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Colorectal Cancer™ UPDATE

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

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INTERVIEWS

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CME Certified

Colorectal Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Colorectal cancer is among the most common types of cancer in the United States, and management strategies are continuously evolving. Published results from ongoing clinical trials lead to the emergence of new therapeutic agents and regimens and changes in the 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 with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Describe the ongoing trials that are evaluating the addition of biologic agents to conventional chemotherapy for the adjuvant treatment of Stage II and Stage III colon cancer.
- Utilize biomarkers to identify appropriate patients with colorectal cancer (CRC) who may respond to treatment with EGFR inhibitors.
- Compare and contrast the benefits and risks of evidence-based chemobiologic treatment regimens for the front-line management of metastatic CRC.
- Select patients for surgical resection of isolated hepatic and extrahepatic CRC metastases based on assessment of disease burden, anatomic location and residual organ function.
- Appraise the clinical impact of perioperative systemic therapy on local recurrence rates and long-term outcomes for patients with resectable hepatic CRC metastases.
- Describe the preclinical and clinical research on the antitumor mechanisms of angiogenesis inhibitors.

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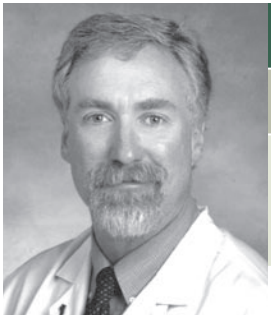


INTERVIEW

Steven A Curley, MD

Dr Curley is Professor of Surgical Oncology and Charles B Barker Chair in Surgery at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-10

Select Excerpts from the Interview

Track 1

DR LOVE: Can you discuss the evolution in the treatment of liver-only colorectal metastases?

DR CURLEY: In the late 1980s and early 1990s, patients who presented with synchronous primary and metastatic disease, had more than three or four liver metastases or had small-volume extrahepatic disease were considered incurable. Now we have data for each of those subsets that show an opportunity for long-term survival.

For example, a number of groups have examined the issue of curative surgery for patients with more than four hepatic metastases, including Rene Adam at the Paul Brousse Hospital (Adam 2003). With surgery alone, these patients have a five-year survival rate in the range of 20 to 25 percent.

However, if we add adjuvant or neoadjuvant chemotherapy, their five-year survival rate at MD Anderson is 51 percent (Pawlik 2006; [1.1]). Approximately 20 percent are alive and disease free at five years, while the other 30 percent are alive with disease. Essentially, we have changed the landscape for these patients in that they are living longer.

1.1

MD Anderson Experience: Surgical Treatment of Multiple Colorectal Liver Metastases (CRLMs)

"Similar to other contemporary reports, in the current study, the overall actuarial 5-year survival rate for patients undergoing surgery for four or more CRLMs was 50.9%. This favorable overall survival rate most likely relates to the fact that patients included in the current analysis were highly selected. Every patient had no extrahepatic disease at the time of initial surgical treatment, most received neoadjuvant chemotherapy (89.9%), almost two thirds (72.7%) had a reduction in tumor size following preoperative chemotherapy, all patients underwent thorough intraoperative ultrasonography to avoid missing small hepatic lesions, and only 19 patients had a positive surgical resection margin."

SOURCE: Pawlik TM et al. *J Gastrointest Surg* 2006;10(2):240–8. **Abstract**

Track 3

DR LOVE: What is your approach for a patient who presents with primary colorectal cancer and potentially resectable metastatic disease?

DR CURLEY: If the patient presents with an asymptomatic or minimally symptomatic primary tumor, we frequently begin with three months of systemic chemotherapy and then we restage the disease. At MD Anderson, our data from the past five years showed that in 24 percent of these patients the primary tumor essentially disappeared. We still resect the primary tumor. Surgery reveals that although some patients are pathologic complete responders, an even larger number have remaining microscopic disease. We resect the liver metastases because we believe it will impact survival.

If the patient had a symptomatic primary tumor, in most cases I would resect the primary and stage the liver disease with intraoperative ultrasonography. Then I would administer systemic chemotherapy and resect the metastases later.

DR LOVE: What if the liver metastases disappear on imaging after treatment?

DR CURLEY: Data have demonstrated that microscopic disease was still present in 85 percent of such cases (Benoist 2006), which tells us that even though we downsize the tumor, we still need to examine the area where the tumor existed and try to include that in our resection.

DR LOVE: Do you make exceptions for which you still resect the metastatic disease before using chemotherapy?

