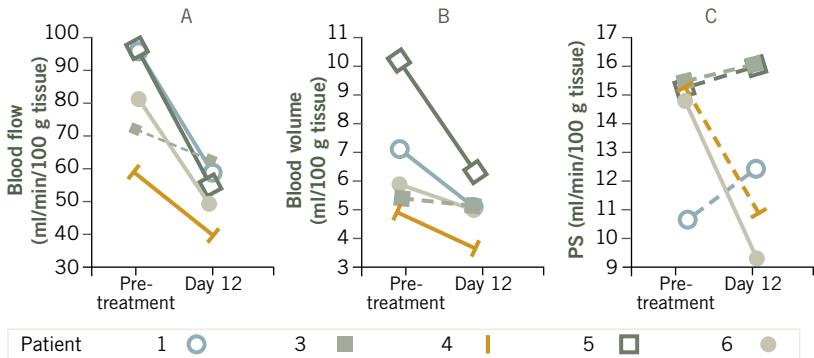
Effect of Anti-VEGF on Normalization of Tumor Vasculature



Anti-VEGFR treatment prunes immature blood vessels and decreases the diameter of residual vessels. The tumor vasculature becomes less tortuous and more organized, with improved perivascular cells and basement membrane coverage.

SOURCE: Reproduced with permission. Jain RK et al. *Nat Med* 2001;7(9):987-9. No abstract available

Effect of Anti-VEGF Therapy on Blood Flow and Volume and Vascular Permeability



SOURCE: Reproduced with permission. Willett CG et al. *Nature Med* 2004;10(2):145-7. [Abstract](#)

The last activity of anti-VEGF therapy is vasoconstriction. If you look at all the clinical trials, you'll note that there's an immediate effect on blood flow. And now that we're using both CT scan and MRI, you can see a decrease in blood flow and permeability after one or two doses of an anti-VEGF agent.

This is likely the result of blocking endothelial nitric oxide synthase, and whereas in tumor vessels you have vasodilation, if you knock out the VEGF pathway, you'll knock out nitric oxide synthase and get a relative vasoconstriction. This occurs relatively rapidly and is consistent with nitric oxide biology.

Use of capecitabine in the metastatic setting with oxaliplatin and bevacizumab

► **DR MEROPOL:** Howard Hochster's studies — TREE-1 and TREE-2 — addressed various combinations of fluoropyrimidines and oxaliplatin, with and without bevacizumab. In terms of response rates, the capecitabine/oxaliplatin regimen and bevacizumab had a response rate that is respectable and comparable to what's seen with modified FOLFOX6 and bevacizumab.

► **DR HOFF:** FOLFOX is still very attractive, but some patients don't like to carry the pump. I would have no problem with a patient taking CAPOX and bevacizumab, with the caveat that I don't think we can do the dosing that has been presented in most trials — with the exception of TREE-2, of course. I think that's a much more reasonable dosing to use in the United States.

► **DR SALTZ:** Jim Cassidy and I have a two-by-two study that is FOLFOX versus CAPOX plus or minus bevacizumab. Accrual is complete, and the data are maturing. Unfortunately, the vast majority of patient accrual is in Europe, so we'll still have to wrestle with the Americanization of the capecitabine dose, depending on what we see.

In terms of patient acceptability of pumps and infusions and so on, I think the type of pump used is highly important. Patients are largely, in the community, getting mechanical pumps provided by infusion services, and they hate them. They're heavy and have bells and whistles that go off at odd hours. They're very conspicuous.

What we've been using routinely in our practice at Memorial are the plastic, disposable pumps, which unfortunately are not reimbursable by Medicare. We've recently made the decision to absorb the cost. Our patients love them to the point where if we ever have a malfunction and we try to switch them to the mechanical pump, they flat out refuse and insist on going back to the disposables. The use of the disposable pump solves so many of the problems that the patients complain about. It makes the infusion schedules a whole lot more manageable.

Trials of bevacizumab with capecitabine

The BOND-2 trial presented at ASCO by Len Saltz was a randomized Phase II trial of cetuximab, bevacizumab and irinotecan or cetuximab and bevacizumab in patients who had previously received irinotecan in metastatic colorectal cancer. The response rate in patients who received the three drugs — irinotecan/cetuximab and bevacizumab — was 37 percent, and in the patients who just received the two antibodies alone, the response rate was 20 percent. These results are provocative when one looks at historical data, suggesting that cetuximab and irinotecan in a similar population would have a response rate of about 20 percent, and cetuximab alone would have a response rate of about 10 percent in these patients.

► **DR LENZ:** One of the important issues with the high efficacy rate from the combination of the targeted agents, particularly bevacizumab and cetuximab, is, Do we move more effective agents, despite their cost, into front-line treatment?

New clinical trial questions in metastatic disease

► **DR LENZ:** There are a number of important questions that need to be addressed in clinical trials.

Should we move cetuximab into the first-line setting? Should we combine all the biologics in front line for all patients or selected patients? Should we use cetuximab in combination with irinotecan in oxaliplatin/bevacizumab failures? Should we move it to second line and not to third line? Should cetuximab combine with nonirinotecan combinations such as FOLFOX?

Should we use bevacizumab for life? There's certainly controversy about this, since we have no clue about the mechanism of resistance. When patients have disease progression, is the mechanism still in place, and should we just replace cytotoxic treatment and continue bevacizumab?

One of the most interesting and exciting data sets at ASCO was presented by Len Saltz — the BOND-2 trials. Since the combination of bevacizumab/cetuximab and irinotecan or the combination of the two antibodies alone showed significant activity in form of response and time to tumor progression, would this continued synergism exist in patients who are bevacizumab refractory? Again the question, Would the continuation of bevacizumab play a role in these refractory patients?

One of the goals in the future would be not only to increase prolongation of overall survival, which we have done with the biologics, but also basically develop a shoulder which can create a cure rate of maybe 20, 30, 40, 50 percent, depending on the patient selection.

Intrahepatic chemotherapy: Dinosaur or cutting-edge therapy?

► **DR HALLER:** I'm not wild about HIA FUDR, quite frankly. I just don't see the rationale for it. I think we have systemic therapies that have response rates that are equally high. The data with FUDR are restricted to very small populations of patients. I think it's a dinosaur.

► **DR ELLIS:** I agree with the term "dinosaur."

► **DR WOLMARK:** Let me respond to the "dinosaur." It may be a dinosaur or it may not. I think it's worthwhile to prove that it is or is not a dinosaur. That, in and of itself, probably would not be sufficient to launch this trial. I think what is a sufficient rationale to launch this trial is the fact that liver surgeons do not communicate with each other. The fact that we're putting a vehicle in place where liver surgeons are doing clinical trials, I think, is an extremely important outcome of this study.

If this doesn't particularly inspire you, hopefully the next study will, and the mechanism will be in place with a group of skilled colorectal surgeons who do hepatic resections, primed to do randomized prospective clinical trials.

► **DR VENOOK:** I still suspect there's a niche role for HIA FUDR, and we still look at it in some protocol settings. I think it was a matter of trying to stretch fluoropyrimidines as far as we could make them go before we had other agents. What this research did in my opinion — and it's a little self-serving to say this, because we did a lot of work with this — is it demonstrated that patients with hepatic metastases may be a subset of patients where you can make a very big impact in their disease. So we still do HIA FUDR on protocol.

