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Gastrointestinal Cancer™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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Gastrointestinal Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Colorectal cancer (CRC) is a common and potentially lethal type of cancer, and its clinical management is continuously evolving. Although non-CRC gastrointestinal (GI) tumors are less frequently encountered individually, the cancer-related deaths in that subcategory surpass those attributed to CRC. Published results from ongoing trials continuously lead to the emergence of novel biomarkers and new therapeutic targets and regimens, thereby altering existing management algorithms. 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, *Gastrointestinal Cancer Update* uses one-on-one discussion with leading GI oncology investigators. By providing access to the latest scientific developments and the perspectives of experts in the field, this CME activity assists medical oncologists with the formulation of up-to-date management strategies.

LEARNING OBJECTIVES

- Summarize key findings from clinical studies of emerging therapeutic regimens for pancreatic cancer.
- Assess the role of molecular markers in optimizing therapeutic decisions for patients with early or advanced CRC.
- Counsel patients with Stage II colon cancer about their individual risk of recurrence based on clinical, pathologic and genomic biomarkers, and consider adjuvant therapeutic options.
- Formulate a treatment plan for patients with synchronous primary CRC and liver-only metastases.
- Utilize clinical and molecular biomarkers to select optimal systemic treatment strategies for patients with gastric or gastroesophageal cancer.
- Communicate the benefits and risks of existing and emerging systemic interventions to patients with advanced hepatocellular carcinoma.
- Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials.

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INTERVIEW

David H Ilson, MD, PhD

Dr Ilson is Professor of Medicine at Weill Cornell Medical College and Attending Physician at Memorial Hospital in New York, New York.

Tracks 1-15

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: Would you discuss the use of preoperative therapy for patients with esophageal cancer?

DR ILSON: Most cancer centers in the United States endorse chemotherapy and radiation therapy as preoperative treatments for gastric cancer. Two recent studies from Europe give weight to that approach. One study was a small, head-to-head comparison for patients with T3-4 adenocarcinoma of the

gastroesophageal (GE) junction and cardia. Patients were randomly assigned to receive three months of chemotherapy alone followed by surgery or chemotherapy and radiation therapy followed by surgery. Although it was an underpowered study, much higher rates of pathologic complete response were seen with chemoradiation therapy — approximately 16 percent — versus chemotherapy alone — two percent. Significant trends toward better survival in the chemoradiation therapy group were also reported (Stahl 2009).

The second trial that emphasized the value of preoperative chemoradiation therapy was a randomized trial of 363 patients with adenocarcinoma or squamous cancer (Gaast 2010). The trial compared surgery alone to preoperative chemoradiation therapy followed by surgery.

Preoperative chemoradiation therapy led to an improvement in median survival — 49 months versus 26 months — and a 25 percent higher rate of curative resection compared to surgery alone. Fifteen to 20 percent incremental improvements in survival over three years were also reported. Many of us believe this large, well-conducted randomized trial establishes preoperative chemotherapy and radiation therapy as an acceptable standard.

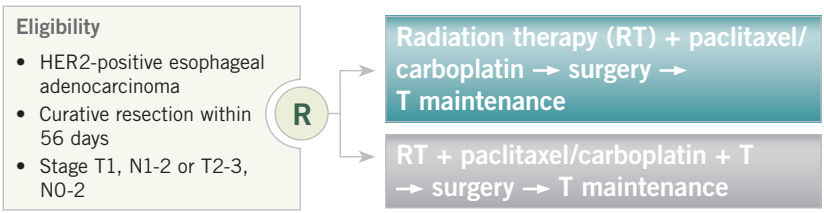
Many upcoming research studies, including an ongoing HER2-directed study in esophageal and GE junction cancers (1.1), are building on this idea to evaluate weekly carboplatin/paclitaxel and radiation therapy as preoperative therapy. Patients with HER2-positive tumors will be randomly assigned to chemotherapy and radiation therapy with or without trastuzumab.

DR LOVE: What is the rationale for the use of trastuzumab?

DR ILSON: In a recently published study of patients with HER2-positive gastric or GE junction cancer who were randomly assigned to receive cisplatin with capecitabine or fluorouracil with or without trastuzumab, the addition of trastuzumab was associated with significant benefits in response rate, progression-free survival and overall survival. A nearly three-month improvement was observed in overall survival (Bang 2010; [1.2]). As a result, the FDA has

1.1 **Phase III Trial of Multimodal Chemotherapy with or without Trastuzumab (T) in Patients with Resectable HER2-Positive Esophageal Adenocarcinoma**

Protocol IDs: RTOG-1010, NCT01196390 **Target Accrual:** 480 (Open)



www.clinicaltrials.gov, July 2011.

approved the use of trastuzumab in HER2-positive GE junction and gastric cancers for first-line treatment of metastatic disease.

