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Colorectal Cancer™ UPDATE

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

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POINT-COUNTERPOINT:
ADJUVANT THERAPY OF STAGE II COLON CANCER

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CME Certified

Colorectal Cancer Update

A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

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

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 2 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Marshall, Saltz, Cassidy, Ravdin and Wolmark 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.

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UPCOMING EDUCATIONAL EVENTS

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

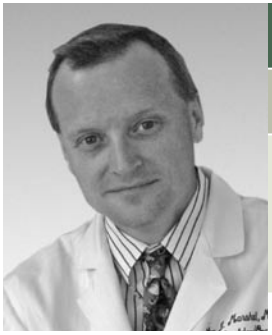
NSABP Semi-Annual Meeting
April 27-30, 2007
Jacksonville, Florida
Event website: **www.nsabp.pitt.edu/Future_Meetings.asp**

SWOG Spring Group Meeting
May 2-6, 2007
Chicago, Illinois
Event website: **www.swog.org/visitors/Spring07GpMtg.asp**

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

ECOG Semi-Annual Meeting
June 8-10, 2007
Washington, DC
Event website: **www.ecog.org**

RTOG Semi-Annual Meeting
June 21-24, 2007
Philadelphia, Pennsylvania
Event website: **www.rtog.org**



INTERVIEW

John L Marshall, MD

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

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Track 2 Use of bevacizumab after discontinuation of chemotherapy or beyond disease progression

Track 3 Incorporation of panitumumab into clinical practice

Track 4 Infusion reactions with cetuximab versus panitumumab

Track 5 Treatment of potentially curable metastatic disease

Track 6 Management of synchronous primary and metastatic disease

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Track 2

DR LOVE: What is your general approach to management of metastatic colorectal cancer in clinical practice?

DR MARSHALL: I tend to follow an OPTIMOX-type strategy. Whether I'm administering OPTIMIRI or OPTIMOX, I back off from irinotecan or oxaliplatin after I see the optimum response, which is usually around four months of therapy. Generally, I continue with 5-FU and bevacizumab.

The recent OPTIMOX-2 data have given us permission to not administer any agent during the chemotherapy-free window, so you could stop treatment

altogether (Maindrault-Goebel 2006; [1.1]). However, as a clinical trialist, I believe that may be the ideal opportunity to bring in new medicines.

We are beginning to design more trials to test new agents in the chemotherapy-free window to see if they are able to stabilize or prolong progression.

When patients reprogress on one regimen, I change to the other base chemotherapy. However, many physicians like to resume the old chemotherapy: If the patient was on oxaliplatin, they bring back the oxaliplatin, and if the patient was on irinotecan, they bring back the irinotecan.

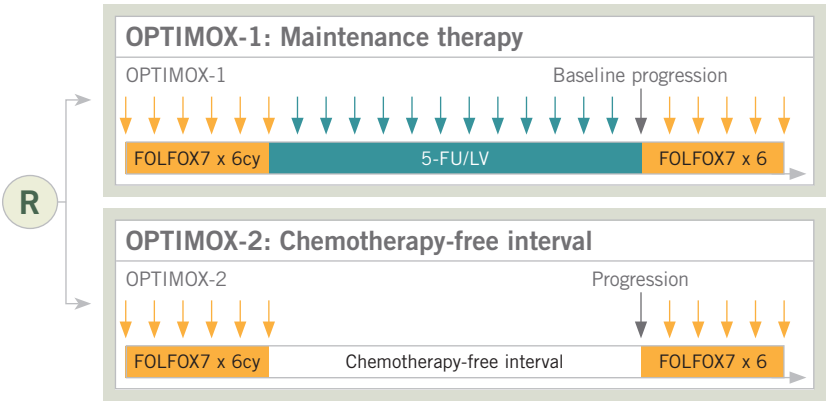
DR LOVE: When you switch regimens, do you continue the bevacizumab?

DR MARSHALL: At that point, I frequently bring in an EGFR blocker, even though that has not yet been established by the data. More recent trials support the practice of not waiting until the disease becomes irinotecan refractory before bringing in an EGFR inhibitor. In fact, data for the EGFR inhibitors now indicate that in almost every setting they've been tested in — last line, second line, and now we have some first-line data — they've shown a positive impact (Tabernero 2004).

1.1

OPTIMOX-2: A Phase II Study of Maintenance Therapy or Chemotherapy-Free Intervals After FOLFOX for Patients with Metastatic Disease

OPTIMOX-2 study design



"Maintenance therapy improves PFS but duration of disease control is the same with or without maintenance. It is too early to know the impact of chemotherapy-free interval on survival. Median chemotherapy-free interval is 4.6 months and could be better in patients with no adverse prognostic factors. Duration of disease control is higher than in the previous OPTIMOX-1 study and shows that the oxaliplatin stop and go strategy is active.