I generally agree it's a dinosaur. I agree with Norman, though. It could be that it eradicates microscopic disease in the liver better than systemic therapy. What I'm pessimistic about is the ability to really do a meaningful study in

this modality across the NSABP. Quality control is a huge problem with intra-arterial FUDR, and I really would be stunned if they can pull it off and really not get into all sorts of complications.

► **DR GOLDBERG:** Most of the HIA data come from a single sophisticated center where there's an individual who is totally committed to it. We need to expand it out into the nation to see if it's really a viable tool. Having said that, Nancy Kemeny has been a proponent of this with over 20 years of investigation, and if you read the data she's provided, it does result in dramatic responses in some circumstances. I actually disagree with my colleague from Pennsylvania that this is a dinosaur. I think that this is a cutting-edge therapy that may have some benefit to it, and before we dispense with it, we ought to really be sure that we consider all the possibilities.

► **DR SALTZ:** The discussion here illustrates the extreme importance of a study such as NSABP-C-09, because you have opinion leaders who have given this matter a lot of thought and who have differences of opinion. That's the perfect situation for a clinical trial. I really hope that the trial can be done. I'm concerned that it may not happen, because everybody thinks they know the answer already. Some people know one answer and some people know another answer, but I think everyone has a strong opinion. I am worried about how many surgeons and medical oncologists and patients will agree to leave the decision of a pump to a coin toss.

FDA approval of FOLFOX for Stage III but not Stage II disease

► **DR WOLMARK:** The MOSAIC trial motivated something that changed clinical practice; namely, it motivated the FDA on November 4, 2004 to approve oxaliplatin in combination with infusional FU/leucovorin for adjuvant Stage III colon cancer. The approval was based on improvement in disease-free survival. This is unprecedented, both for its approval in the adjuvant setting and for the FDA to do its own unplanned subset analysis. And in that regard, I completely agree with Axel's editorial criticizing this approach. Where will it stop? For that matter, if you were to take the one positive-node population and add it to Stage II, you will also get nonsignificance. So once we've accepted the concept, once we've perjured ourselves, where do we stop? We have provided them with the imprimatur to proceed in this manner.

Adjuvant chemotherapy for Stage II disease

► **DR LENZ:** I usually recommend FOLFOX treatment, but I also discuss capecitabine, with the X-ACT data. I basically don't use any more bolus 5-FU. That has disappeared from our clinics, so we use either capecitabine or FOLFOX. We don't use FOLFIRI anymore. There are certain circumstances where FOLFOX is not appropriate, or patients will not accept the efficacy of the FOLFOX data and the potential side effects, and they are better candidates for capecitabine.

► **DR HOFF:** It's very rare a patient to whom I would offer 5-FU/leucovorin. For patients who cannot receive oxaliplatin, would you rather use FOLFIRI or capecitabine? Personally, I would use capecitabine.

► **DR MEROPOL:** The implication of these past few comments is that we would offer FOLFOX to all healthy patients for whom we were considering adjuvant therapy. But I think it's worth noting that the benefit of FOLFOX versus 5-FU and leucovorin alone in patients with Stage II disease, in absolute terms, is quite small. You're treating 100 patients to benefit just a few. So at the expense of long-term neurotoxicity or in an effort to avoid long-term neurotoxicity, one might trade off that few percent and offer just a fluoropyrimidine to an otherwise healthy patient with Stage II disease for whom you'd like to offer adjuvant therapy.

Are patients with Stage II colon cancer being offered the option of adjuvant chemotherapy?

3 Risk of Recurrence and Use of Adjuvant Chemotherapy Survey of 100 US-Based Medical Oncologists

How likely are you to recommend adjuvant chemotherapy to a 55-year-old woman with colon cancer (Stage II) or breast cancer with each of the following risks of recurrence?

	10% risk of recurrence		20% risk of recurrence		30% risk of recurrence	
	Colon	Breast	Colon	Breast	Colon	Breast
Very likely	12%	23%	33%	75%	61%	94%
More likely than unlikely	31%	44%	39%	19%	31%	2%
More unlikely than likely	26%	23%	20%	2%	6%	2%
Very unlikely	31%	10%	8%	4%	2%	2%

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

► **DR WOLMARK:** Clearly there is heterogeneity in the treatment of breast and colorectal cancer (Figure 3). Perhaps the heterogeneity is in the people treating the disease rather than in the people with the disease, and it's not the medical oncologist alone.

In colon cancer, you see an unprecedented unplanned subset analysis by the FDA. Can you imagine the FDA doing this kind of thing in breast cancer? They would have advocates lined up to basically tear them limb from limb had they tried that. So wherein lies the atresia? Perhaps we ought to take a look at ourselves. Are we really responding to the needs of our patients as they perceive these needs? And are we providing them with adequate information to allow them to make an informed choice together with our input?

► **DR HOFF:** I agree with Norm that a lot of the difference in management of colon and breast cancer is not the patients but the physicians, because in colon

cancer, for 40 years we only had 5-FU/leucovorin and a 15 percent response rate. This led to a nihilistic mentality. Sometimes we forget that some of our patients with CRC — as we just saw with Neil’s data — are willing to risk a lot for a modest benefit. And I think we have to discuss this with our patients. The clinical trials in Stage II disease have been very small, but the QUASAR trial, the NSABP meta-analysis and IMPACT all support that there is a small benefit for patients with Stage II disease.

► **DR MEROPOL:** There have also been a lot of recent discussions about the cost of therapy, but decisions about what is an acceptable cost maybe shouldn’t be left in the hands of us healthy people and healthy legislatures and government, who are not the people who are the consumers of this product.

Our group has applied this concept to the case of people with advanced cancer. We’ve already reported a study in which we asked patients to describe how much of their life’s fullness has been lost due to their current cancer illness. These were patients considering Phase I clinical trials. We gave them a pie chart to show either zero percent of their life’s fullness has been lost due to their current illness all the way to 100 percent.

And it turns out that this assessment of loss of life’s fullness predicted who would and would not choose to go on a Phase I clinical trial. Consistent with the hypothesis was that people who had lost the most in terms of their life’s fullness or perceived the greatest loss were the most likely to go on a Phase I clinical trial.

So people with cancer, and particularly with advanced cancer, are different than us healthy people in terms of what is rational decision-making for them. And they’re different than other stakeholders and decision makers with regard to what’s appropriate therapy. And I think this has important implications for how society defines what is an acceptable cost for an acceptable benefit in terms of cancer therapy.

Irinotecan in the adjuvant setting

► **DR GROTHEY:** When we look at the overall picture of adjuvant therapy, we have three irinotecan trials, and two of them are really negative, and one is negative. And we have two oxaliplatin trials with different 5-FU backbones, both of which show that it works. It’s a very simple conclusion. Oxaliplatin is appropriate adjuvant therapy, combined with fluoropyrimidines. And I would assume that the CAPOX data will also be positive.

The FLOX data set is also a strong indicator that we can probably get away with a lower cumulative dose of oxaliplatin, and it adds to the fact that the next trial design — which we’re trying to do at an international level — is going to address duration of therapy, which has implications for patients’ quality of life, cost efficiency, et cetera.

► **DR MEROPOL:** At this point, given the totality of the evidence in unselected populations, I’m not in favor of using FOLFIRI in the adjuvant setting,

period. I think the challenge for us is to recognize that oxaliplatin and irinotecan are not completely cross-resistant, and so there are going to be some people who would benefit from oxaliplatin but not irinotecan, and vice versa. The challenge for us is to figure out how to identify those subgroups.

