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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 among the most common cancer types diagnosed in the United States, and its clinical management is continuously evolving. Although less frequently encountered individually, the collection of other "non-CRC" gastrointestinal (GI) tumors accounts for more per annum cancer-related deaths than tumors of the colon and rectum combined. Published results from ongoing trials lead to the emergence of new therapeutic agents and regimens, novel biomarkers influencing treatment selection and alterations to 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* utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest scientific developments and expert perspectives, this CME activity assists medical oncologists with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Apply the results of emerging clinical research to the best-practice management of GI cancer originating within (CRC) and outside of (non-CRC) the colon and rectum.
- 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.
- Communicate the benefits and risks of existing and emerging anti-VEGF and anti-EGFR biologic therapy to patients with metastatic CRC.
- Evaluate data on novel combination regimens for advanced pancreatic cancer.
- 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 cancer.
- Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials.

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Visit **www.ResearchToPractice.com** to listen to or download an additional 45 minutes from the interviews with Drs O'Reilly, Berlin and Zhu.

WEB TRACKS

Jordan D Berlin, MD

1 Results of a Phase III trial and meta-analysis of gemcitabine with or without capecitabine for advanced pancreatic cancer (PC)
2 Clinical trials of combination targeted therapy with tyrosine kinase inhibitors and monoclonal antibodies in advanced PC
3 Clinical algorithm for advanced PC
4 Theoretical rationale and emerging data for nanoparticle albumin-bound (*nab*) paclitaxel in PC
5 Use of standard- versus fixed-dose rate of gemcitabine for advanced PC
6 Targeted agents and pathways in PC
7 Perspective on the current state of therapeutic advances in PC

Andrew X Zhu, MD, PhD

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3 Efficacy and safety of gemcitabine, oxaliplatin and bevacizumab in advanced biliary tract cancer
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5 Hepatic toxicities associated with systemic therapy in patients with metastatic colorectal cancer to the liver
6 Potential benefits and risks of bevacizumab in combination with chemotherapy for patients with hepatic metastases
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Eileen M O'Reilly, MD

1 **Case discussion:** A 68-year-old woman has a 20-cm, biopsy-confirmed Child-Pugh A hepatocellular carcinoma (HCC) and an alpha-fetoprotein level of >90,000 ng/mL
2 Use of bland hepatic arterial embolization for a patient with bulky, symptomatic HCC
3 Dosing sorafenib in the treatment of advanced HCC
4 Mechanism(s) of action of sorafenib in HCC
5 Key clinical investigational strategies and agents in HCC
6 Combination therapy with bevacizumab/erlotinib in advanced HCC
7 Identification of individuals at risk for the development of PC

INTERVIEW

Eric Van Cutsem, MD, PhD

Professor Van Cutsem is Professor of Medicine and Head of the Digestive Oncology Unit at the University Hospital Gasthuisberg/Leuven in Leuven, Belgium.

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Select Excerpts from the Interview

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DR LOVE: Can you review the study you reported at ASCO last year evaluating trastuzumab in gastric cancer?

PROF VAN CUTSEM: The Phase III ToGA trial screened approximately 3,800 patients with advanced gastric cancer and identified 22 percent as having HER2-positive disease. Patients with HER2-positive disease experienced significantly improved overall survival when trastuzumab was added to standard chemotherapy consisting of 5-fluorouracil or capecitabine and cisplatin (Van Cutsem 2009; [1.1]).

Chemotherapy was administered in three-week cycles for a maximum of six cycles, and trastuzumab could be continued until disease progression or toxicity. No difference was observed in symptomatic cardiac, hematological or gastrointestinal adverse events. Currently, adjuvant trials of trastuzumab in HER2-positive early gastric cancer are also being planned.

I believe that we have reached a plateau of survival with various combination chemotherapies in gastric cancer, and any additional advantage is likely to come from combining targeted agents with active chemotherapy regimens.