Based on these results we believe that we can safely stop modified FOLFOX7 after only 6 cycles, especially in patients with a response or stabilization and no adverse prognostic factors. Chemotherapy-free interval is maintained in the next GERCOR study, DREAM, which will evaluate maintenance therapy with targeted drugs alone."

SOURCE: Maindrault-Goebel F et al. Presentation. ASCO 2006;**Abstract 3504**.

DR LOVE: When you make this decision with the patient whose disease is progressing, do you factor in how they responded to the treatments?

DR MARSHALL: Yes. If they progressed rapidly or didn't respond well, I'm less enthusiastic about keeping a drug on board, so I'll switch it. But if they've received a nice benefit from a drug, I don't usually give that up.

With bevacizumab, you can recognize a change in the biology of these tumors — they slow down. It's not necessarily that the tumors respond further, it's just that you have "turned them off," so I hesitate to pull patients off of bevacizumab. Clinically, that's what we're seeing — this quieting of colon cancer and long-term survivors with metastatic disease.

Track 3

DR LOVE: Where does panitumumab currently fit into your treatment algorithm?

DR MARSHALL: One of the most common questions I'm getting right now is, "I've used cetuximab. Should I now administer panitumumab?" My answer has been no.

However, I'm beginning to gain a little more experience with this patient population, and I administer a lot of BOND-2, last-line regimens (Saltz 2005). Recognizing that BOND-2 is with anti-EGFR or anti-VEGF treatment-naïve patients, I will not let patients continue to progress without combining EGF and VEGF inhibitors at some point. Clinically, when you put the two antibodies together, you see fairly consistent activity, even in the nonnaïve and the previously exposed patient.

I have been using cetuximab, and now I have patients who would like to take the week off. They're coming to me and saying, "Can I switch off and go to panitumumab?" and I say, "Sure." What's interesting is that when I do so, I see a little more renewed activity. I'm also seeing a renewed rash. A lot of patients whose cetuximab rash quieted down are now receiving panitumumab.

Track 5

DR LOVE: Can you discuss your approach to potentially curable metastatic disease?

DR MARSHALL: In general, I am increasingly adopting a chemotherapy-first approach. In my opinion, patients who are going to benefit the most from a surgical approach — a resection of the metastatic lesion — are those who respond to chemotherapy (Delaunoit 2005).

The marker, if you will, of a responding metastatic lesion is encouraging and powerful, so more and more patients are being offered surgery for oligometastatic disease. We're now having an opposite problem — a good problem.

I'm taking care of a young man right now who has a rectal tumor with two liver metastases and is on a capecitabine trial.

After two rounds of CAPOX and bevacizumab, he has had such a good response that we can barely see his two liver metastases, and his rectal lesion has shown a nice response.

If I keep going too much more with chemotherapy, we're not going to be able to find the lesions to resect. Not that I think chemotherapy cured the patient, but the lesions are now not detectable. What a good problem to have. Now we have to dance that dance and make sure we don't mismanage the rectal area and that he still has a shot at a liver resection.

Our decision is that after four cycles we're going to restage his cancer, then pause and administer neoadjuvant radiation therapy, maintaining some capecitabine and probably some oxaliplatin during that radiation therapy. We will restage after that, and then most likely perform a rectal resection, and at the same time, instead of a lobectomy, perform radiofrequency ablation on the residual tumors.

DR LOVE: What is seen histologically in people who have clinical complete responses in the liver?

DR MARSHALL: A lot of these people still have residual disease, but some don't.

DR LOVE: How do you decide whether or not to resect the area?

DR MARSHALL: It's a good question. For this particular patient, I called the surgeon and asked, "What would you do if you got in there and you couldn't see it?" He knows anatomically where the lesions were, so he can resect the region that they were in. It's also important to note that even when traditional imaging shows nothing, an ultrasound can find areas of disease. I was a little nervous when this patient's response was so good, thinking that we then wouldn't be able to perform what we hoped would be a curative resection on his liver.

Track 8

DR LOVE: What is your approach to Stage II disease?

DR MARSHALL: On one side, it's clear that we're dramatically overtreating patients. We're administering chemotherapy to 100 patients to help what may be three to six people in the long run. I'm not fundamentally against that, but I would like to figure out who may benefit and administer chemotherapy to them. We are trying to recruit to a clinical trial (ECOG-E5202) that groups patients according to the tumor's genetic markers, and we've had some luck.

For the most part, patients are interested in pursuing chemotherapy. Patients with education — whether it's fair education or not — will opt to receive chemotherapy. My feeling is that community physicians are treating more of

these people than they were before. They're also using a lot more capecitabine in this patient population.

DR LOVE: So for the patient at lower risk, some physicians are opting for capecitabine alone because they "want to do something."

DR MARSHALL: Yes, which doesn't make sense to me. If you're going to do it, do it. The data say that FOLFOX would pick up a couple more people than capecitabine by itself. I've heard Aimery de Gramont say this, and I agree with him. If I were a Stage II patient, I'd rather receive three months of FOLFOX than six months of capecitabine alone.