Treatment of rectal cancer

- ▶ **DR VENOOK:** Bevacizumab obviously has great potential in the rectal cancer setting. Chris Willett's paper in *Nature Medicine* was a very clever and interesting development. These were patients with primary or locally advanced rectal cancer who received a single dose of bevacizumab and, in 12 days, were re-evaluated with imaging and biopsy and then received 5-FU/radiotherapy. Blood flow, blood volume and tumor vasculature all were impacted by a single dose of bevacizumab to these tumors that were in situ. So certainly, there's biological activity of bevacizumab alone, and I think this really needs to be looked at in neoadjuvant studies.
- ▶ **DR HOFF:** We try to put these patients on protocol as much as possible. Right now, we have a preoperative Phase II protocol with capecitabine, bevacizumab and radiation therapy. If patients cannot participate in this study, we usually use preoperative capecitabine with radiation therapy. ■

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PRESENTATION

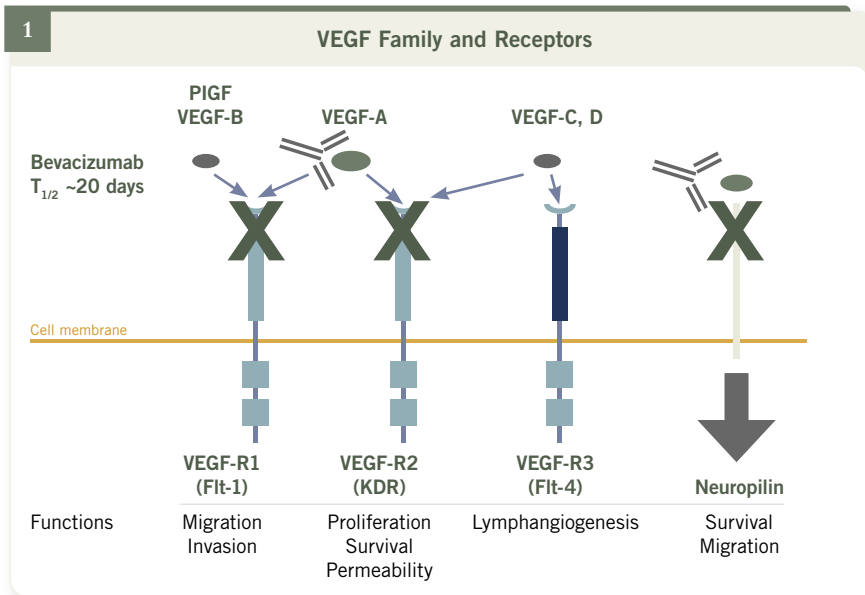
Lee M Ellis, MD

Dr Ellis is a Professor of Surgery and Cancer Biology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

FOLFOX4 with or without Bevacizumab in Previously Treated Advanced Colorectal Cancer: Results from ECOG-E3200*
Colorectal Cancer Update Think Tank Meeting • June 24, 2005

This year’s ASCO meeting was quite exciting, particularly with regards to targeted therapies.

As a brief review of the biology behind the system, VEGF-A, or VEGF, is a prototypical member of a family of ligands, which includes about five or six family members with similar homology derived from different genes.



* Presented at Research To Practice Colorectal Cancer Update Think Tank Meeting, New York, New York, June 24, 2005.

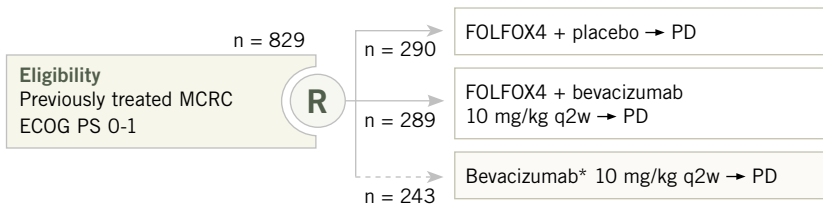
Slide 1

There are three tyrosine kinase receptors for VEGF — VEGF-R-1, R-2 and R-3 — which mediate various functions that are listed here. There's a novel receptor for VEGF — neuropilin — that is not a tyrosine kinase receptor, and we think it mediates survival and migration signals.

In regards to agents targeting VEGF that we'll discuss today, bevacizumab has a half-life of about 20 days and binds VEGF and essentially acts like a sponge, preventing it from binding to its receptors. So inhibition of VEGF-A with bevacizumab can block activation of VEGF-R-1, R-2 and neuropilin.

2

ECOG 3200 Trial Design



- Primary end point: OS
- Secondary end points: ORR, PFS, safety

* Third arm discontinued after predetermined interim analysis demonstrated the inferiority of bevacizumab compared with FOLFOX4.

SOURCE: Giantonio BJ et al. Presentation. ASCO 2005; [Abstract 2](#).

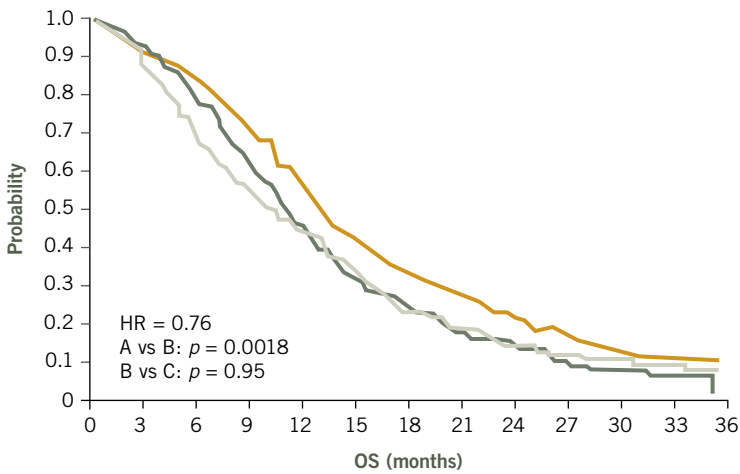
Slide 2

Bruce Giantonio was the lead investigator in ECOG-E3200. In this trial, patients were previously treated with fluoropyrimidines and irinotecan for metastatic colorectal cancer and had a good ECOG performance status.

Patients were randomized to one of three arms: FOLFOX plus placebo, FOLFOX plus bevacizumab — and of note, this is a higher dose of bevacizumab than was used in Herb Hurwitz's trial reported at ASCO 2003 — or bevacizumab as a single agent at the higher dose. The third arm was discontinued after an interim analysis demonstrated inferiority of bevacizumab compared to FOLFOX alone or FOLFOX plus bevacizumab.

Slide 3

Overall survival was significantly improved in the patients who received FOLFOX plus bevacizumab compared to patients who received FOLFOX alone or bevacizumab alone. Surprisingly, the survival curve for bevacizumab seems to mirror that of FOLFOX4, but I think this will be sorted out a little better when we look at progression-free survival on the next slide.



	Total	Dead	Alive	Median
■ A: FOLFOX4 + bevacizumab	289	246	43	12.9
■ B: FOLFOX4	290	257	33	10.8
■ C: Bevacizumab	243	216	27	10.2

SOURCE: Reproduced with permission. Giantonio BJ et al. Presentation. ASCO 2005; [Abstract 2](#).

Slide 4

You see an improvement in progression-free survival in patients who received bevacizumab in addition to FOLFOX versus FOLFOX alone.