DR CURLEY: Not all tumors respond to systemic chemotherapy, and some may progress, so I always ask myself whether the tumor would become unresectable if the disease progressed. In those cases, I have performed the liver resection first, followed by systemic chemotherapy and finally resection of the primary tumor.

DR LOVE: Do you ever resect the primary tumor and the liver metastases in the same procedure?

DR CURLEY: It depends on the volume of the liver resection. The liver needs a lot of protein and energy to heal itself. We and others have shown that we can do both if we are not performing a major resection. However, when removing 75 or 80 percent of the liver, it would be too risky to perform the two procedures at once.

Track 6

DR LOVE: How many weeks do you wait between the use of bevacizumab and surgery, when feasible, and have you run into problems with wound healing?

DR CURLEY: We wait six weeks (Kesmodel 2008; [1.2]). Recently, we presented data at the Society of Surgical Oncology meeting showing that when we discontinued bevacizumab six weeks before surgery, the complication rate was not increased after major liver resections. We examined not only wound healing but also liver regeneration because of the experimental data suggesting that bevacizumab impairs regeneration (Zorzi 2008).

DR LOVE: Have you observed problems with bowel perforation in patients who received bevacizumab?

DR CURLEY: Among the patients whom we treated with FOLFOX/bevacizumab for Stage IV disease with an intact primary tumor, a few experienced perforation. We always warn patients to report certain symptoms right away. We are then forced to operate on these patients at an inopportune time, because they've received bevacizumab.

Track 7

DR LOVE: Beyond hepatic metastases, what other sites may be considered surgically resectable?

DR CURLEY: Frequently patients with liver metastases also have metastases in the lymph nodes in the porta hepatis, and a lymphadenectomy in those cases has potential for survival benefit. More commonly, we see patients who present with either synchronous or metachronous liver and lung metastases. They may have resectable liver metastases, or they may already have undergone liver resection and then present with one or two lung metastases that are technically resectable. We and several others have data that show surgical

treatment of those lung metastases can provide a long-term survival benefit for a subset of patients (Pfannschmidt 2007; [1.3]). ■

1.2

Preoperative Bevacizumab (BV) and Postoperative Complication Rates among Patients Undergoing Hepatic Surgery for Colorectal Cancer Liver Metastases

"[I]n this study, the addition of BV to neoadjuvant cytotoxic CTX in patients who have CRC liver metastases was not associated with an increase in postoperative complications. In addition, there was no association between postoperative complications and the time interval from BV discontinuation to surgery, although all patients underwent surgery at least 30 days after the last BV dose. These data suggest that BV may be administered in combination with neoadjuvant CTX before resection of CRC liver metastases without increasing postoperative morbidity.

Although the optimal timing of surgery in patients who receive BV requires additional investigation, in this study there was no statistically significant increase in complication rates in patients who received BV within 31 to 60 days (n = 40) of surgery. Therefore, on the basis of these results, we still recommend waiting at least 6 weeks from discontinuation of BV to surgery."

SOURCE: Kesmodel SB et al. *J Clin Oncol* 2008;26(32):5254-60. **Abstract**

1.3

Surgical Resection of Pulmonary Metastases from Colorectal Cancer: A Systematic Review of Published Series

"There is a substantial body of evidence from retrospective case series demonstrating that resection of colorectal pulmonary metastases can be performed safely with a low mortality rate. For a subset of highly selected patients, the overall results of a 5-year actuarial survival rate ranged between 38.3% and 63.7% (median, 52.5%). These outcomes exceed those normally associated with metastatic colorectal cancer and are well comparable with surgical resection for colorectal liver metastases."

SOURCE: Pfannschmidt J et al. *Ann Thorac Surg* 2007;84(1):324-38. **Abstract**

SELECT PUBLICATIONS

Adam R. **Chemotherapy and surgery: New perspectives on the treatment of unresectable liver metastases.** *Ann Oncol* 2003;14(Suppl 2):13-6. **Abstract**

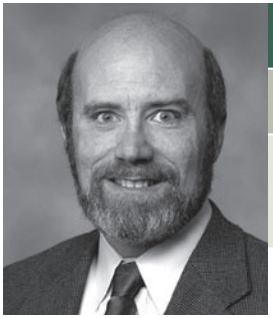
Benoist S et al. **Complete response of colorectal liver metastases after chemotherapy: Does it mean cure?** *J Clin Oncol* 2006;24(24):3939-45. **Abstract**

Kesmodel SB et al. **Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases**. *J Clin Oncol* 2008;26(32):5254-60. **Abstract**

Pawlik TM et al. **Debunking dogma: Surgery for four or more colorectal liver metastases is justified.** *J Gastrointest Surg* 2006;10(2):240-8. **Abstract**

Pfannschmidt J et al. **Surgical resection of pulmonary metastases from colorectal cancer: A systematic review of published series.** *Ann Thorac Surg* 2007;84(1):324-38. **Abstract**

Zorzi D et al. **Chemotherapy with bevacizumab does not affect liver regeneration after portal vein embolization in the treatment of colorectal liver metastases.** Society of Surgical Oncology 2008;**Abstract 66**.