DR LOVE: What about using capecitabine with oxaliplatin (CAPOX) in the adjuvant setting?

DR MARSHALL: The metastatic data with capecitabine and oxaliplatin, whether it's infusion or bolus, are positive. So it is probably fine, and then I put in my little asterisk and say, "But I've been wrong before." ■

SELECT PUBLICATIONS

André T et al. **Phase II study of an optimized 5FU-oxaliplatin strategy (OPTIMOX2) with celecoxib in metastatic colorectal cancer: A GERCOR study.** *Proc ASCO* 2004;**Abstract 3554**.

De Gramont A et al. **Targeted agents for adjuvant therapy of colon cancer.** *Semin Oncol* 2006;33(Suppl 11):42-5. **Abstract**

Delaunoit T et al. **Chemotherapy permits resection of metastatic colorectal cancer: Experience from Intergroup N9741.** *Ann Oncol* 2005;16(3):425-9. **Abstract**

Lenz HJ. **Anti-EGFR mechanism of action: Antitumor effect and underlying cause of adverse events.** *Oncology (Williston Park)* 2006;20(5 Suppl 2):5-13. **Abstract**

Maindrault-Goebel F et al. **OPTIMOX-2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC). A GERCOR study.** *Proc ASCO* 2006;**Abstract 3504**.

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.** Gastrointestinal Cancers Symposium 2005a;**Abstract 169b**.

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

Tabernero JM et al. **An international phase II study of cetuximab in combination with oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX-4) in the first-line treatment of patients with metastatic colorectal cancer (CRC) expressing epidermal growth factor receptor (EGFR). Preliminary results.** *Proc ASCO* 2004;**Abstract 3512**.

Vincenzi B et al. **The new era in the treatment of advanced colorectal cancer patients: The role of monoclonal antibodies.** *Expert Opin Emerg Drugs* 2006;11(4):665-83. **Abstract**

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. No abstract available

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

Leonard B Saltz, MD

Dr Saltz is Professor of Medicine at the Weill Medical College of Cornell University and Attending Physician and Colorectal Disease Management Team Leader at Memorial Sloan-Kettering Cancer Center in New York, New York.

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Track 1 Introduction

Track 2 XELOX-1/NO16966: CAPOX or FOLFOX4 with or without bevacizumab as first-line therapy

Track 3 Continuation of therapy until progression on a first-line trial of IFL with or without bevacizumab

Track 4 Impact of the addition of bevacizumab to chemotherapy on response rate

Track 5 Clinical implications of XELOX-1/NO16966 and the use of CAPOX

Track 6 Evaluating alternative schedules of capecitabine

Track 7 Clinical implications of XELOX-1/NO16966 and the use of bevacizumab in combination with first-line chemotherapy

Track 8 Use of chemotherapy holidays

Track 9 Safety of a 10-minute infusion of bevacizumab

Track 10 Phase I study of oral agent S-1 in combination with oxaliplatin and bevacizumab in patients with advanced solid tumors

Track 11 Evaluation of routine antihistamine premedication after the first two doses of cetuximab

Track 12 Geographic variation in cetuximab-associated infusion reactions

Track 13 Pharmacokinetics of cetuximab administered every two weeks

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Track 15 Predictors of response to tyrosine kinase EGFR inhibitors

Track 16 Impact of physical activity on colon cancer recurrence and survival

Select Excerpts from the Interview

Track 2

DR LOVE: Can you talk about the background of the XELOX-1/NO16966 study that you presented at the ASCO GI Cancers Symposium?

DR SALTZ: XELOX-1/NO16966 was a study that Jim Cassidy and I led together (Saltz 2007; Cassidy 2007). It started out as a straightforward comparison of CAPOX and FOLFOX in the first-line metastatic setting and was designed to be a noninferiority study. Shortly after we began accrual, new data

emerged indicating that bevacizumab added a clinically meaningful benefit to IFL chemotherapy (Hurwitz 2004).

Those findings caused us to rethink our study and repackage it as a two-by-two randomization, in which patients were randomly assigned to CAPOX or FOLFOX first, then to that regimen combined with either placebo or bevacizumab (2.1).

The study had two primary endpoints, with progression-free survival being the target in both cases. One endpoint was noninferiority of CAPOX versus FOLFOX, and Jim Cassidy presented those data at the 2007 ASCO GI Symposium (Cassidy 2007). At that meeting, I discussed the superiority question of adding bevacizumab to front-line oxaliplatin-based chemotherapy (Saltz 2007). The end of the story is that it was a positive study.