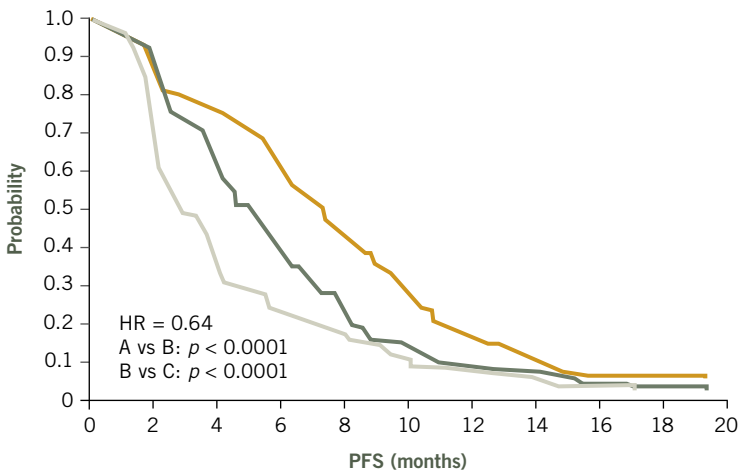
However, PFS for the bevacizumab-alone arm was significantly less than that for FOLFOX, suggesting that the survival benefit achieved with bevacizumab as a single agent was probably due to postprogression therapy, although this has not been sorted out yet. Dr Giantonio will try to obtain these data in the near future, prior to publication.

Slide 5

Response rates are very consistent across bevacizumab trials, where you see an approximate 10 percent improvement in response rates when you add bevacizumab to chemotherapy. In this case, the overall response rate for FOLFOX plus bevacizumab is 22 percent versus 9.2 percent in FOLFOX alone.

As a single agent, bevacizumab had a three percent response rate. That is interesting in and of itself, but it's clearly not as good as chemotherapy or chemotherapy plus bevacizumab.

E3200: Progression-Free Survival



	Total	Fail	Cens	Median
■ A: FOLFOX4 + bevacizumab	273	228	45	7.2
■ B: FOLFOX4	273	241	32	4.8
■ C: Bevacizumab	229	215	14	2.7

SOURCE: Reproduced with permission. Giantonio BJ et al. Presentation. ASCO 2005; [Abstract 2](#).

Slide 6

We always have to look at toxicity, and with all anti-VEGF agents, hypertension is a toxicity. This occurred in the FOLFOX plus bevacizumab arm, as well as the bevacizumab-alone arm. There were some episodes of bleeding. This was relatively rare, but it was still a minor concern within the investigations.

Neuropathy appeared to be a little bit higher in the FOLFOX plus bevacizumab arm, probably due to prolonged administration of the regimen. One thing we always have to look out for in bevacizumab trials is bowel perforation. Again, there was a slight increase in bowel perforation in those patients who received bevacizumab versus those patients who received chemotherapy alone. It's not a high incidence, but it's very consistent among the various trials in colon cancer.

E3200: Response Rates

	FOLFOX4 + bevacizumab n = 271	FOLFOX4 n = 271	Bevacizumab n = 230
OR*	21.8%	9.2%	3.0%
CR	1.9%	0.7%	0%
PR	19.9%	8.5%	3.0%
SD	51.7%	45.0%	29.1%

* FOLFOX + B vs FOLFOX: $p < 0.0001$

SOURCE: Giantonio BJ et al. Presentation. ASCO 2005; [Abstract 2](#).

	FOLFOX4 + bevacizumab (n = 287)		FOLFOX4 (n = 284)		Bevacizumab (n = 234)		p
	GI/II	GI/IV	GI/II	GI/IV	GI/II	GI/IV	
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](#).

Slide 7

In conclusion, ECOG-E3200 demonstrates that the addition of bevacizumab to FOLFOX in second-line therapy improves efficacy in regard to progression-free survival, response rates and overall survival. The efficacy of FOLFOX can be improved with targeted therapy and in this trial, bevacizumab was utilized, but I think there's also some interesting data with cetuximab.

We have to be cognizant of hypertension, bowel perforations and hemorrhage with bevacizumab. They are infrequent, but they're important adverse events. Single-agent bevacizumab in second-line therapy was inferior to FOLFOX, and at this time, there is no role for single-agent bevacizumab in metastatic colorectal cancer. ■

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- The addition of BV to FOLFOX in second-line therapy improves efficacy (PFS, RR, OS)
 - Efficacy of FOLFOX can be improved with targeted therapy (BV, Cetuximab?)
 - Be cognizant of HTN, bowel perforations and hemorrhage (infrequent, but important)
 - Single-agent BV in second-line therapy was inferior to FOLFOX (currently, there is no role for use of BV as a single agent in mCRC)

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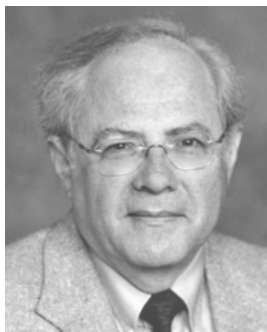
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PRESENTATION

Norman Wolmark, MD

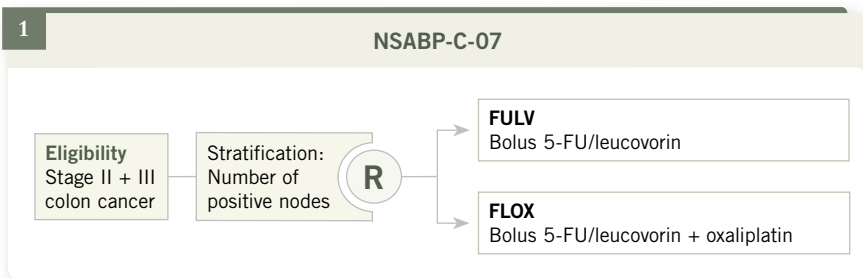
Dr Wolmark is Professor and Chairman of the Department of Human Oncology at Allegheny General Hospital, Professor at Drexel University College of Medicine and Chairman of the National Surgical Adjuvant Breast and Bowel Project in Pittsburgh, Pennsylvania.

A Phase III Trial Comparing FULV to FULV + Oxaliplatin in Stage II or III Carcinoma of the Colon: Results of NSABP-C-07*

Colorectal Cancer Update Think Tank Meeting
June 24, 2005

Slide 1

We present data from NSABP Protocol C-07, where patients with Stage II and III colon cancer were stratified only by the number of positive nodes and then randomized to leucovorin-modulated 5-FU or FLOX.