DR LOVE: What is the frequency of HER2-positive gastric cancer?

DR ILSON: The rate of HER2-positive tumors is approximately 16 percent for more distal gastric cancer and as high as 20 to 32 percent for proximal GE junction tumors. More diffuse gastric cancers may be positive only six percent of the time compared to the intestinal gastric cancers, which are positive 16 percent of the time (Janjigian 2010). Overall, we expect about a 15 to 20 percent HER2 positivity rate using either FISH or IHC.

1.2

ToGA: Efficacy and Cardiac Events from a Phase III Study of the Addition of Trastuzumab to First-Line Chemotherapy for HER2-Positive Advanced Gastric Cancer

Efficacy	FC (n = 290)	FC + T (n = 294)	Hazard ratio	*p*-value
Overall survival	11.1 mo	13.8 mo	0.74	0.0046
Progression-free survival	5.5 mo	6.7 mo	0.71	0.0002
Overall response rate	35%	47%	—	0.0017
Duration of response	4.8 mo	6.9 mo	0.54	<0.0001

F = fluoropyrimidine; C = cisplatin; T = trastuzumab

Bang YJ et al. *Lancet* 2010;376(9742):687-97.

Tracks 9, 11

DR LOVE: What are some of the latest developments in the treatment of pancreatic cancer?

DR ILSON: Surgery in combination with adjuvant chemotherapy improves survival modestly. We've made improvements using systemic chemotherapy to treat metastatic disease, and the advent of erlotinib improved one-year survival. Most recently, a Phase III trial of combination chemotherapy in pancreatic cancer reported the first survival benefit in nearly 20 years.

This combination, FOLFIRINOX, improved overall survival, more than tripled response rate and almost doubled progression-free survival when compared to gemcitabine alone. One-year survival increased from 20 percent to 48 percent (Conroy 2011; [1.3]).

In the targeted therapy arena, other than erlotinib, drugs like bevacizumab and cetuximab have not yielded any benefit in metastatic disease. We are evaluating a host of new agents — PARP inhibitors and other more specifically targeted agents. The treatment of pancreatic cancer remains a huge challenge, and only a minority of patients are candidates for curative surgery.

DR LOVE: Would you discuss the issue of tolerability and dosing with the FOLFIRINOX regimen?

DR ILSON: I tend to individualize chemotherapy dosing by considering performance status and age. I believe the FOLFIRINOX parent regimen is probably intolerable for elderly patients, so dose adjustments must be made. Alternatively, you can begin with FOLFOX, assess toxicity and add the irinotecan component at cycle two or three if FOLFOX is well tolerated.

Many practitioners believe they have to follow lockstep published chemotherapy protocols, but chemotherapy is not one size fits all, and you can individualize dosing based on the tolerance of your patient.

1.3

Efficacy of FOLFIRINOX versus Gemcitabine in a Phase III Study of Initial Therapy for Stage IV Pancreatic Cancer

	Gemcitabine (n = 171)	FOLFIRINOX (n = 171)	Hazard ratio	*p*-value
ORR	9.4%	31.6%	Not reported	0.001
PFS	3.3 mo	6.4 mo	0.47	<0.001
OS	6.8 mo	11.1 mo	0.57	<0.001

ORR = overall response rate; PFS = progression-free survival; OS = overall survival

Conroy T et al. *N Engl J Med* 2011;364(19):1817-25.

Tracks 10, 12

DR LOVE: What other targeted therapies are under evaluation in pancreatic cancer?

DR ILSON: We are evaluating erlotinib in combination with gemcitabine compared to standard adjuvant gemcitabine alone. The RTOG is sponsoring a randomized national trial. That trial will also open in Europe and is supported through the Intergroup and the SWOG cooperative group (1.4).

It is hoped that this trial will address two questions: (1) Does a targeted agent that seems to work in metastatic disease contribute any benefit in the adjuvant setting? (2) Does the addition of radiation therapy after adjuvant chemotherapy improve outcomes compared to adjuvant chemotherapy alone?

DR LOVE: Outside of a research setting, how do you decide whether to add erlotinib to gemcitabine in metastatic disease?