INTERVIEW

Steven R Alberts, MD

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

Tracks 1-16

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the EORTC trial 40983 evaluating perioperative chemotherapy for resectable liver metastases?

DR ALBERTS: This trial was designed to determine whether we could administer three months of neoadjuvant chemotherapy to a patient with potentially resectable hepatic metastases and not hinder the ability to perform the surgery, either by causing liver toxicity or by allowing disease progression to a point at which the tumor is no longer resectable. Then, if the surgery was successful, three more months of chemotherapy was administered postoperatively, and this regimen was compared to surgery alone.

A statistically significant progression-free survival advantage was observed for the perioperative chemotherapy arm. However, a bar was set for a hazard ratio of 0.71 or less, which was not reached (Nordlinger 2008; [2.1]). With some reservations about the outcome, investigators are considering a trial of adjuvant therapy versus perioperative therapy, and the EORTC is evaluating the combination of biologic agents with the chemotherapy to try to enhance that perioperative outcome.

Another point to consider is that the patients enrolled in the trial were generally at good risk in that they typically had only one or two liver metastases. In that group — particularly patients with only one liver metastasis — the benefit of chemotherapy beyond surgery may be fairly small, depending on what agents the patient received in the past. Had we evaluated patients with three to five liver metastases, among whom the rate of recurrence is much higher, we might have seen a better outcome.

2.1

Trial Evaluating the Benefit of Perioperative FOLFOX4 for Patients with Potentially Resectable CRC Hepatic Metastases

Protocol ID: EORTC-40983; Accrual: 364 (Closed)

	Perioperative FOLFOX4 + surgery	Surgery alone	HR (95.66% CI)	*p*-value
Three-year progression-free survival				
All patients randomly assigned (n = 182, 182)	35.4%	28.1%	0.79 (0.62-1.02)	0.058
All patients who underwent resection (n = 151, 152)	42.4%	33.2%	0.73 (0.55-0.97)	0.025
Reversible postoperative complications (n = 159, 170)	25%	16%	—	0.04
Postoperative death (n = 159, 170)	1%	1%	—	—

HR = hazard ratio; CI = confidence interval

SOURCE: Nordlinger B et al. *Lancet* 2008;371(9617):1007-16. **Abstract**

Track 2

DR LOVE: What systemic strategies are being considered for converting liver metastases from unresectable to resectable?

DR ALBERTS: One approach is to try to maximize chemotherapy. Traditionally, the trials have used either FOLFOX or FOLFIRI, but a recent European trial for metastatic colorectal cancer evaluated "FOLFIRINOX" — the combination of 5-FU, leucovorin, irinotecan and oxaliplatin. The secondary endpoint in this trial was the rate of resection for patients with initially unresectable, liver-only disease, and it demonstrated a much higher rate of downsizing leading to surgery with FOLFIRINOX (Ychou 2008; [2.2]).

Another strategy is to combine biologic agents with chemotherapy (Samalin 2008; [FOLFIRINOX with cetuximab]). Based on the recent K-ras data, we may need to screen patients: If the tumor has a wild-type K-ras expression, we would consider an EGFR inhibitor, such as cetuximab or panitumumab, and if K-ras is mutated, we would consider an agent such as bevacizumab.

2.2

Phase II Study of Fluorouracil/Leucovorin, Irinotecan and Oxaliplatin (FOLFIRINOX) for Unresectable Colorectal Metastases in the Liver (N = 34)

Efficacy	Percentage
Preoperative response rate	70.6%
Hepatic resection	82.4%
Achievement of R(0) resection	26.5%
Clinical complete remission rate after surgery	79.4%
Two-year overall survival	83%

SOURCE: Ychou M et al. *Cancer Chemother Pharmacol* 2008;62(2):195-201. **Abstract**

Track 3

DR LOVE: What is your approach when you are trying to convert a potentially resectable tumor and the patient has received no previous systemic therapy?

DR ALBERTS: One of the critical steps is to evaluate the patient in collaboration with the surgeon. If the surgeon agrees that downsizing the tumor may make it resectable, then the data, mainly from two prospective clinical trials, suggest that FOLFOX and FOLFIRI are equivalent in terms of the response rates in downsizing.