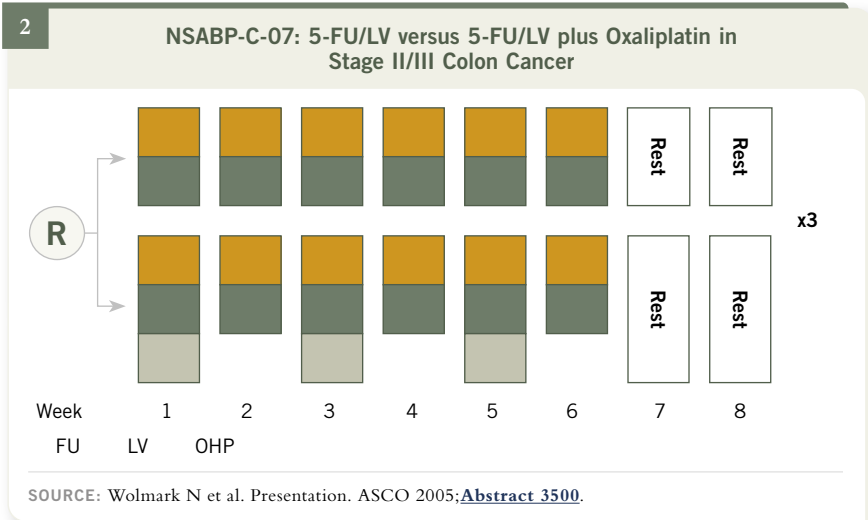
Slide 2

This was a typical NSABP trial, where the control arm was the RPMI (Roswell Park Memorial Institute) or NSABP regimen, FU/leucovorin, 500/500 mg/m², given six out of eight weeks, with a two-week rest, for a total of three cycles, or the same regimen, to which three doses of oxaliplatin were added on weeks one, three and five at 85 mg/m². Between February of 2000 and November 2002, 2,400 patients were randomized. The mean time on study for this analysis is 34 months, which we will compare to the

* Presented at Research To Practice Colorectal Cancer Update Think Tank Meeting, New York, New York, June 24, 2005.

37-month disclosure at ASCO 2005 of the MOSAIC trial. The primary prespecified protocol endpoint was disease-free survival, and it's important to define this, since it seems that people arbitrarily define this in any number of different ways. Disease-free survival is defined as an event if it was a first recurrence, a second primary cancer or death from any cause.

The trial had a 90 percent power to detect a 5.4 percent increase in disease-free survival.



Slide 3

Approximately 29 percent of the population had Stage II disease. These were very well distributed, which is not surprising, since this trial was stratified according to the number of positive nodes, and we expected to see this distribution.

3 C-07 Patient Characteristics

Positive Nodes	FULV %	FLOX %
0	28.8	28.9
1-3	45.7	44.8
≥4	25.3	25.6

SOURCE: Wolmark N et al. Presentation. ASCO 2005; [Abstract 3500](#).

Slide 4

Overall toxicity for the RPMI regimen, as you all know, is gastrointestinal. The addition of oxalipatin increased this toxicity, but not by very much: Fifty percent Grade III toxicity for the FLOX arm compared to 41 percent for the FU/leucovorin arm.

Clearly, with oxalipatin, neurotoxicity is the most worrisome toxic outcome. I remind you that Grade III neurotoxicity using the scale for NSABP Protocol C-07 — a combined Sanofi-NCI neurotoxicity scale — is defined as paresthesias, dysesthesias, with pain or interference with activities of daily living.

Slide 5

If we now examine neurotoxicity for the entire population that received oxaliplatin, we see that 85 percent had some degree of neurotoxicity during treatment.

Twelve months following the cessation of treatment, this neurotoxicity dropped to 29 percent.

4

C-07 Overall Toxicity (%)

Grade	FULV	FLOX
0-II	49	38
III	41	50
IV	9	10
V	1	1

SOURCE: Wolmark N et al. Presentation. ASCO 2005; [Abstract 3500](#).

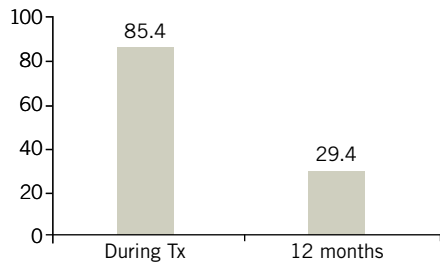
Slide 6

Of greater interest is Grade III neurotoxicity, and during treatment this was eight percent. Twelve months following the cessation of treatment, this dropped to a half percent.

Now certainly, the neurotoxicity during treatment is less than the 12.4 percent reported in the MOSAIC trial. Most likely, this is due to the fact that C-07 utilized a lower cumulative dose of oxaliplatin — approximately three quarters of the cumulative dose at 765 mg/m² — compared to a gram in the MOSAIC trial.

5

Grade > I (All) Neurotoxicity (%)



SOURCE: Wolmark N et al. Presentation. ASCO 2005; [Abstract 3500](#).

Slide 7

Eighty-seven percent of patients received full-dose oxaliplatin during the first cycle, 69 percent during the second cycle and 63 percent during the third cycle. Overall, 73 percent of the oxaliplatin-treated cohort received protocol-stipulated cumulative dose.

6

Oxaliplatin Protocol-Stipulated Cumulative Dose

C-07	765 mg/m ²
MOSAIC	1,020 mg/m ²

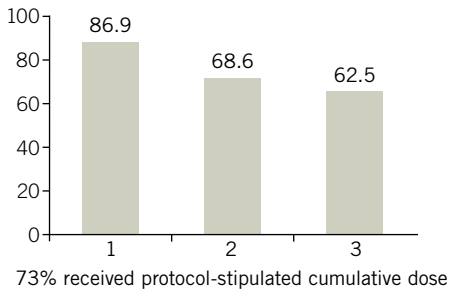
SOURCE: Wolmark N et al. Presentation. ASCO 2005; [Abstract 3500](#).

Slide 8

The only unanticipated toxicity was a transmural enterocolitis, requiring hospitalization and rehydration. It was seen more often in women than men in both arms, and there seemed to be an excess in the FLOX arm: 4.5 percent versus 2.7 percent.

7

Percent of Full Dose Oxaliplatin/Cycle



SOURCE: Wolmark N et al. Presentation. ASCO 2005; [Abstract 3500](#).

Slide 9

The overall number of deaths during treatment, however, was equal in both groups: 14 deaths in the FU/leucovorin and 15 in the FLOX arm.

Slide 10

We can now address the primary endpoint of this trial, which was disease-free survival. There is a highly significant prolongation in disease-free survival when oxaliplatin is added to leucovorin-modulated 5-FU, with a p -value less than 0.004.

There is a striking similarity between the results of NSABP Protocol C-07 and the MOSAIC trial, given similar follow-up times. The three-year disease-free survival with oxaliplatin in C-07 was 76.5 and was 77.9 percent in the MOSAIC trial. The absolute delta was 4.9 percent for the NSABP trial and 5.1 percent in MOSAIC. The hazard ratio was 0.79 for the NSABP and 0.77 for the MOSAIC at similar follow-up times.

The C-07 findings led us to conclude that the addition of oxaliplatin to weekly bolus FU/leucovorin significantly improves three-year disease-free survival in patients with Stage II and III colon cancer. The data confirm and extend the results of the MOSAIC trial.

8

C-07 Bowel Wall Injury

	N
FULV	34 (2.7%)
FLOX	56 (4.5%)

SOURCE: Smith RE et al. *Proc ASCO GI 2004*; [Abstract 195](#).

9

C-07 Deaths During Treatment

	N
FULV	14 (1.1%)
FLOX	15 (1.2%)

SOURCE: Wolmark N et al. Presentation. ASCO 2005; [Abstract 3500](#).

10

Benefit from Oxaliplatin in NSABP-C-07 and MOSAIC Trials

	3y DFS	Δ	HR
C-07	76.5%	4.9%	0.79
MOSAIC	77.9%	5.1%	0.77

SOURCES: Wolmark N et al. Presentation. ASCO 2005; [Abstract 3500](#); de Gramont A et al. Presentation. ASCO 2003; [Abstract 1015](#).