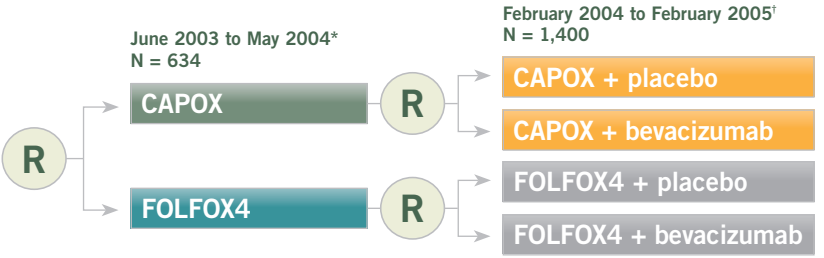
The primary endpoint of progression-free survival was improved with the addition of bevacizumab to front-line oxaliplatin-based therapy. The *p*-value was 0.0023, and the hazard ratio was 0.83. The incremental improvement was 1.4 months. This confirms the original study of IFL with or without bevacizumab that Dr Hurwitz published (Hurwitz 2004; [2.2]).

However, the study was not as positive as we had hoped it would be in two respects. First, we would have liked to see more improvement from the addition of bevacizumab than we did. Second, we would have liked to see patients in all the arms do better than they did.

2.1

Phase III Trial of CAPOX/Bevacizumab versus FOLFOX4/Bevacizumab as First-Line Therapy for Patients with Metastatic Colorectal Cancer

Protocol IDs: NO16966; NCT00069095
Accrual: 1,400 (Closed)



CAPOX = oxaliplatin and capecitabine; FOLFOX4 = oxaliplatin, leucovorin, fluorouracil

* Initial two-arm, open-label study

† Protocol amended to a two-by-two placebo-controlled design after Phase III bevacizumab data became available

SOURCES: NCI Physician Data Query, January 2007; Saltz LB et al. Presentation. Gastrointestinal Cancers Symposium 2007;**Abstract 238**.

2.2

Progression-Free Survival and Response Rates in First-Line Trials of Metastatic Colorectal Cancer (CRC) Treated with Chemotherapy with or without Bevacizumab

Outcome variable	NO16966 (Saltz 2007) First-line CRC CT* vs CT* + bev	AVF2107 (Hurwitz 2004) First-line CRC CT† vs CT† + bev
PFS		
HR	0.83	0.58
p-value	0.0023	<0.0001
PFS (on treatment)		
HR	0.63	0.54
p-value	<0.0001	<0.0001
Response rate	49% vs 47%	35% vs 45%
p-value	0.99	0.004

CT = chemotherapy; bev = bevacizumab; PFS (on treatment) = progression-free survival; patients were censored at time of last scan showing nonprogressive disease if progressive disease or any-cause death occurred beyond 28 days after final dose of treatment.

* FOLFOX or CAPOX

† IFL

SOURCES: Saltz LB et al. Presentation. Gastrointestinal Cancers Symposium 2007;**Abstract 238**; Hurwitz H et al. *N Engl J Med* 2004;350(23):2335-42. **Abstract**

We had a sense that if we took FOLFOX, which was a superior regimen to IFL, and added bevacizumab, we would start to see a median target progression-free survival of around one year, and we did not see that in the study. The median progression-free survival was 9.4 months. So bevacizumab helps, it is appropriate to add to front-line therapy and it improves progression-free survival in that population, but we wanted to understand why the differences were more modest than we'd hoped.

This difference is, in all likelihood, accountable by early discontinuation of chemotherapy before progression in patients in our study. When we consider what happened on this trial, more than half of the patients discontinued for reasons other than progression or death, and our best hypothesis is that much of this discontinuation was due to what are likely to be oxaliplatin-based known toxicities — neurotoxicity, primarily — and although the study permitted investigators to discontinue oxaliplatin and continue the fluoropyrimidines and the bevacizumab, most of the investigators didn't do that.

What we see in the study is that when oxaliplatin stopped, everything stopped — and everything stopped several months before progression or death.

DR LOVE: What about in the Hurwitz trial?

DR SALTZ: In the Hurwitz study, when people stopped, it was almost always for either progression or death. I believe that what this indicates is that the oxaliplatin-based regimens are a bit more subtle and require careful under-

standing to be used in their optimal sense. In order to obtain the most benefit from the addition of bevacizumab, we would hypothesize that it is important to continue both the bevacizumab and whatever active chemotherapy drugs are tolerable until progression.

We see a big difference in terms of how many patients received treatment up until progression on this trial versus the Hurwitz study, and we hypothesize that it may largely account for the more modest benefit seen in progression-free survival.

DR LOVE: It makes sense when you think about it — if you continue the fluoropyrimidine and bevacizumab, you would delay progression compared to stopping everything. What fraction of patients were entered from the United States in your trial versus in Hurwitz's?

DR SALTZ: The Hurwitz study was predominantly a United States study. Our study accrued 90 percent outside the US.

Track 5

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

DR SALTZ: First, the study satisfies me regarding the noninferiority of CAPOX versus FOLFOX. That does not mean everybody should run out and use CAPOX — it means it is an option that can be considered and that may be appropriate for some patients.

I believe capecitabine is a good alternative for motivated patients who can be counted on to take their medications, to be aware of toxicity, to hold their medication, to contact their treating physician if toxicity develops, to get the numbers right, to not miss a dose, to not double up on doses and to adhere to the regimen of 14 days on, seven days off.