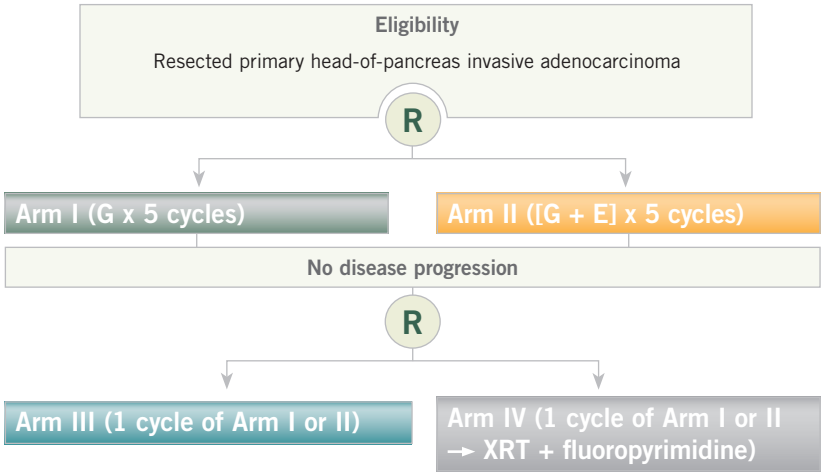
DR ILSON: Before the FOLFIRINOX study, erlotinib was the only drug associated with a survival benefit in metastatic pancreatic cancer. Erlotinib is associated with an increased survival increment of about seven percent. Given the recent data on combination chemotherapy regimens, I begin by using a combination chemotherapy regimen if the patient has a good performance status.

If the patient's disease stabilizes or responds, I may later add erlotinib, given its potential to increase benefit. We know the addition of erlotinib is beneficial in patients who receive gemcitabine monotherapy, but we don't know what it adds to combination treatment in pancreatic cancer. I administer it selectively along with gemcitabine monotherapy and usually add it later so patients aren't subjected to the additional toxicity up front. It is not known if erlotinib is useful in addition to combination therapy, but it is approved for use with gemcitabine-based treatment, so it's a consideration for use in select patients. ■

1.4

Gemcitabine (G) with or without Erlotinib (E) Followed by Chemotherapy with or without Radiation Therapy (XRT) for Patients with Resected Pancreatic Cancer

Protocol IDs: RTOG-0848, CTSU **Target Accrual:** 950 (Open)



NCI Physician Data Query, April 2010; **www.rtog.org**.

SELECT PUBLICATIONS

Bang YJ et al. **Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial.** *Lancet* 2010;376(9742):687-97.

Conroy T et al. **FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.** *N Engl J Med* 2011;364(19):1817-25.

Gaast AV et al. **Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study.** *Proc ASCO* 2010;**Abstract 4004**.

Janjigian YY et al. **HER2 status of patients with gastric cancer (GC) in the United States.** Gastrointestinal Cancers Symposium 2010;**Abstract 30**.

Stahl M et al. **Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction.** *J Clin Oncol* 2009;27(6):851-6.

INTERVIEW

David A Geller, MD

Dr Geller is the Richard L Simmons Professor of Surgery at the University of Pittsburgh School of Medicine and Co-Director of the UPMC Liver Cancer Center in Pittsburgh, Pennsylvania.

Tracks 1-15

Track 1 **Case discussion:** A 52-year-old man with mildly symptomatic Stage IV colon cancer and bilobar hepatic metastases receives preoperative FOLFOX/bevacizumab followed by a synchronous resection

Track 2 Management of asymptomatic metastatic CRC (mCRC)

Track 3 Criteria for determination of resectability status in hepatic-only mCRC

Track 4 NSABP-FC-6 study: Neoadjuvant mFOLFOX7 and cetuximab for unresectable K-ras wild-type CRC with hepatic-only metastases

Track 5 Pre- versus postoperative therapy for resected liver metastases in mCRC

Track 6 Laparoscopic liver resection of mCRC and hepatocellular carcinoma (HCC)

Track 7 **Case discussion:** A 72-year-old man with obstructing Stage IV colon cancer and a 5-cm liver lesion undergoes laparoscopic right colectomy and receives two cycles of FOLFOX/bevacizumab prior to liver resection

Track 8 Tumor response to preoperative FOLFOX/bevacizumab for mCRC

Track 9 Bevacizumab and perioperative wound-healing complications

Track 10 **Case discussion:** A 60-year-old woman with Stage II HCC and multiple comorbidities awaits transplant after laparoscopic radiofrequency ablation (RFA)

Track 11 Treatment options for HCC

Track 12 Survival rates with resection versus transplant in HCC

Track 13 Key recent advances with sorafenib as treatment for advanced HCC and ongoing studies in adjuvant therapy

Track 14 Role of transarterial chemoembolization (TACE) in HCC

Track 15 TACE with or without sorafenib in unresectable HCC

Select Excerpts from the Interview

Track 1

Case discussion

A 52-year-old man with mildly symptomatic Stage IV colon cancer and bilobar hepatic metastases receives preoperative FOLFOX/bevacizumab followed by a synchronous resection of the primary tumor and metastases.