The benefit of oxaliplatin does not appear to be dependent on the schedule of FU/leucovorin administration, and the data support the use of weekly bolus FU/leucovorin in combination with oxaliplatin in adjuvant colon cancer. ■

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PRESENTATION

James Cassidy, MD

Dr Cassidy is a Professor of Oncology and Head of the Cancer Research UK's Department of Medical Oncology at the University of Glasgow in Bearsden, Glasgow.

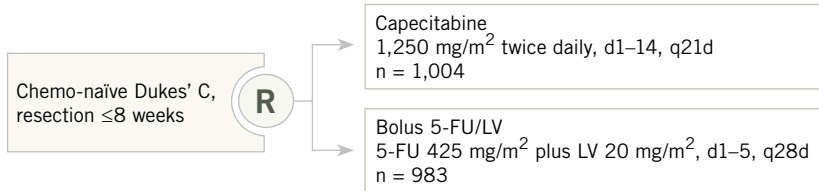
Capecitabine versus Bolus 5-FU/Leucovorin as Adjuvant Therapy for Colon Cancer: X-ACT Trial Results*

Colorectal Cancer Update Think Tank Meeting
June 24, 2005

1

X-ACT Trial in Adjuvant Treatment of Dukes' C Colon Cancer

Recruitment 1998–2001



- 1° endpoint
 - Disease-free survival (DFS)
- 2° endpoints
 - Relapse-free survival (RFS)
 - Overall survival
 - Tolerability (NCIC CTC)
 - Pharmacoeconomics
 - QoL

SOURCE: Cassidy J et al. Presentation. ASCO 2005; [Abstract 3586](#).

Slide 1

This is the design of the X-ACT trial, with capecitabine in the “European” dosing, as it has become known. The trial was for Dukes’ C, Stage III colon cancer patients. The standard arm was the Mayo Clinic regimen, which we can argue about, and the primary endpoint was disease-free survival, with a

* Presented at Research To Practice Colorectal Cancer Update Think Tank Meeting, New York, New York, June 24, 2005.

number of secondary endpoints, and I'll show you some of those. We were trying to show equivalence or noninferiority.

Slide 2

Here's the schedule of treatments: A very standard Mayo Clinic regimen of bolus 5-FU/leucovorin repeated for six cycles versus eight cycles of capecitabine, so the same duration of therapy. It was six cycles in one and eight cycles in the other arm, to make it the six months.

Slide 3

Disease-free survival was the primary endpoint, and this has now been updated with an extra few months of follow-up since the original ASCO 2004 presentation. Preplanned statistical analyses were performed to test equivalence as well as superiority. Note that both are shown on the same slide. It doesn't quite meet the test of superiority, but we stand by the way that we do these trials and statistics, and it comes very, very close.

Slide 4

This is relapse-free survival, where it passes that magical figure of 0.05. You can read into that what you wish. If you use the endpoints that were used in some of the later trials — the PETACC trials — I don't know quite where this would fit if you start to change the definitions around. We have no intention of going back and reanalyzing this with a whole set of new endpoints.

Slide 5

This is overall survival, and again, this was updated at ASCO. I remind you that what we were trying to do was to show equivalence. The trial was powered to show equivalence, and we don't really expect it to show anything other than that. So if you look at the DFS and the RFS differences as being a bonus on top of that equivalence, then I think that's the right way to look at this trial. I don't believe, with 100 years of follow-up, that we're likely to see a difference in overall survival with this trial.

2 X-ACT Treatment Schedules

Capecitabine
1,250 mg/m² twice daily

Treatment (days 1–14)	Rest (days 15–21)
	Repeat cycle x 8 (24 weeks)

OR

Bolus 5-FU/LV
IV leucovorin 20 mg/m² + IV 5-FU 425 mg/m²

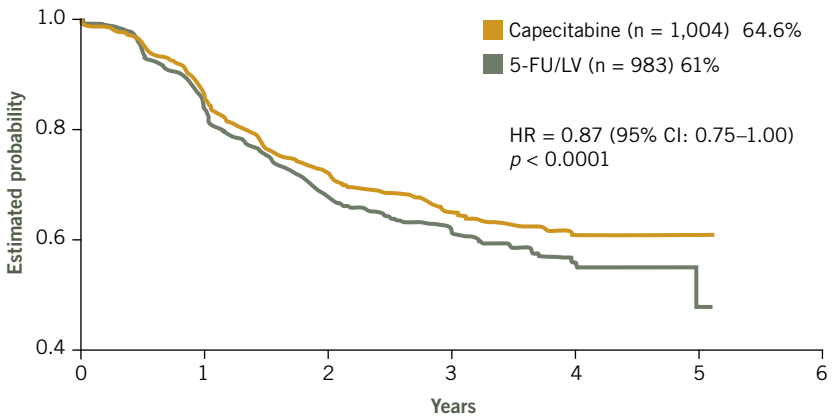
Day

1	2	3	4	5	8	15	21	28
↑	↑	↑	↑	↑				
							Repeat cycle x 6 (24 weeks)	

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

3

Strong Trend to Superior DFS (ITT)

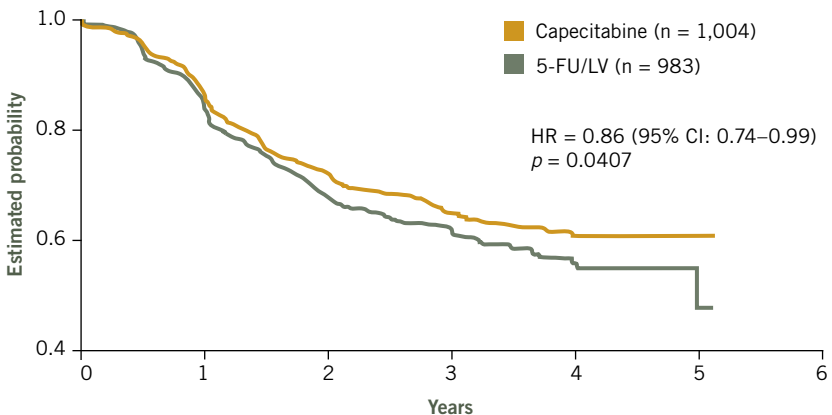


Median follow-up 51 months

SOURCE: Twelves C et al. Presentation. ASCO 2005; [Abstract 3521](#).

4

Capecitabine versus Bolus 5-FU/LV: Superior Relapse-Free Survival (ITT)

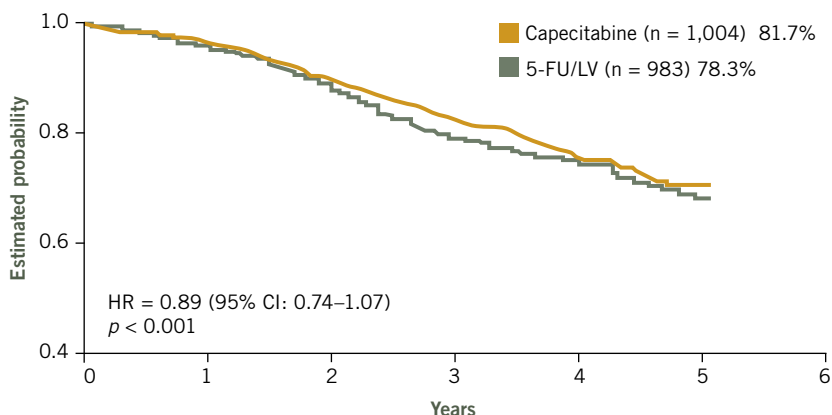
SOURCE: Cassidy J. Presentation. *Colorectal Cancer Update* Think Tank Meeting 2005. No abstract available

Slide 6

There are some differences in where patients relapse, with fewer relapses in liver and lymph nodes, but then that's what you'd expect, because that's where the predominant site of relapse would be anyway. So there's nothing particularly astounding in that observation.