I still tend to favor either FOLFOX or FOLFIRI, which I use to equal degrees, as my front-line cytotoxic regimen. However, previously, I would tell people that I haven't seen data to tell me that CAPOX is an acceptable alternative, but now I have.

Track 7

DR LOVE: What are the clinical implications of the bevacizumab data from XELOX-1/NO16966?

DR SALTZ: The study confirms prior studies that showed bevacizumab increases progression-free survival (Giantonio 2005; Hurwitz 2004). I believe it justifies my continued feeling that bevacizumab is an appropriate component of first-line chemotherapy except for patients that have a significant contraindication, such as a history of significant arterial thrombotic events, serious wound-healing issues and so on.

As with other trials, it indicates nothing about whether bevacizumab should be continued in multiple lines of therapy. The revised package insert for bevacizumab says it is approved for first- or second-line therapy — it does not say first *and* second-line therapy — so it is my practice to use bevacizumab in one line of therapy. I use it in first-line therapy unless there is a contraindication. If that contraindication is resolved so that bevacizumab becomes appropriate to use in second- or third-line therapy, then I might consider it. ■

SELECT PUBLICATIONS

Cassidy J et al. **XELOX vs FOLFOX4: Efficacy results from XELOX-1/NO16966, a randomized phase III trial in first-line metastatic colorectal cancer (MCRC).** Gastrointestinal Cancers Symposium 2007;**Abstract 270**.

D'Angelica M et al. **Lack of evidence for increased operative morbidity after hepatectomy with perioperative use of bevacizumab: A matched case-control study.** *Ann Surg Oncol* 2007;14(2):759-65. **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**.

Goldberg RM. **Advances in the treatment of metastatic colorectal cancer.** *Oncologist* 2005;10(Suppl 3):40-8. **Abstract**

Gotlib V et al. **Skin rash secondary to bevacizumab in a patient with advanced colorectal cancer and relation to response.** *Anticancer Drugs* 2006;17(10):1227-9. **Abstract**

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

Kuo T, Fisher GA. **Current status of small-molecule tyrosine kinase inhibitors targeting epidermal growth factor receptor in colorectal cancer.** *Clin Colorectal Cancer* 2005;5(Suppl 2):62-70. **Abstract**

Patel DD, Goldberg RM. **Cetuximab-associated infusion reactions: Pathology and management.** *Oncology (Williston Park)* 2006;20(11):1373-82. **Abstract**

Reidy DL et al. **Bevacizumab 5 mg/kg can be safely infused over ten minutes.** Gastrointestinal Cancers Symposium 2007;**Abstract 355**.

Saltz LB et al. **Bevacizumab in combination with XELOX or FOLFOX4: Efficacy results from XELOX-1/NO16966, a randomized phase III trial in the first-line treatment of metastatic colorectal cancer (MCRC).** Gastrointestinal Cancers Symposium 2007;**Abstract 238**.

Saltz LB. **Metastatic colorectal cancer: Is there one standard approach?** *Oncology (Williston Park)* 2005;19(9):1147-54. **Abstract**

Saltz LB et al. **Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group.** *N Engl J Med* 2000;343(13):905-14. **Abstract**

Scappaticci FA et al. **Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab.** *J Surg Oncol* 2005;91(3):173-80. **Abstract**

Tyagi P, Grothey A. **Commentary on a phase III trial of bevacizumab plus XELOX or FOLFOX4 for first-line treatment of metastatic colorectal cancer: The NO16966 trial.** *Clin Colorectal Cancer* 2006;6(4):261-4. **Abstract**

Vallbohmer D et al. **Molecular determinants of cetuximab efficacy.** *J Clin Oncol* 2005;23(15):3536-44. **Abstract**

Van Cutsem E et al. **Oral capecitabine: Bridging the Atlantic divide in colon cancer treatment.** *Semin Oncol* 2005;32(1):43-51. **Abstract**

INTERVIEW

James Cassidy, MD

Dr Cassidy is Cancer Research UK Professor of Oncology and Academic Head of the Centre for Oncology and Applied Pharmacology in the Division of Cancer Sciences and Molecular Pathology at the University of Glasgow in Bearsden, Glasgow.

Tracks 1-14

Track 1 Introduction

Track 2 XELOX-1/NO16966: CAPOX or FOLFOX4 with or without bevacizumab as first-line therapy

Track 3 Comparable efficacy and tolerability of CAPOX and FOLFOX

Track 4 Geographic variation in the tolerability of fluoropyrimidines

Track 5 Potential impact of discontinuing bevacizumab and chemotherapy concomitantly before progression

Track 6 Continuation of bevacizumab with a fluoropyrimidine after discontinuation of oxaliplatin off protocol

Track 7 Role of xaliproden as a neuroprotectant during oxaliplatin administration

Track 8 Efficacy of xaliproden in the prevention of and recovery from neuropathy

Track 9 AVANT adjuvant trial: FOLFOX with or without bevacizumab or CAPOX with bevacizumab

Track 10 Bevacizumab and long-term safety

Track 11 Potential advantages of panitumumab, a fully humanized monoclonal antibody against EGFR

Track 12 Incorporation of combination biologic therapies in adjuvant clinical trials

Track 13 Oral small-molecule pan-VEGFR tyrosine kinase inhibitor AZ2171

Track 14 Novel agents in development for colorectal cancer

Select Excerpts from the Interview

Track 3

DR LOVE: Can you review the data you presented at the ASCO GI Cancers Symposium on the XELOX-1/NO16966 trial?