DR GELLER: This patient was mildly symptomatic but had no bleeding or obstruction. This now presents a dilemma: What are the options for a patient who has synchronous Stage IV colon cancer and liver metastases?

One is to consider resection up front followed by chemotherapy. The second option is to administer a few cycles of chemotherapy up front, restage in three months and then perform resections. The third option is to resect the primary tumor if a hepatic surgeon is not available, then administer systemic therapy followed by a liver resection three or four months later.

We discussed this patient at a tumor board, and I favored three months of neoadjuvant FOLFOX/bevacizumab. When the primary tumor is in place, the concern is always that bevacizumab will induce bleeding, especially in rectal cancer. This man was relatively young, was not anemic and no clinical bleeding was present. In that setting, I always favor being as aggressive as possible and administer a four-drug regimen, with standard chemotherapy and a biologic agent.

In my practice, chemotherapy is discontinued three weeks prior to performing hepatic resection, and bevacizumab is held during the last cycle of chemotherapy.

The repeat imaging showed near resolution of PET activity in the primary tumor and 20 to 30 percent shrinkage in the two liver tumors. His symptoms resolved quickly, he tolerated the therapy without difficulty and we performed a synchronous resection.

The final pathology was T3N1M1, with negative margins in the colon and liver. He resumed chemotherapy with bevacizumab, which was held for the first cycle to avoid wound-healing issues. He completed his systemic treatment, and his three-, six- and nine-month scans were fine.

Tracks 3, 5

DR LOVE: In terms of determining whether liver metastases are resectable, it seems that two primary issues must be considered. First is whether a metastasis is impinging on a critical structure, such as the portal vein, and the second issue is whether, if all of the disease is removed, the patient has adequate residual hepatic function, usually requiring more than 30 percent of the liver remaining. Do you follow this paradigm?

DR GELLER: Those are both valid and important points. When I assess resectability, three issues come to mind: vascular inflow, vascular outflow and future liver remnant. Thirty percent is right on target. However, 30 percent liver remnant is much different in a 38-year-old than it is in a 70-year-old with diabetes, morbid obesity and a fatty liver. When you add chemotherapy for that older patient with comorbidities, you have to consider the quality of liver reserve — 30 percent may not be adequate.

DR LOVE: What are your thoughts about the NSABP-C-11 study?

DR GELLER: NSABP-C-11 is a Phase III clinical trial addressing the specific question of whether patients with potentially resectable hepatic colorectal cancer metastases benefit from neoadjuvant systemic therapy. We don't know the answer yet. Nordlinger's EORTC-40983 study was published in *The Lancet* in 2008 (Nordlinger 2008; [2.1]). In that multicenter trial patients were randomly assigned to either surgery alone or a "chemotherapy sandwich" approach consisting of three months of up-front chemotherapy followed by liver resection and then three months of adjuvant chemotherapy. This study did not address the specific benefits of the neoadjuvant therapy.

In the NSABP-C-11 study patients with resectable liver metastases are randomly assigned to surgery followed by systemic therapy or neoadjuvant therapy, liver resection and chemotherapy (2.2).

2.1

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

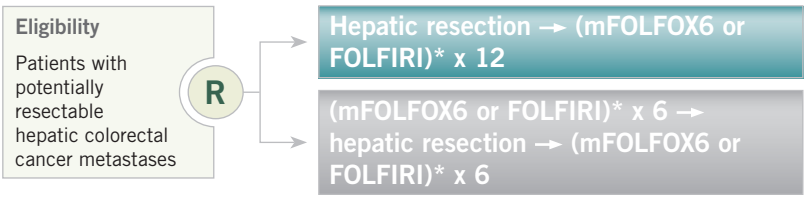
	Perioperative FOLFOX4 + surgery	Surgery alone	Hazard ratio	*p*-value
Three-year progression-free survival All patients randomly assigned (n = 182, 182)	35.4%	28.1%	0.79	0.058
All patients who underwent resection (n = 151, 152)	42.4%	33.2%	0.73	0.025
Reversible postoperative complications (n = 159, 170)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

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

2.2

Phase III Study Evaluating the Role of Perioperative Chemotherapy for Patients with Potentially Resectable Hepatic Colorectal Cancer Metastases

Protocol ID: NSABP-C-11 **Accrual:** 670 (Open)



* Dependent upon prior exposure to oxaliplatin

NOTE: Protocol amended to no longer include bevacizumab in combination with chemotherapy

NSABP Protocol Summaries, March 3, 2011.