5

Capecitabine Showed Trend to Improved Overall Survival (ITT)



SOURCE: Cassidy J et al. Presentation. ASCO 2005; [Abstract 3586](#).

6

Fewer Relapses in Liver and Lymph Nodes with Capecitabine

Number of relapses	Capecitabine n = 1,004		Bolus 5-FU/LV n = 983	
	Total	As only site	Total	As only site
Total number of relapses	323		357	
Colon, rectum	58	41	60	43
Lymph nodes	44	20	57	35
Liver	126	93	145	110
Lung	58	35	58	39
Other	101	68	99	65

7

X-ACT Mayo Comparable to Mayo in Other Trials (Dukes' C, Colon Only)

	INT0089* n = 769 ¹	Andre* n = 256 ²	IMPACT n = 313 ³	X-ACT n = 983
Mayo 3-year DFS	63	61	62	61
Mayo 3-year OS	73	81	78	78

* Data points from KM curves

SOURCES: ¹ Haller DG et al. *J Clin Oncol* 2004; In Press.

² André T et al. *J Clin Oncol* 2003;15:2896-903. [Abstract](#)

³ IMPACT. *Lancet* 1995;345(8955):939-44. [Abstract](#)

Slide 7

A question that was raised by us and others as the trial has been discussed is, Was our version of the Mayo regimen somehow an inferior version of the Mayo Clinic regimen?

Slide seven is a cross-trial comparison looking at data from a number of different trials, and which you all know very well is basically saying, no, that's not an explanation for this. So the Mayo Clinic regimen that we used was pretty much the standard and achieved much the same as would be achieved in any other type of trial.

Slide 8

What about differences in treatment exposure? There was the issue of people dose reducing the Mayo Clinic regimen, because certainly, many of us worry about the toxicity profile of the Mayo Clinic regimen, and that's one of the things that we were criticized for: "You picked the most toxic regimen to compare this with."

If that was the case, then one might expect there to be lots more dose reductions in that arm, and actually, that's not what happened at all. They came out roughly the same.

The other part to that, of course, is there are dose reductions in the capecitabine arm. It's not a "shoot it and forget it" treatment. Physicians must look after the patients to assess for side effects.

Slide 9

However, there's less toxicity with capecitabine, and I don't believe anybody would argue with that. The toxicity comes on at a different time, too. It's a bit further on in the treatment, which may or may not be beneficial to your patients.

There are different ways of looking at that. With the Mayo Clinic regimen you tend to get your toxicity early on, and you can modify the treatment early on. With capecitabine, the converse probably happens.

Slide 10

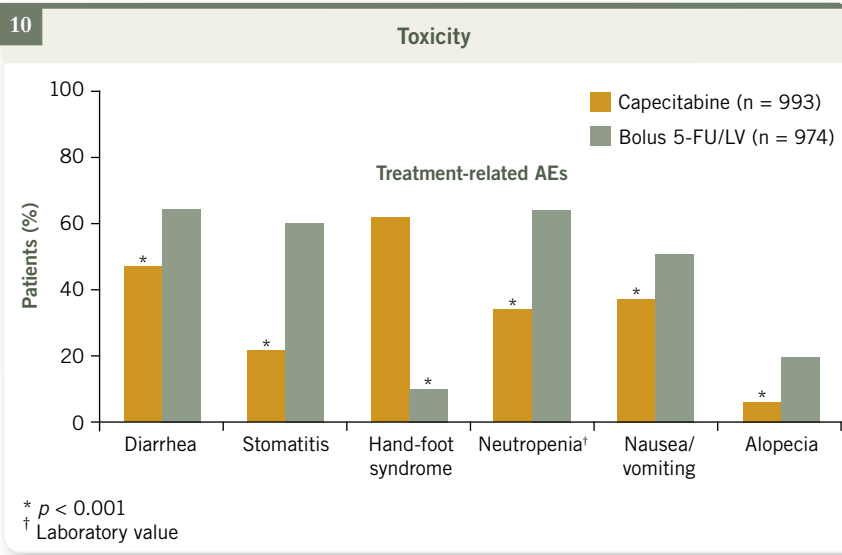
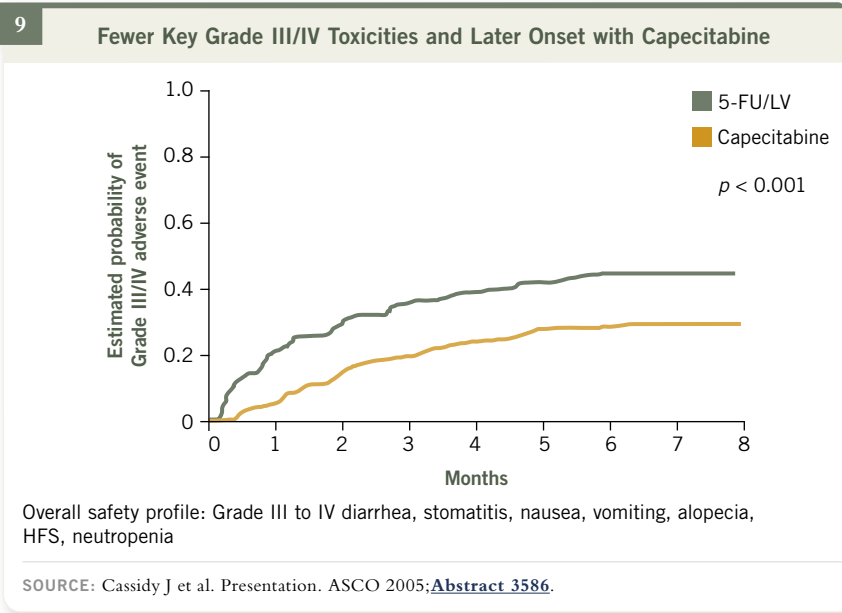
These are the side effects that were seen, which are, in general, a bit less for capecitabine but higher for hand-foot syndrome, which is what we'd expect

8

Treatment Exposure

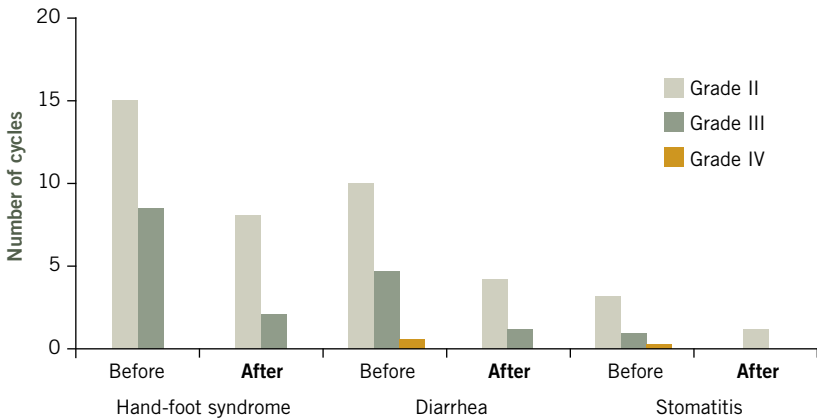
- Median dose intensity
 - Capecitabine 93% (quartiles 77-100%)
 - Bolus 5-FU/LV 92% (quartiles 78-100%)
- Patients completing >12 weeks treatment at full dose
 - Capecitabine 75%
 - Bolus 5-FU/LV 67%
- Majority of patients completed the full course of treatment
 - Capecitabine 84% completed all 8 cycles
 - Bolus 5-FU/LV 89% completed all 6 cycles

and what we've seen in all the metastatic disease trials. So there's nothing surprising.