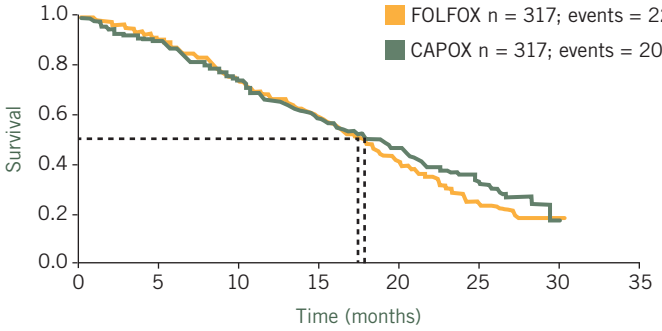
DR CASSIDY: The initial randomization was to CAPOX versus FOLFOX. There's absolutely no chance statistically that CAPOX has any inferiority, and we're even more confident now that we have overall survival statistics to back that up (Cassidy 2007; [3.1]). We're confident that CAPOX is noninferior to FOLFOX. The lines cross each other depending on the populations used — the intent-to-treat or the eligible patient populations.

One consideration in trying to pick a winner between these regimens is the side-effect profile of the regimen (3.2). In my mind, that discussion has no clear winner.

What swings it for me is what we started off with, which was the hypothesis that CAPOX would be a simpler treatment for patients and would be easier to deliver. That's what makes CAPOX the better regimen.

3.1

Overall Survival: CAPOX versus FOLFOX as First-Line Therapy for Metastatic Colorectal Cancer



HR = 0.89 [97.5% CI: 0.72–1.11] (ITT)
HR = 0.93 [97.5% CI: 0.74–1.16] (EPP)

ITT = intent-to-treat population
EPP = eligible patient population

SOURCE: With permission. Cassidy J et al. Gastrointestinal Cancers Symposium 2007;**Abstract 270**.

Track 5

DR LOVE: Can you discuss the bevacizumab results from the trial?

DR CASSIDY: A progression-free survival advantage was evident with the addition of bevacizumab to both chemotherapy regimens (Cassidy 2006a).

One issue that caused some people concern is that the quantum of benefit with the bevacizumab- and oxaliplatin-containing regimens is less than what was seen with IFL and bevacizumab in the original Hurwitz data. The absolute difference in median progression-free survival associated with bevacizumab in the Hurwitz data was about four months (Hurwitz 2004), and in our study it's about one and a half months (Saltz 2007). We've been thoroughly examining why that might be.

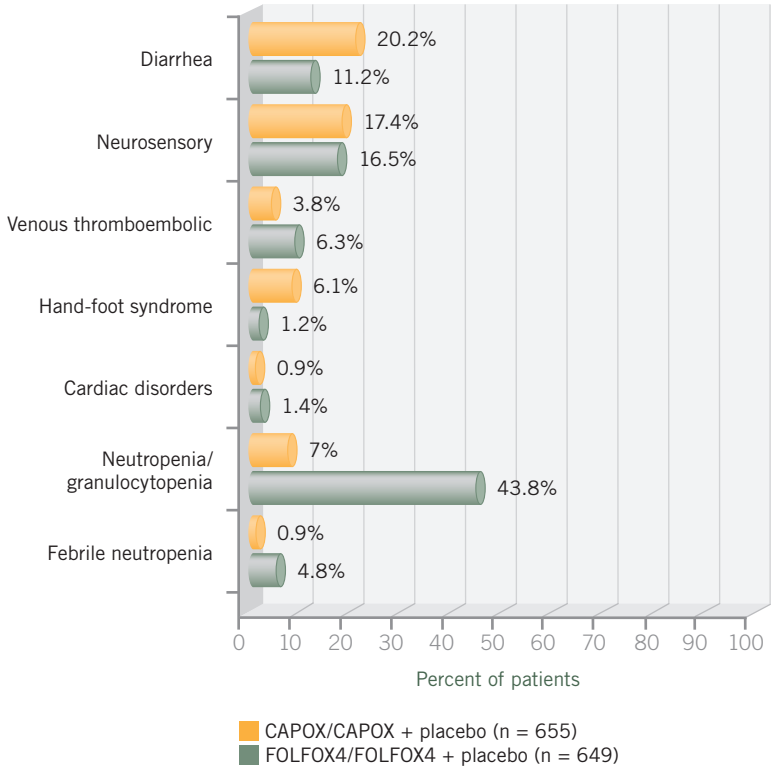
The best hypothesis we have at the moment is that although the protocol allowed patients to stop oxaliplatin or the fluoropyrimidine and continue bevacizumab, the majority of patients discontinued bevacizumab when the chemotherapy stopped. That occurred at around six months for a large proportion of the patients in the trial (Saltz 2007). In contrast, most of the patients in the Hurwitz trial continued bevacizumab for a longer time — until progression.