I believe most clinicians in the United States are more comfortable using FOLFOX. However, FOLFIRI is not any less efficacious in this setting. Probably the best option for downsizing the tumor rapidly would be FOLFOX

and a biologic agent. Some data with disease treatment in the metastatic setting at any site, not only for colorectal liver-only metastases, suggest that combining cetuximab with FOLFIRI or FOLFOX increases the response rate (Tabernero 2007; Ciuleanu 2008).

Obviously we need to take into account the K-ras status of the tumor. In my practice, if a patient is chemotherapy naïve, I use either FOLFOX or FOLFIRI — preferably FOLFOX — combined with cetuximab. If the tumor has a K-ras mutation, then I typically add bevacizumab.

DR LOVE: What is your first-line therapy for metastatic disease in clinical practice?

DR ALBERTS: Generally I recommend chemotherapy with bevacizumab. However, with the evolving data on K-ras and evidence from two large European studies, the CRYSTAL (Van Cutsem 2008) and OPUS (Bokemeyer 2008) trials, which evaluated FOLFIRI or FOLFOX with cetuximab, we have a good rationale for using cetuximab in the front-line setting, and I have done so recently.

Tracks 9-10

DR LOVE: What are some of the research strategies now being tested in the adjuvant setting?

DR ALBERTS: We are awaiting the results of NSABP-C-08, evaluating FOLFOX with or without bevacizumab. Data from this trial may be available in 2009 or 2010. If bevacizumab demonstrates a benefit, then FOLFOX with bevacizumab will likely become the new standard. The question then would be how to build on this trial.

The other approach under investigation is FOLFOX with or without cetuximab in the NCCTG-N0147 trial. That trial is still accruing patients, and we may not have data for another three years. In the meantime, I don't sense a firm direction.

DR LOVE: Would you summarize the safety data that were presented at the last ASCO meeting from the NSABP-C-08 trial?

DR ALBERTS: Patients on the FOLFOX with bevacizumab arm received this regimen for a full year, so concern was raised about toxicities, such as bleeding and bowel perforation. However, the safety data revealed no significant increase in these side effects with bevacizumab (Allegra 2008; [2.3]).

In terms of bowel perforations, one thought is that perhaps in the advanced setting, metastatic disease is attached to the bowel wall and that, with a rapid regression, somehow leads to a perforation. Obviously, everybody is pleased about these data, and if C-08 turns out to be a positive trial, we know it is safe to use this approach. ■

2.3

Initial Safety Report of NSABP-C-08: Adjuvant FOLFOX6 with or without Bevacizumab (Bev) in Stage I to III Colorectal Cancer

Endpoint	FOLFOX6 (n = 1,356)	FOLFOX6 + bev (n = 1,354)	*p*-value
GI perforation	0.15%	0.3%	ns
Hemorrhage	1.9%	1.9%	ns
Cardiac ischemia	0.76%	1.51%	ns
CNS ischemia	0.38%	0.45%	ns
Peripheral arterial ischemia	0.23%	0	ns
Thrombocytopenia (Grade III+)	3.4%	1.4%	<0.001
Allergic reaction (Grade III+)	4.7%	3.1%	0.03
Hypertension (Grade III+)	1.8%	12%	<0.0001
Any pain (Grade III+)	6.3%	11.1%	<0.0001
Proteinuria (Grade III+)	0.8%	2.7%	<0.001
Wound complications (Grade III+)	0.3%	1.7%	<0.001
18-month mortality	1.33%	1.35%	1.0

SOURCE: Allegra CJ et al. *Proc ASCO* 2008;**Abstract 4006**.

SELECT PUBLICATIONS

Allegra CJ et al. **Initial safety report of NSABP C-08, a randomized phase III study of modified 5-fluorouracil (5-FU)/leucovorin (LCV) and oxaliplatin (OX) (mFOLFOX6) with or without bevacizumab (bev) in the adjuvant treatment of patients with stage II/III colon cancer.** *Proc ASCO* 2008;**Abstract 4006**.

Bokemeyer C et al. **KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer (mCRC) with FOLFOX with or without cetuximab: The OPUS experience.** *Proc ASCO* 2008;**Abstract 4000**.

Ciuleanu TE et al. **A randomized, open-label CECOG phase II study evaluating the efficacy and safety of FOLFOX6 + cetuximab versus FOLFIRI + cetuximab as first-line therapy in patients (pts) with metastatic colorectal cancer (mCRC).** *Proc ASCO* 2008;**Abstract 4032**.