Track 13

DR LOVE: What is your perception of the role of sorafenib in hepatocellular carcinoma (HCC)?

DR GELLER: Medical oncologists are using sorafenib frequently now for HCC. Five years ago we had no real systemic chemotherapies that showed promise in HCC, but it's important to realize that sorafenib is not a "wonder drug." In the SHARP trial, 602 patients received either sorafenib or placebo, and the data were humbling in that the survival benefit was about three months (2.3). That being said, it's important that sorafenib was approved because it opens the door for clinical trials with combination therapies.

We recently completed an adjuvant trial of sorafenib after surgical resection or local ablation, and we expect to see those data presented in the next year (2.4). Can we now administer sorafenib after resection or ablation, and does that improve survival? Can we combine it with chemoembolization or with yttrium-90? It's an exciting era. Even though no single agent is a "wonder drug," some of the best results in colon cancer occur when we combine three and four drugs, such as adding bevacizumab and/or cetuximab to the standard front-line chemotherapy. Now we're seeing that same approach for HCC. ■

2.3

SHARP Trial: Sorafenib in Advanced Hepatocellular Carcinoma

	Sorafenib (n = 299)	Placebo (n = 303)	Hazard ratio	*p*-value
Median overall survival	10.7 mo	7.9 mo	0.69	<0.001
Median time to radiologic progression	5.5 mo	2.8 mo	0.58	<0.001
Overall response rate	2%	1%	—	0.05

Llovet JM et al. *N Engl J Med* 2008;359(4):378-90.

2.4

Phase III Study of Sorafenib as Adjuvant Treatment for Hepatocellular Carcinoma

Protocol IDs: STORM, NCT00692770 **Accrual:** 1,115 (Closed)

www.clinicaltrials.gov, May 2011.

SELECT PUBLICATION

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.

INTERVIEW

Alan P Venook, MD

Dr Venook is Professor of Clinical Medicine at the University of California in San Francisco, California.

Tracks 1-17

Track 4

DR LOVE: What is known about the combination of TACE and sorafenib for HCC?

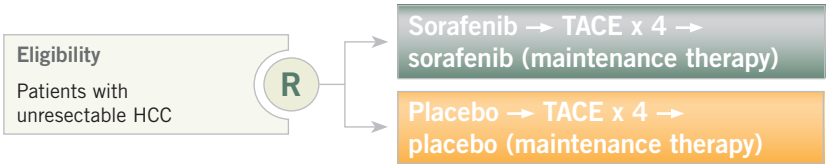
DR VENOOK: A study evaluating TACE with sorafenib in patients with advanced HCC, presented at the 2010 Gastrointestinal Cancers Symposium, showed no benefit (Okita 2010). However, sorafenib was not administered until after the embolization. Part of the issue might have been tumor revascularization because factors are proliferating after you perform embolization that would promote vessel formation, but in this study they did not use sorafenib for weeks after the embolization so it's hard to see why it would have worked.

The current ECOG-E1208 study is evaluating TACE with or without sorafenib and will attempt to address this issue. Sorafenib is administered continuously, except for the time immediately around the TACE, when there is concern about bleeding from the arterial stick (3.1).

3.1

Phase III Study of Transarterial Chemoembolization (TACE) with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC)

Protocol ID: ECOG-E1208 **Target Accrual:** 400 (Open)



www.clinicaltrials.gov, May 2011.

Tracks 11-13

Case discussion

A 41-year-old man with a 7-cm right cecal mass and pulmonary and hepatic metastases exhibits a complete response to six cycles of FOLFIRI/bevacizumab.

DR VENOOK: This was a healthy 41-year-old with the exception of the large tumor in his right colon. The tumor occupied about half to two thirds of the lumen of the cecum, yet it was asymptomatic except for some pain. He had no bleeding or obstruction.

The relevant issue here is how to approach the asymptomatic primary. One could argue, "Why start with chemotherapy?" From my perspective, you may only get one chance to administer chemotherapy. If you perform an operation and the patient has a complication, then you may not get an opportunity to administer chemotherapy.