DR LOVE: How do you approach these cases in a clinical setting with regard to that issue?

DR CASSIDY: We would continue patients on therapy until progression. When patients develop oxaliplatin neuropathy, then we reduce the dose of oxaliplatin or we discontinue the oxaliplatin. We would continue with the fluoropyrimidine and bevacizumab.

3.2

Common Treatment-Related Grade III/IV Adverse Events: CAPOX versus FOLFOX



SOURCE: Cassidy J et al. Gastrointestinal Cancers Symposium 2007;**Abstract 270**.

Track 7

DR LOVE: Can you discuss your work with xaliproden?

DR CASSIDY: Xaliproden is a potential neuroprotector. It was initially tested in patients with amyotrophic lateral sclerosis, but it didn't work well. It's also been tested in patients with Alzheimer's disease, and the results with those patients are not yet known.

I previously presented data evaluating xaliproden as a potential neuroprotector for oxaliplatin-associated neuropathy (Cassidy 2006b). The second trial is essentially a confirmatory trial, but we are also trying to address some questions that arose from the first trial.

In the preclinical models of oxaliplatin- and platinum-associated neuropathy, the drug was active. That's what set the ball rolling in terms of trying to conduct clinical trials. If you have something that prevents the neuropathy associated with oxaliplatin, then you can do two things.

First, you can administer more oxaliplatin, which might mean more activity. Second, you can administer the same amount of oxaliplatin and avoid the neurotoxicity. I believe both of those options are sensible and reasonable. We chose to deliver the same amount of oxaliplatin and reduce the neuropathy, not to administer more oxaliplatin.

DR LOVE: What do we know about the ability of xaliproden to prevent oxaliplatin-associated neuropathy?

DR CASSIDY: The first trial demonstrated a reduction in Grade III neuropathy and an increase in Grade II neuropathy. It appeared as if you shifted patients into a lower grade of neuropathy (Cassidy 2006b). The controversial aspect of that trial was that we didn't consider the duration of neuropathy after stopping chemotherapy. For example, could you shorten the recovery period from neuropathy? We need to consider that in the second trial.

We also demonstrated that no decrease occurred in the activity of the chemotherapy (Cassidy 2006b). Oncologists worry about an agent being used to prevent toxicity affecting activity. In the first trial, we definitely convinced ourselves that was not the case. Xaliproden is an unfinished story, and the next trial should provide a definitive answer to the question about neuropathy. It's a bigger trial being conducted with more detailed neurophysiology.

Track 13

DR LOVE: Can you discuss the new anti-VEGF agent, AZD2171?

DR CASSIDY: AZD2171 blocks all three VEGF receptors. It's a bit different from bevacizumab in that it doesn't sequester the ligand, but it blocks the receptors. Theoretically, that has advantages, and in preclinical models it does appear to offer some advantages over bevacizumab.

The Horizon trials — which are planned and ongoing — are evaluating AZD2171 with FOLFOX versus FOLFOX with bevacizumab as second-line therapy (Horizon I), and the addition of AZD2171 to FOLFOX or CAPOX as first-line therapy (Horizon II). Further on in the development pipeline are plans to conduct a trial that will be a straight head-to-head comparison of FOLFOX/bevacizumab to FOLFOX/AZD2171 as first-line therapy (Horizon III).

DR LOVE: Can you talk about how it's administered and what the side effects are?

DR CASSIDY: The side effects are, so far, similar to what has been seen with bevacizumab. Vague side effects like fatigue and problems with hypertension occur — class effects you might expect. I haven't seen anything in the toxicity profile that makes me see it as significantly different from bevacizumab. It's an orally administered drug, and it's administered daily, which is clearly an advantage over bevacizumab for long-term administration. ■

SELECT PUBLICATIONS

Baka S et al. **A review of the latest clinical compounds to inhibit VEGF in pathological angiogenesis.** *Expert Opin Ther Targets* 2006;10(6):867-76. **Abstract**

Cassidy J et al. **XELOX vs FOLFOX4: Efficacy results from XELOX-1/NO16966, a randomized phase III trial in first-line metastatic colorectal cancer (MCRC).** Gastrointestinal Cancers Symposium 2007;**Abstract 270**.

Cassidy J et al. **First efficacy and safety results from XELOX-1/NO16966, a randomised 2x2 factorial phase III trial of XELOX vs FOLFOX4 + bevacizumab or placebo in first-line metastatic colorectal cancer (MCRC).** ESMO Congress 2006a;**Abstract LBA3**.