Nordlinger B et al. **Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): A randomised controlled trial.** *Lancet* 2008;371(9617):1007-16. **Abstract**

Samalin E et al. **Interim analysis of a multicenter phase II trial evaluating cetuximab in combination with FOLFIRINOX (LV5FU + irinotecan + oxaliplatin) as first-line treatment of metastatic colorectal cancer (mCRC) patients.** Gastrointestinal Cancers Symposium 2008;**Abstract 375**.

Tabernero J et al. **Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer.** *J Clin Oncol* 2007;25(33):5225-32. **Abstract**

Van Cutsem E et al. **KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience.** *Proc ASCO* 2008;**Abstract 2**.

Ychou M et al. **Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): A phase II study in colorectal cancer patients with non-resectable liver metastases.** *Cancer Chemother Pharmacol* 2008;62(2):195-201. **Abstract**

INTERVIEW

Leonard B Saltz, MD

Dr Saltz is Professor of Medicine at 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.

Tracks 1-13

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Would you discuss the reported data from the CRYSTAL trial, including the K-ras data presented at ASCO?

DR SALTZ: This was a 1,200-patient study investigating the addition of cetuximab to FOLFIRI as first-line therapy — half of the patients received FOLFIRI and half received FOLFIRI with cetuximab. The outcome of that study was technically positive, but in my opinion it was disappointing (Van Cutsem 2007; [3.1]).

Progression-free survival, the specified primary endpoint, was improved in the overall study to a statistically significant degree, with a *p*-value of 0.048 (Van Cutsem 2007; [3.1]). The actual improvement in progression-free survival, however, was 27 days. I believe this raises the question of what is a clinically significant versus a statistically significant improvement.

I'm concerned that the skin toxicity associated with cetuximab has been underappreciated in terms of the significant impediment it imparts on quality of life. The rash can be painful or itchy, and the paronychial cracking, the paper-cut feeling in the fingers and toes, can become painful.

The CRYSTAL study demonstrated that progression-free survival is statistically significantly better with the addition of cetuximab to front-line therapy (Van Cutsem 2007; [3.1]). My interpretation, however, is that for the overall population, the incremental toxicity and probably the incremental costs are difficult to justify.

At ASCO, Dr Van Cutsem presented the results for patients for whom they had archived tissue and were able to evaluate K-ras mutation status. They studied the outcomes for the patients whose tumors had a wild-type K-ras gene versus those whose tumors had a mutant K-ras gene (Van Cutsem 2008).

The data suggest that for the patients whose tumors had a K-ras mutation, cetuximab added no value. The curves and outcomes data for those patients were the same with FOLFIRI as with FOLFIRI/cetuximab. The patients whose tumors had wild-type K-ras, approximately 60 to 65 percent of patients

3.1

CRYSTAL Trial: A Phase III Randomized Study of FOLFIRI with or without Cetuximab as First-Line Therapy for EGFR-Expressing Metastatic Colorectal Cancer

Efficacy	FOLFIRI + cetuximab (n = 599)	FOLFIRI (n = 599)	*p*-value
Median PFS	8.9 months	8.0 months	0.048
One-year PFS rate	34%	23%	—
Overall response rate*	46.9%	38.7%	0.0038

Safety: Grade III/IV adverse events	FOLFIRI + cetuximab (n = 600)	FOLFIRI (n = 602)
Neutropenia	26.7%	23.3%
Diarrhea	15.2%	10.5%
Skin reactions†	18.7%	0.2%
Infusion related	2.3%	0

PFS = progression-free survival

* Complete response + partial response

† No Grade IV skin reactions

SOURCE: Van Cutsem E et al. *Proc ASCO* 2007;**Abstract 4000**.

in the study, derived more substantial benefit when cetuximab was added (Van Cutsem 2008; [3.2]).

These data can be interpreted in two ways. First, patients whose tumors have a K-ras mutation do not benefit from cetuximab and, therefore, ought not receive cetuximab in this scenario. Second, patients whose tumors have wild-type K-ras derive a greater degree of benefit from cetuximab (Van Cutsem 2008).

Instead of a 0.9-month progression-free survival benefit, it was a 1.2-month progression-free survival benefit. So now, instead of 27 days we're up to 36 days. One must ask, should a median 36-day improvement in progression-free survival define a standard treatment? I don't believe so. ■

3.2

CRYSTAL Trial: Efficacy of FOLFIRI with or without Cetuximab as First-Line Therapy According to K-ras Status

Wild-type K-ras	FOLFIRI + cetuximab (n = 172)	FOLFIRI (n = 176)	*p*-value
Median PFS	9.9 months	8.7 months	0.017
Overall response rate*	59.3%	43.2%	0.0025
Mutant K-ras	FOLFIRI + cetuximab (n = 105)	FOLFIRI (n = 87)	*p*-value
Median PFS	7.6 months	8.1 months	0.47
Overall response rate	36.2%	40.2%	0.46

PFS = progression-free survival

* Complete response + partial response

SOURCE: Van Cutsem E et al. *Proc ASCO* 2008;**Abstract 2**.