Some data relevant to this setting were presented at ASCO 2010 (McCahill 2010). On the Phase II NSABP-C-10 study, patients with synchronous metastatic disease and primary tumors in place received FOLFOX/bevacizumab. The study evaluated the likelihood of complications and what

percentage of patients went on to surgery. The study accrued about 90 patients and reported that 14 percent had a need for intervention — 10 patients required surgical intervention (McCahill 2010). Those data support the idea that you can administer chemotherapy in this setting, although it's a balancing act. We've all observed that the primary tumors melt away in these patients.

For this patient I requested that the far extent of the disease be tattooed because I wanted to know how far it extended into the right colon. Doing so is important because if you get a spectacular response it may make sense to resect the primary as a palliative maneuver in a patient with well-controlled metastatic disease if any tumor is left in the cecum.

DR LOVE: So what happened with this patient?

DR VENOOK: We administered FOLFIRI/bevacizumab and he had an excellent response. His symptoms disappeared in the first couple weeks and he's now received six cycles of FOLFIRI/bevacizumab. He's also had marked diminution of disease in his lung and liver.

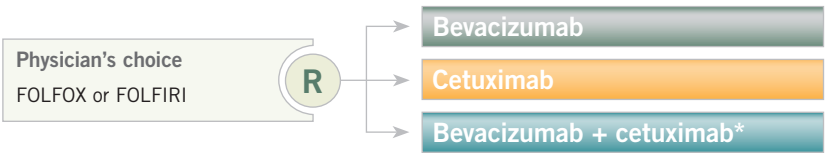
DR LOVE: Is there any interest in evaluating cases with extraordinary responses such as this one for genome sequencing?

DR VENOOK: In our CALGB-C80405 study (3.2), which is evaluating chemotherapy with bevacizumab or cetuximab, one of the correlative science studies takes the extremes — patients who fare exceptionally well or very poorly — and performs selected genome analysis. That's where we may have the best chance of finding an important genetic mutation or polymorphism. ■

3.2

CALGB-C80405 Study: Chemotherapy and Biologic Agents Alone or in Combination for the Treatment of Metastatic Colorectal Cancer

Target Accrual: 2,300 (Open)



* Arm III (bevacizumab + cetuximab) closed to accrual as of September 10, 2009

NCI Physician Data Query, May 2011.

SELECT PUBLICATIONS

McCahill LE et al. **A phase II trial of 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) chemotherapy plus bevacizumab (bev) for patients (pts) with unresectable stage IV colon cancer and a synchronous asymptomatic primary tumor: Results of NSABP C-10.** *Proc ASCO* 2010;**Abstract 3527**.

Okita K et al. **Phase III study of sorafenib in patients in Japan and Korea with advanced hepatocellular carcinoma (HCC) treated after transarterial chemoembolization (TACE).** Gastrointestinal Cancers Symposium 2010;**Abstract LBA128**.

INTERVIEW

Neal J Meropol, MD

Dr Meropol is Dr Lester E Coleman, Jr Professor of Cancer Research and Therapeutics and Chief of the Division of Hematology and Oncology at Case Western Reserve University School of Medicine and University Hospitals Case Medical Center in Cleveland, Ohio.

Tracks 1-10

Track 1 Assessment of outcomes associated with the use of the Onco*type* DX Recurrence Score® in adjuvant therapy decisions in Stage II colon cancer via the Markov model

Track 2 Use of molecular profiling to individualize systemic therapy for patients with colon cancer

Track 3 Similarities and differences in the use of the Onco*type* DX assay in breast and colon cancer

Track 4 Integration of predictive markers into the next generation of clinical trials

Track 5 ECOG-E5202 study: FOLFOX with or without bevacizumab for resected Stage II colon cancer at high risk for recurrence based on molecular markers

Track 6 Perspective on the current role of the Onco*type* DX colon cancer assay

Track 7 Impact of the ToGA trial results on clinical practice: Use of HER2 testing and first-line chemotherapy/trastuzumab for HER2-positive advanced GC

Track 8 Use of TKIs and mTOR inhibitors for pancreatic neuroendocrine tumors

Track 9 Integration of sorafenib with current regional therapeutic approaches for HCC

Track 10 Amount of remnant liver volume, not number of hepatic metastases, should determine resectability

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the data you presented at the 2011 Gastrointestinal Cancers Symposium on the use of the Onco*type* DX assay in adjuvant therapy decisions for Stage II colon cancer?

DR MEROPOL: Adjuvant therapy for Stage II colon cancer represents a challenge for all of us, and we're eager for a better method of selecting patients who will benefit the most from adjuvant therapy.