Cassidy J et al. **Randomized double blind (DB) placebo (Plcb) controlled phase III study assessing the efficacy of xaliproden (X) in reducing the cumulative peripheral sensory neuropathy (PSN) induced by the oxaliplatin (Ox) and 5-FU/LV combination (FOLFOX4) in first-line treatment of patients (pts) with metastatic colorectal cancer (MCRC).** *Proc ASCO* 2006b;**Abstract 3507**.

Cassidy J et al. **XELOX (capecitabine plus oxaliplatin): Active first-line therapy for patients with metastatic colorectal cancer.** *J Clin Oncol* 2004;22(11):2084-91. **Abstract**

Diaz-Rubio E et al. **Capecitabine (Xeloda) in combination with oxaliplatin: A phase I, dose-escalation study in patients with advanced or metastatic solid tumors.** *Ann Oncol* 2002;13(4):558-65. **Abstract**

Fan F et al. **Expression and function of vascular endothelial growth factor receptor-1 on human colorectal cancer cells.** *Oncogene* 2005;24(16):2647-53. **Abstract**

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**

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

Saltz LB et al. **Bevacizumab (Bev) in combination with XELOX or FOLFOX4: Efficacy results from XELOX-1/NO16966, a randomized phase III trial in the first-line treatment of metastatic colorectal cancer (MCRC).** Gastrointestinal Cancers Symposium 2007;**Abstract 238**.

Susman E. **Xaliproden lessens oxaliplatin-mediated neuropathy.** *Lancet Oncol* 2006;7(4):288. No abstract available

Van Cutsem E et al. **Oral capecitabine: Bridging the Atlantic divide in colon cancer treatment.** *Semin Oncol* 2005;32(1):43-51. **Abstract**

Wainberg Z, Hecht JR. **Panitumumab in colon cancer: A review and summary of ongoing trials.** *Expert Opin Biol Ther* 2006;6(11):1229-35. **Abstract**

Wedge SR et al. **AZD2171: A highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer.** *Cancer Res* 2005;65(10):4389-400. **Abstract**

Williams KJ et al. **Combining radiotherapy with AZD2171, a potent inhibitor of vascular endothelial growth factor signaling: Pathophysiologic effects and therapeutic benefit.** *Mol Cancer Ther* 2007;6(2):599-606. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the OPTIMOX-2 trial, FOLFOX therapy was reintroduced upon reprogression following a chemotherapy-free interval after initial response to FOLFOX.**
   a. True
   b. False

2. **The BOND-2 trial evaluated concurrent administration of _____.**
   a. Bevacizumab and capecitabine
   b. Capecitabine and cetuximab
   c. Bevacizumab, cetuximab and irinotecan

3. **XELOX-1/NO16966, a Phase III study of first-line treatment of metastatic colorectal cancer, showed that progression-free survival significantly improved when bevacizumab was added to oxaliplatin-based therapy.**
   a. True
   b. False

4. **Among patients treated with first-line oxaliplatin-based therapy during XELOX-1/NO16966, the hazard ratio for the addition of bevacizumab for on-treatment progression-free survival was _____.**
   a. 0.83
   b. 0.58
   c. 0.63
   d. 0.54

5. **In a randomized Phase III trial, patients treated with CAPOX had _____ than those treated with FOLFOX.**
   a. More Grade III/IV diarrhea
   b. Less Grade III/IV neutropenia
   c. Less Grade III/IV diarrhea
   d. Both a and b
   e. Both b and c

6. **In the XELOX-1/NO16966 study, the addition of bevacizumab to FOLFOX or CAPOX improved progression-free survival by about _____.**
   a. One and a half months
   b. Four months
   c. 10 months
   d. One week

7. **The Horizon I trial is evaluating _____ versus _____ as second-line therapy for patients with metastatic colorectal cancer.**
   a. FOLFOX, FOLFOX with bevacizumab
   b. AZD2171 with FOLFOX, FOLFOX
   c. AZD2171 with FOLFOX, FOLFOX with bevacizumab

8. **Xaliproden is a potential neuroprotective agent being studied for the prevention of oxaliplatin-associated neurotoxicity.**
   a. True
   b. False

9. **Studies conducted by Dr Hurwitz indicated that the addition of bevacizumab to _____ improved progression-free survival for patients with metastatic colorectal cancer.**
   a. Capecitabine
   b. 5-FU
   c. IFL
   d. FOLFOX

10. **How is AZD2171 administered?**
    a. Daily orally
    b. Daily IV infusion
    c. IV infusion every three weeks

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

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

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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Leonard B Saltz, MD	5 4 3 2 1	5 4 3 2 1
James Cassidy, MD	5 4 3 2 1	5 4 3 2 1
Peter M Ravdin, MD, PhD	5 4 3 2 1	5 4 3 2 1
Norman Wolmark, MD	5 4 3 2 1	5 4 3 2 1

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Colorectal Cancer™

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