Another targeted agent worth mentioning is bevacizumab, which has shown activity in combination with chemotherapy in Phase II trials (Shah 2006; Jhawer 2009; [1.2]). Bevacizumab is currently being evaluated in the Phase III AVAGAST trial, which randomly assigned more than 700 patients with metastatic gastric cancer to capecitabine/cisplatin with or without

1.1

ToGA: Efficacy and Safety of Trastuzumab with 5-Fluorouracil or Capecitabine and Cisplatin in HER2-Positive Advanced Gastric Cancer

	Overall survival	Overall response rate	Asymptomatic ejection fraction decrease (<50% and ≥10%)
Trastuzumab + chemotherapy (n = 294)	13.8 months	47.3%	4.6%
Chemotherapy	11.1 months	34.5%	1.1%
p-value	0.0046	0.0017	—

Van Cutsem E et al. *Proc ASCO* 2009;**Abstract LBA4509**.

1.2

Phase II Studies of Bevacizumab and Chemotherapy Combinations in Advanced Gastric Cancer

Regimen	No. of patients	Median survival (CI)	Response rate in patients with measurable disease
Irinotecan, cisplatin and bevacizumab[1]	47	12.3 months (11.3-17.2 months)	65%
Docetaxel, cisplatin, 5-fluorouracil and bevacizumab[2]	42	Not reached (14.5-not reached)	64%

[1] Shah MA et al. *J Clin Oncol* 2006;24(33):5201-6; [2] Jhawer M et al. Gastrointestinal Cancers Symposium 2009;**Abstract 10**.

bevacizumab. The primary endpoint is overall survival, and the trial is expected to be reported at ASCO 2010.

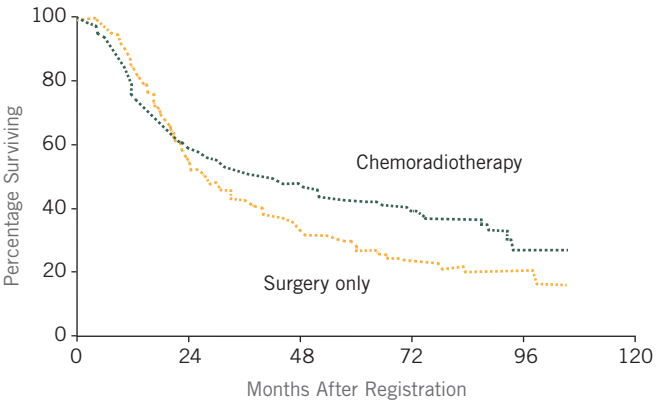
Among other targeted agents, ongoing prospective randomized Phase III trials are investigating the addition of anti-EGFR antibodies such as cetuximab or panitumumab to standard chemotherapy for patients with advanced gastric cancer. These anti-EGFR antibodies are similar to one another. However, in certain regions of the United States infusion reactions have been observed more frequently with cetuximab.

DR LOVE: What are your thoughts on the optimal management of potentially resectable gastric cancer?

PROF VAN CUTSEM: Among patients with potentially resectable gastric or gastroesophageal junction tumors, three different strategies have shown improvement in survival. These three approaches have been adopted in various parts of the world. The Japanese practice extensive lymph node resection followed by adjuvant S-1, an oral fluoropyrimidine (Sakuramoto 2007), the Europeans use perioperative chemotherapy (Cunningham 2006) and in the United States, physicians incorporate chemoradiation therapy after surgery (Macdonald 2001; [1.3]).

1.3

Improvement in Overall Survival with Postoperative Chemoradiation Therapy



Macdonald JS et al. **Chemotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction.** *N Engl J Med* 2001;345(10):725-30. Copyright 2001 Massachusetts Medical Society. All rights reserved.

Tracks 10-11

DR LOVE: What is the current status of adjuvant chemotherapy in Stage II colon cancer and the ability to predict recurrence with RT-PCR assays?

PROF VAN CUTSEM: The QUASAR trial evaluated the survival benefit from chemotherapy among patients with CRC at a low risk of recurrence.

More than 3,200 patients were enrolled, and close to 90 percent had Stage II disease. Patients were randomly assigned to fluorouracil with folinic acid or to observation only.