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Chung CH et al. **Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose.** *N Engl J Med* 2008;358(11):1109-17. **Abstract**

Karapetis CS et al. **K-ras mutations and benefit from cetuximab in advanced colorectal cancer.** *N Engl J Med* 2008;359(17):1757-65. **Abstract**

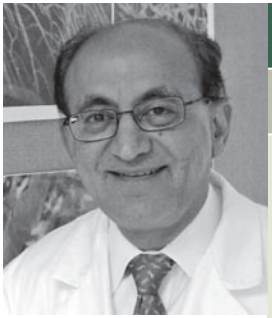
Lièvre A et al. **KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab.** *J Clin Oncol* 2008;26(3):374-9. **Abstract**

Saltz LB et al. **Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study.** *J Clin Oncol* 2008;26(12):2013-9. **Abstract**

Scope A et al. **Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption.** *J Clin Oncol* 2007;25(34):5390-6. **Abstract**

Van Cutsem E et al. **KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience.** *Proc ASCO* 2008;**Abstract 2**.

Van Cutsem E et al. **Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): The CRYSTAL trial.** *Proc ASCO* 2007;**Abstract 4000**.



INTERVIEW

Rakesh K Jain, PhD

Dr Jain is Andrew Werk Cook Professor of Tumor Biology at Harvard Medical School and Director of the Edwin L Steele Laboratory for Tumor Biology in the Department of Radiation Oncology at Massachusetts General Hospital in Boston, Massachusetts.

Tracks 1-13

Track 1	Early investigations of tumor vasculature and chemotherapy delivery
Track 2	Improvement of drug delivery by normalization of the tumor-vascular environment
Track 3	Anti-angiogenic effects of common cancer therapies
Track 4	Bevacizumab alone or in combination with chemoradiation therapy in rectal cancer: Antivascular effects and tumor response
Track 5	Correlation of biomarkers with the effect of chemoradiation therapy/bevacizumab in rectal cancer
Track 6	Circulating endothelial and progenitor cells and response to anti-angiogenic agents
Track 7	Rationale for studies of radiation therapy with bevacizumab
Track 8	Tumor normalization and edema reduction with cediranib in the treatment of glioblastoma multiforme
Track 9	Effect of anti-VEGF agents on endothelial and tumor cells
Track 10	Effect of bevacizumab on ascites and edema via reduced vascular permeability
Track 11	Unelucidated long-term risks of adjuvant bevacizumab
Track 12	Anti-VEGF therapy-associated fatigue
Track 13	In memoriam: Dr Judah Folkman

Select Excerpts from the Interview

Tracks 2-3

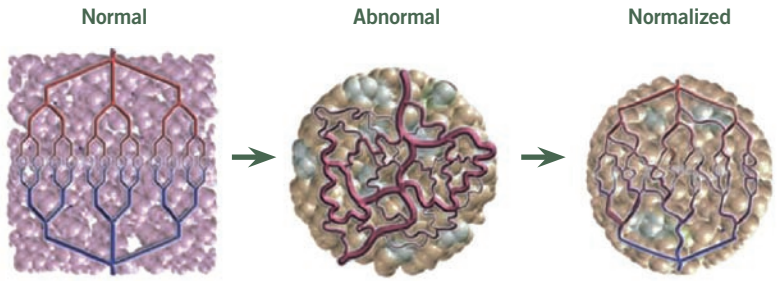
DR LOVE: What were your thoughts as you saw the clinical data evolve in the field of anti-angiogenesis, particularly the observation that in colon, breast and lung cancer bevacizumab seemed to work better with chemotherapy?

DR JAIN: In 1996, we naïvely believed that we could destroy the tumor vasculature by blocking VEGF with bevacizumab. We learned that bevacizumab reduced blood vessel density, but then there was a second wave of angiogenesis, which resulted in tumor relapse. This suggested that we needed to get rid of the source of the angiogenic molecules — VEGF, FGF, IL6, IL8, et cetera — which meant killing cells with chemotherapy or radiation therapy.