We're now in an era when a number of new platforms are under development to evaluate gene expression in colon cancer as a way to predict which tumors will relapse and which are destined never to relapse. One such platform that

is now commercially available is the Onco*type* DX colon cancer assay, which is a 12-gene expression platform that predicts risk of recurrence at three years based on a study of archived material from the European QUASAR study (Kerr 2009; [4.1]).

In our study we used the Markov model to assess outcomes associated with the use of the Onco*type* DX assay in terms of how such a tool in Stage II colon cancer would affect the use of adjuvant therapy and affect patient outcomes and costs (Meropol 2011). We asked the question, if you use a gene expression profile like Onco*type* DX to select patients for adjuvant therapy, will you come up with a different pattern of care than you would if you used the typical clinical parameters?

The Markov model cycles an imaginary patient through various health states. One pathway evaluates what the side effects are and what's gained and lost if you administer adjuvant therapy, and then another pathway evaluates the patient if you don't administer adjuvant therapy.

We aimed to evaluate whether using the Onco*type* DX assay would increase or decrease the number of quality-adjusted life years — so not only length of life but also the quality of life for the years of life remaining. We found that treatment decisions based on Onco*type* DX reduced adjuvant chemotherapy use by 17 percent, and overall in the population of patients with Stage II colon cancer in our model, an increase in quality-adjusted survival was associated with a decrease in chemotherapy use.

4.1

QUASAR/Onco*type* DX Results: Recurrence Risk in Prespecified Recurrence Risk Groups (n = 711)

Recurrence risk group	Range of Recurrence Score	Proportion of patients	Kaplan-Meier estimates of recurrence risk at 3 years*
Low	<30	43.7%	12%
Intermediate	30-40	30.7%	18%
High	≥41	25.6%	22%

* With surgery alone

Kerr D et al. *Proc ASCO* 2009;**Abstract 4000**.

Track 5

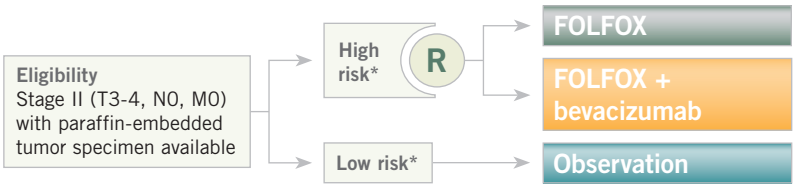
DR LOVE: What is the status of the ECOG-E5202 trial for patients with Stage II colon cancer?

DR MEROPOL: One of the objectives of this study for patients with Stage II colon cancer was to validate whether we could identify a population at low risk based on microsatellite instability and 18q loss of heterozygosity. Patients with 18q loss of heterozygosity were hypothesized to be in a higher-risk group, as

4.2

FOLFOX with or without Bevacizumab for Patients with Resected Stage II Colon Cancer at High Risk for Recurrence

Protocol ID: ECOG-E5202 **Target Accrual:** 3,610 (Closed)



* Patients who are at high risk based on microsatellite instability (MSI) and loss of heterozygosity (LOH) at chromosome 18q are randomly assigned to one of two treatment arms. Patients who are at low risk based on MSI and 18q LOH are assigned to observation.

NCI Physician Data Query, May 2011.

was the group of patients who did not have microsatellite instability or deficient mismatch repair.

Enrolled patients would have their tumors assessed for microsatellite instability and loss of 18q. Patients who were in the low-risk group were observed without adjuvant therapy and their tissue was banked for future research. The patients in the higher-risk group were randomly assigned to receive standard adjuvant therapy with FOLFOX or FOLFOX with bevacizumab (4.2).

Based on emerging data suggesting that bevacizumab does not add to the benefits of FOLFOX in the adjuvant setting (Allegra 2011), the ECOG-E5202 study was recently closed to further accrual. Because a large number of patients had already been accrued to the study, we will definitely be able to validate or refute the prognostic utility of deficient mismatch repair and 18q in the patients on this study.

Even though the sample size in the randomized arm was not sufficient to have a high power, we will be able to perform an exploratory analysis of whether bevacizumab affected outcomes in the population with Stage II disease, keeping in mind that other studies of bevacizumab in the adjuvant setting were largely of patients with Stage III disease. ■

SELECT PUBLICATIONS

Allegra CJ et al. **Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: Results of NSABP protocol C-08.** *J Clin Oncol* 2011;29(1):11-6.

Kerr D et al. **A quantitative multigene RT-PCR assay for prediction of recurrence in stage II colon cancer: Selection of the genes in four large studies and results of the independent, prospectively designed QUASAR validation study.** *Proc ASCO* 2009;**Abstract 4000**.