Adjuvant chemotherapy improved survival among patients with Stage II CRC, although the absolute benefit is small — 3.6 percent at five years (Gray 2007). Some patients benefit from this approach. However, many patients with Stage II disease don't need chemotherapy in the adjuvant setting.

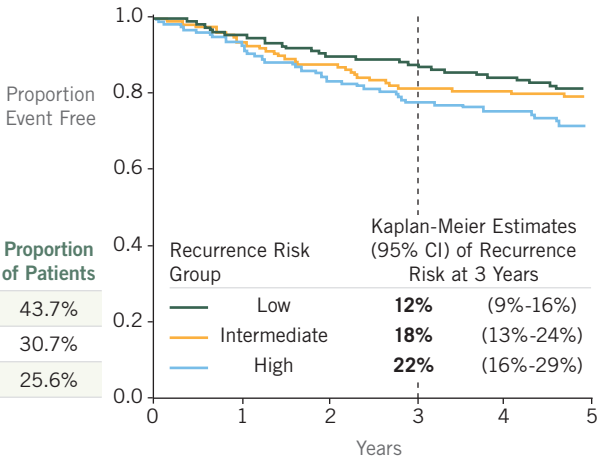
QUASAR investigators have also been studying a genomic profile and presented data at ASCO 2009 on a validated genomic signature that has independent prognostic value in Stage II colon cancer (Kerr 2009; [1.4]).

The assay establishes a Recurrence Score® that provides a range of recurrence risk between 12 and 22 percent. However, the data did not show the colon cancer assay to be predictive of chemotherapy benefit. This genomic signature may add an extra factor when evaluating patients with Stage II colon cancer for adjuvant chemotherapy.

1.4

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

Recurrence Risk Group	Range of RS	Proportion of Patients
Low	<30	43.7%
Intermediate	30-40	30.7%
High	≥41	25.6%



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

Track 16

DR LOVE: Would you discuss research on oral VEGF inhibitors in colon cancer?

PROF VAN CUTSEM: Cediranib is a once-daily, orally available VEGF inhibitor. A randomized Phase II trial in the second-line setting showed activity of cediranib in combination with FOLFOX for patients with mCRC (Cunningham 2008; [1.5]).

HORIZON II is a Phase III study evaluating cediranib in the first-line setting and has randomly assigned patients to FOLFOX with placebo or cediranib. HORIZON III is being conducted in the United States and compares FOLFOX/bevacizumab to FOLFOX/cediranib as first-line therapy for patients with mCRC. ■

1.5

HORIZON I: A Phase II Randomized Study Comparing FOLFOX/Cediranib to FOLFOX/Bevacizumab as Second-Line Therapy for Metastatic Colorectal Cancer

	FOLFOX + cediranib (20 mg)	FOLFOX + cediranib (30 mg)	FOLFOX + bevacizumab
Progression-free survival	5.8 months	7.2 months	7.8 months
Partial response rate	18%	19%	27%

Cunningham D et al. *Proc ASCO* 2008;**Abstract 4028**.

SELECT PUBLICATIONS

Cunningham D et al. **A Phase II double blind randomized multicenter study of cediranib with FOLFOX versus bevacizumab with FOLFOX in patients with previously treated metastatic colorectal cancer.** *Proc ASCO* 2008;**Abstract 4028**.

Cunningham D et al. **Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer.** *N Engl J Med* 2006;355(1):11-20.

Gray R et al. **Adjuvant chemotherapy versus observation in patients with colorectal cancer: A randomised study.** *Lancet* 2007;370(9604):2020-9.

Jhawer M et al. **Phase II study of modified docetaxel, cisplatin, 5-FU, and bevacizumab in metastatic gastroesophageal carcinoma.** Gastrointestinal Cancers Symposium 2009;**Abstract 10**.

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**.

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Shah MA, Ajani JA. **Gastric cancer — An enigmatic and heterogeneous disease.** *JAMA* 2010;303(17):1753-4.

Shah MA et al. **Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in metastatic gastric or GE junction adenocarcinoma.** *J Clin Oncol* 2006;24(33):5201-6.