Parallel to our preclinical work, clinical reports were being published that demonstrated that combining anti-VEGF therapy with chemotherapy was effective. This was paradoxical because blood vessels are necessary to deliver chemotherapy and the oxygen necessary for radiation therapy. How could we destroy the vasculature with agents such as bevacizumab and expect better outcomes?

These clinical observations led to the hypothesis that perhaps we were destroying some vessels and repairing the remainder so they become more normal. I published the normalization hypothesis in a commentary in *Nature Medicine* in 2001 (Jain 2001). We had preclinical evidence in 1998 that if testosterone is removed from testosterone-dependent tumors, VEGF is lowered in a similar manner as with bevacizumab and the blood vessels became straighter, narrower and more normal (4.1). We observed the same phenomenon with trastuzumab, except that it worked not by lowering VEGF but by upregulating thrombospondin, which is an endogenous anti-angiogenic molecule. That's when I realized that the abnormal vasculature resulted from an abundance of proangiogenic molecules and a paucity of anti-angiogenic molecules.

4.1 **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: Reprinted by permission from **Macmillan Publishers Ltd**: Jain RK. *Nat Med* 2001;7(9):987-9. No abstract available

Tracks 4-5, 7

DR LOVE: Would you discuss the trial you were involved with evaluating chemoradiation therapy with bevacizumab for patients with rectal cancer, which was presented at ASCO this year?

DR JAIN: The protocol was a Phase I/II dose-escalation trial. The initial dose of bevacizumab was five milligrams per kilogram. The trial design was such that we could view the effect on tumor biology of bevacizumab alone or in combination with chemotherapy.

I do not know of any other trial in which so much information has been obtained from so few patients. The patients received bevacizumab initially by itself, followed by chemotherapy, radiation therapy and bevacizumab. Then a rest of seven to nine weeks was followed by surgical resection (Willett 2008; [4.2]). The results were presented at ASCO 2008. We have to be cautious in interpreting the data because it was not a randomized trial. Three-year overall survival and three-year local control rates were 100 percent, and disease-free survival was approximately 90 percent (Willett 2008).

I believe as soon as our work is written up and others can see the results of this Phase II trial, it calls for a randomized Phase III trial. We have plenty of evidence that adding radiation therapy to this neoadjuvant treatment of bevacizumab combined with chemotherapy is helping patients.

DR LOVE: At a basic level, I guess the idea would be that you're increasing the normal distribution of blood to allow radiation therapy to function more effectively?

DR JAIN: Yes, the key rationale is to improve oxygenation. You don't need to increase blood flow. You simply have to distribute it more uniformly because the blood flow is heterogeneous in tumors. Some regions receive decent amounts of oxygen, and other regions are hypoxic. Those hypoxic regions, unfortunately, can harbor tumor cells that can lead to relapse. ■

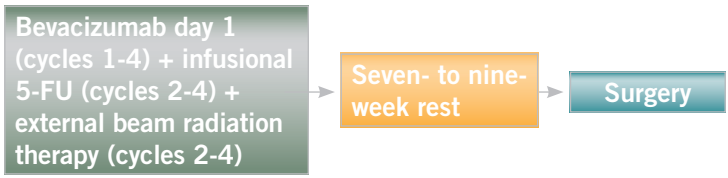
4.2

Phase I/II Trial of Neoadjuvant Bevacizumab/5-FU/Radiation Therapy in Patients with Locally Advanced Rectal Cancer

Accrual: 25 (Closed)

Eligibility

- T3/T4 rectal cancer



SOURCE: Willett CG et al. *Proc ASCO* 2008;**Abstract 4096**.

SELECT PUBLICATIONS

Giantonio BJ et al; Eastern Cooperative Oncology Group Study E3200. **Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200.** *J Clin Oncol* 2007;25(12):1539-44. **Abstract**

Jain RK. **Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy.** *Nat Med* 2001;7(9):987-9. No abstract available

Willett CG et al. **Correlation of blood and physiologic markers with effect of bevacizumab (BV) with chemoradiation therapy in rectal cancer (RC).** *Proc ASCO* 2008;**Abstract 4096**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the MD Anderson experience with surgical treatment for multiple colorectal liver metastases, the actuarial five-year survival rate for patients with four or more metastases was approximately _____.**
   a. 20 percent
   b. 30 percent
   c. 40 percent
   d. 50 percent

2. **In the CRYSTAL trial, the addition of cetuximab to first-line chemotherapy significantly improved overall survival for patients with metastatic colorectal cancer.**
   a. True
   b. False

3. **A systematic review of published series evaluating outcome of surgical resection of pulmonary metastases from colorectal cancer revealed a median actuarial five-year survival rate of approximately _____.**
   a. 10 percent
   b. 25 percent
   c. 35 percent
   d. 50 percent