Meropol N et al. **Use of a multigene prognostic assay for selection of adjuvant chemotherapy in patients with stage II colon cancer: Impact on quality-adjusted life expectancy and costs.** Gastrointestinal Cancers Symposium 2011;**Abstract 491**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In a Phase III study of patients with Stage IV pancreatic cancer, the overall response rate in those who received treatment with FOLFIRINOX was nearly _____ that of those who received gemcitabine.**
   a. Double
   b. Triple
   c. Half
   d. None of the above

2. **In a randomized trial of adjuvant chemoradiation therapy in 363 patients with mostly gastric adenocarcinomas, preoperative use of carboplatin/paclitaxel/radiation therapy improved survival by _____ compared to surgery alone.**
   a. 23 months
   b. 11 months
   c. 13 months
   d. 12 months

3. **The rate of HER2-positive tumors is as high as 25 percent in distal gastric cancers and about 16 percent in more proximal GE junction tumors.**
   a. True
   b. False

4. **STORM is a Phase III study evaluating adjuvant sorafenib for patients with HCC who have achieved a confirmed complete response after surgical resection or local ablation.**
   a. True
   b. False

5. **The Phase III ECOG-E1208 study is evaluating TACE with or without _____ for patients with unresectable HCC.**
   a. Imatinib
   b. Sunitinib
   c. Sorafenib

6. **The Phase II NSABP-C-10 trial evaluated _____ for patients with unresectable Stage IV colon cancer and a synchronous asymptomatic primary tumor.**
   a. FOLFOX in combination with bevacizumab
   b. FOLFIRI in combination with bevacizumab
   c. FOLFOX in combination with cetuximab
   d. FOLFIRI in combination with cetuximab

7. **In an analysis reported by Meropol and colleagues, treatment decisions based on the use of the Onco*type* DX assay and a patient's years of life remaining without cancer recurrence reduce adjuvant chemotherapy use by 17 percent compared to current treatment patterns.**
   a. True
   b. False

8. **In CALGB-C80405, which evaluates chemotherapy in combination with either bevacizumab or cetuximab or both bevacizumab and cetuximab for previously untreated metastatic colorectal cancer, the chemotherapy regimen used is _____.**
   a. FOLFOX
   b. FOLFIRI
   c. FOLFOX or FOLFIRI at the discretion of the physician

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 1, 2011

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

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
HER2-directed therapies in gastric cancer management	4 3 2 1	4 3 2 1
FOLFIRINOX dosing in advanced pancreatic cancer	4 3 2 1	4 3 2 1
Molecular profiling to individualize systemic therapy for colon cancer	4 3 2 1	4 3 2 1
TACE with or without sorafenib in unresectable HCC	4 3 2 1	4 3 2 1
ECOG-E5202: FOLFOX with/without bevacizumab for resected Stage II colon cancer at high risk for recurrence based on molecular markers	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No

If no, please explain: .....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice; no changes will be made
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): .....

If you intend to implement any changes in your practice, please provide one or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

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

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

- Summarize key findings from clinical studies of emerging therapeutic regimens for pancreatic cancer . . . . . 4 3 2 1 N/M N/A
- Assess the role of molecular markers in optimizing therapeutic decisions for patients with early or advanced CRC . . . . . 4 3 2 1 N/M N/A
- Counsel patients with Stage II colon cancer about their individual risk of recurrence based on clinical, pathologic and genomic biomarkers, and consider adjuvant therapeutic options. . . . . 4 3 2 1 N/M N/A
- Formulate a treatment plan for patients with synchronous primary CRC and liver-only metastases. . . . . 4 3 2 1 N/M N/A
- Utilize clinical and molecular biomarkers to select optimal systemic treatment strategies for patients with gastric or gastroesophageal cancer . . . . . 4 3 2 1 N/M N/A
- Communicate the benefits and risks of existing and emerging systemic interventions to patients with advanced hepatocellular carcinoma. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials . . . . . 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

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 faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
David H Ilson, MD, PhD	4 3 2 1	4 3 2 1
David A Geller, MD	4 3 2 1	4 3 2 1
Alan P Venook, MD	4 3 2 1	4 3 2 1
Neal J Meropol, MD	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 faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

Name:..... Specialty:.....

Professional Designation:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other .....

Street Address:..... Box/Suite:.....

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Telephone:..... Fax:.....

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

Signature:..... Date:.....

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Gastrointestinal Cancer™ UPDATE

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Gastrointestinal Cancer™

U P D A T E

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