Slide 11

Dose reduction, as specified in the protocol, results in what you'd expect. You reduce those major side effects in each of the categories as you go along.



Slide 12

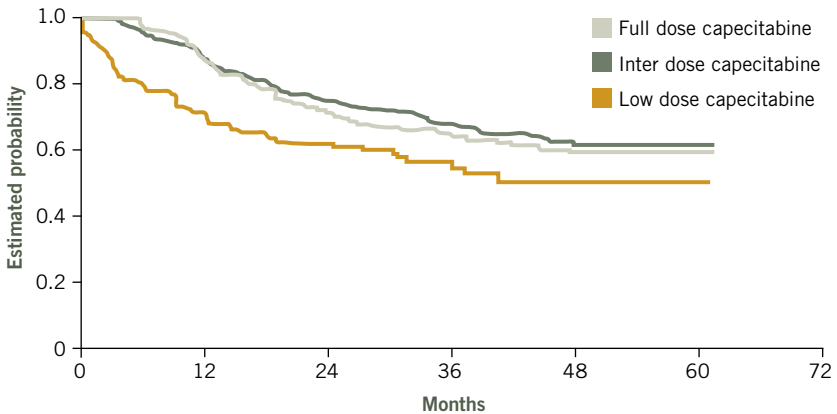
What about older patients? There are a group of patients who are over the age of 70, but there are not very many who are much older than that. So it depends on how you define “old.” When you look at those two groups — less than 70 versus over 70 — there isn’t really a huge difference between those two groups of patients. Hand-foot syndrome stands out as being more, but there’s not a lot of difference in the other side effects.

Improved Tolerability Profile of Capecitabine Maintained in Elderly

	Capecitabine (%)	Bolus 5-FU/LV (%)
	≥70 years (n = 186)	≥70 years (n = 205)
All grades		
Diarrhea	52	68
Stomatitis	23	67
Hand-foot syndrome	63	8
Nausea	33	47
Fatigue	17	19
Neutropenia	4	31

Slide 13

This is an interesting analysis, which looks at the DFS endpoint in those patients who required dose reduction. So there’s full-dose, intermediate-dose and then what’s described as low-dose capecitabine. There isn’t really a huge difference. I have to caution myself and everybody else: That’s not the same as saying if you’d started with a lower dose — aka the American dose — that somehow that would be the answer that you got. It might mean that if you started with a lower dose you would be underdosing about half the patients and that the answer might be quite different.



X-ACT Trial Conclusions

- Disease-free survival for capecitabine at least equivalent to 5-FU/leucovorin
- Capecitabine improved relapse-free survival
- Capecitabine associated with significantly fewer adverse events
- Capecitabine is an effective alternative to IV 5-FU/leucovorin as adjuvant therapy in patients with Stage III disease

Slide 14

The study met the primary objective, which was to show equivalence in the two regimens. The results also indicated a trend to superior DFS and a definite superiority of relapse-free survival. There is not an overall survival advantage, so we have to continually remind everyone that the original goal of the trial was to show equivalence — which has very adequately been done. Capecitabine will be the baseline option for those patients who currently would receive bolus 5-FU. ■

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. In ECOG-E3200, the addition of bevacizumab to FOLFOX compared to FOLFOX alone in patients with previously treated advanced colorectal cancer resulted in significant improvements in _____.
 - a. Response rate
 - b. Progression-free survival
 - c. Overall survival
 - d. All of the above
 - e. None of the above
2. In a presentation by Dr Hecht at ASCO 2005, the addition of the anti-VEGF agent PTK/ZK, or vatalanib, to FOLFOX compared to FOLFOX alone as first-line therapy resulted in significant improvements in _____.
 - a. Response rate
 - b. Progression-free survival
 - c. Overall survival
 - d. All of the above
 - e. None of the above
3. NSABP-C-07 in patients with Stage II or III colon cancer demonstrated no difference in three-year disease-free survival for patients receiving 5-FU/leucovorin compared to FLOX.
 - a. True
 - b. False
4. In NSABP-C-07, significantly more deaths occurred during treatment with FLOX compared to 5-FU/leucovorin.
 - a. True
 - b. False
5. In NSABP-C-07, the protocol-stipulated dose of oxaliplatin was _____ than in the MOSAIC trial.
 - a. Higher
 - b. Lower
 - c. Equivalent
6. In a 2 x 2 factorial design, NSABP-R-04 will evaluate preoperative radiotherapy with either capecitabine or 5-FU with or without _____.
 - a. Cetuximab
 - b. Bevacizumab
 - c. Oxaliplatin
7. In the X-ACT adjuvant trial comparing capecitabine versus bolus 5-FU in patients with Dukes' C colon cancer, capecitabine resulted in _____.
 - a. Trend to superior disease-free survival
 - b. Trend to superior overall survival
 - c. Superior relapse-free survival
 - d. All of the above
 - e. None of the above
8. In the X-ACT trial, bolus 5-FU compared to capecitabine was associated with a significantly higher rate of _____.
 - a. Diarrhea
 - b. Stomatitis
 - c. Neutropenia
 - d. Nausea/vomiting
 - e. Alopecia
 - f. All of the above
9. NSABP-C-09 evaluated capecitabine plus oxaliplatin with or without HIA floxuridine in patients with resected or ablated liver metastases.
 - a. True
 - b. False
10. Based on the MOSAIC trial data, in November 2004, the FDA approved oxaliplatin in combination with infusional 5-FU/leucovorin for the adjuvant treatment of _____ colon cancer.
 - a. Stage II
 - b. Stage III
 - c. Stage II/III
11. MD Anderson will be conducting a neoadjuvant trial evaluating chemoradiation with bevacizumab in patients with rectal cancer.
 - a. True
 - b. False

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GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment and incorporate these data into management strategies in the local and advanced disease settings. 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including the use of oxaliplatin-containing regimens, and the use of capecitabine or intravenous 5-FU, and explain the absolute risks and benefits of these regimens to patients. 5 4 3 2 1 N/A
- Integrate emerging data on biologic therapies into the management strategies for patients with advanced colorectal cancer. 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Lee M Ellis, MD	5 4 3 2 1	5 4 3 2 1
Norman Wolmark, MD	5 4 3 2 1	5 4 3 2 1
James Cassidy, MD	5 4 3 2 1	5 4 3 2 1

COMMENTS ABOUT THESE AND OTHER FACULTY MEMBERS

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity.	5	4	3	2	1	N/A
Related to my practice needs.	5	4	3	2	1	N/A
Will influence how I practice.	5	4	3	2	1	N/A
Will help me improve patient care.	5	4	3	2	1	N/A
Stimulated my intellectual curiosity.	5	4	3	2	1	N/A
Overall quality of material.	5	4	3	2	1	N/A
Overall, the activity met my expectations.	5	4	3	2	1	N/A
Avoided commercial bias or influence.	5	4	3	2	1	N/A

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