4. **In the NSABP-C-08 adjuvant trial, initial safety data revealed that the addition of bevacizumab to FOLFOX resulted in a significant increase in bowel perforations.**
   a. True
   b. False

5. **The CRYSTAL trial evaluated the role of cetuximab in combination with _____ as first-line therapy for metastatic colorectal cancer.**
   a. FOLFOX
   b. CAPOX
   c. FOLFIRI
   d. CAPIRI
   e. All of the above

6. **In the CRYSTAL trial, the addition of cetuximab to first-line chemotherapy significantly improved progression-free survival by approximately _____.**
   a. Six months
   b. Three months
   c. 0.9 months
   d. None of the above

7. **In a study evaluating neoadjuvant chemotherapy with or without bevacizumab, Kesmodel and colleagues observed no increase in postoperative complications among those patients who discontinued bevacizumab at least _____ days prior to surgical resection of colorectal cancer liver metastases.**
   a. 10
   b. 30
   c. 40
   d. 60

8. **In a subgroup analysis of the CRYSTAL trial, patients whose tumors had _____ K-ras did not benefit from the addition of cetuximab to first-line chemotherapy.**
   a. Wild-type
   b. Mutant
   c. Either a or b
   d. None of the above

9. **In a Phase I/II trial, patients with rectal cancer who received neoadjuvant bevacizumab/5-FU/radiation therapy had a three-year _____ of 100 percent.**
   a. Overall survival rate
   b. Local control rate
   c. Disease-free survival rate
   d. Both a and b
   e. Both a and c

10. **Safety data from the NSABP-C-08 adjuvant trial of FOLFOX with or without bevacizumab _____ show a significant increase in bowel perforations in the patients who received bevacizumab.**
    a. Did
    b. Did not

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Colorectal Cancer Update — Issue 3, 2008

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Five-year survival of patients treated with surgery for four or more colorectal cancer liver metastases 4 3 2 1

EORTC-40983 trial of surgery with or without perioperative chemotherapy for patients with resectable colorectal cancer liver metastases 4 3 2 1

Initial safety data from the NSABP-C-08 adjuvant trial of FOLFOX with or without bevacizumab 4 3 2 1

CRYSTAL trial results: FOLFIRI with or without cetuximab for previously untreated, EGFR-expressing metastatic colorectal cancer 4 3 2 1

Antitumor response in the Phase I/II trial of bevacizumab with chemoradiation therapy in patients with locally advanced rectal cancer 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Five-year survival of patients treated with surgery for four or more colorectal cancer liver metastases 4 3 2 1

EORTC-40983 trial of surgery with or without perioperative chemotherapy for patients with resectable colorectal cancer liver metastases 4 3 2 1

Initial safety data from the NSABP-C-08 adjuvant trial of FOLFOX with or without bevacizumab 4 3 2 1

CRYSTAL trial results: FOLFIRI with or without cetuximab for previously untreated, EGFR-expressing metastatic colorectal cancer 4 3 2 1

Antitumor response in the Phase I/II trial of bevacizumab with chemoradiation therapy in patients with locally advanced rectal cancer 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: .....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: .....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will be able to:

- Describe the ongoing trials that are evaluating the addition of biologic agents to conventional chemotherapy for the adjuvant treatment of Stage II and Stage III colon cancer. .....4 3 2 1 N/M N/A
- Utilize biomarkers to identify appropriate patients with colorectal cancer (CRC) who may respond to treatment with EGFR inhibitors. .....4 3 2 1 N/M N/A
- Compare and contrast the benefits and risks of evidence-based chemobiologic treatment regimens for the front-line management of metastatic CRC. .....4 3 2 1 N/M N/A
- Select patients for surgical resection of isolated hepatic and extrahepatic CRC metastases based on assessment of disease burden, anatomic location and residual organ function. .....4 3 2 1 N/M N/A
- Appraise the clinical impact of perioperative systemic therapy on local recurrence rates and long-term outcomes for patients with resectable hepatic CRC metastases. .....4 3 2 1 N/M N/A
- Describe the preclinical and clinical research on the antitumor mechanisms of angiogenesis inhibitors. .....4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey. ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the editor and faculty for this educational activity

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Steven A Curley, MD	4 3 2 1	4 3 2 1
Steven R Alberts, MD	4 3 2 1	4 3 2 1
Leonard B Saltz, MD	4 3 2 1	4 3 2 1
Rakesh K Jain, PhD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the editor and faculty for this activity:

.....

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Professional Designation:

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

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Colorectal Cancer™

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