Van Cutsem E et al. **Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy in first-line HER2-positive advanced gastric cancer (GC).** *Proc ASCO* 2009;**Abstract LBA4509**.

INTERVIEW

Jordan D Berlin, MD

Dr Berlin is Associate Professor of Medicine, Clinical Director of Gastrointestinal Oncology and Medical Director of Clinical Trials Shared Resources at Vanderbilt University Medical Center in Nashville, Tennessee.

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Track 5 Perspective on the utility of Onco*type* DX for patients with Stage II colon cancer

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Track 14 Use of bevacizumab beyond disease progression

Select Excerpts from the Interview

Tracks 4-5

DR LOVE: How do you approach patients with Stage II colon cancer in terms of discussing their risk of recurrence?

DR BERLIN: I try to offer patients numbers on risk of recurrence, and some websites that offer numbers help guide you a little more than simply saying, "Stage II." In breast cancer, highly detailed risk profiles have been developed, and some websites like that exist for colorectal cancer, but many of the data are

from earlier trials and from times when imaging was not what we have now. So interpreting those data carries some risk, but the QUASAR study shows about a three percent benefit with chemotherapy for Stage II colon cancer in general.

The Onco*type* DX presentation at ASCO 2009 of findings from patients in the QUASAR trial was intriguing in this regard. Good preliminary data were presented indicating that something might be available for us in colon cancer similar to what people in breast cancer are using, but this requires further study before I would apply it routinely. The higher-risk group in that data set had a relapse rate of 22 percent, and once that rate moves above 20 percent, that information about risk of relapse can be especially useful in patient care. Another question is whether this Onco*type* DX assay will be helpful above and beyond the pathologic variables we already have, for example, with differentiation or lymphovascular invasion.

In the MOSAIC trial with FOLFOX, patients with higher-risk Stage II disease based on pathologic variables benefitted from treatment. This was a retrospective subset analysis within a prospective trial, but the data are certainly intriguing — similar to the Onco*type* DX data — and we need to test these concepts further.

Tracks 7-10

Case discussion

A 57-year-old man with a primary colon cancer and concurrent unresectable liver oligometastases experiences disease progression while receiving FOLFOX.

DR LOVE: How long was your patient receiving FOLFOX before you concluded that his disease was progressing, and what was your next step?

DR BERLIN: He experienced a significant increase in his blood carcinoembryonic antigen (CEA) level after only two cycles of chemotherapy, so progression was already significant before the third dose. Although the number of liver metastases did not increase, a critical metastasis located next to the portal vein was a challenge for removal, and the FOLFOX did not improve our chances of resection.

We then administered FOLFIRI and panitumumab. We discussed the risks and benefits of this approach. Recent data with the combination in the second-line setting demonstrated an improvement in progression-free survival and response rate (Peeters 2010; [2.1]). He's received four doses and is starting to respond. His CEA level has dropped and his CT scans show an approximately 10 percent decrease in the tumors.

DR LOVE: How is this patient tolerating therapy?

DR BERLIN: He's faring well. We used data from the Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) — which evaluated the effects of preemp-

tive versus reactive treatment of skin toxicities associated with EGFR inhibitors — to develop an algorithm to prevent toxicity (Lacouture 2010).

From the initiation of FOLFIRI/panitumumab, we administered minocycline and recommended moisturizing creams and sunblock when outdoors, and he has not experienced a severe facial rash. We don't use the preemptive treatment approach with all treatment regimens, but we use it fairly often with both panitumumab and cetuximab.

DR LOVE: With this patient, what was your rationale for using panitumumab rather than cetuximab with second-line FOLFIRI?

DR BERLIN: We tend to use more panitumumab, off protocol, in our region of the country because of the high risk of infusion reactions we have experienced with cetuximab. The every other-week schedule with panitumumab is also something of a convenience factor, although data exist to support every other-week schedules with cetuximab as well.

In our area, the infusion reaction rate with cetuximab is 21 percent, whereas outside of the "infusion belt" the reaction rate is approximately one percent. That's a concern for patients, especially the patients who've experienced oxaliplatin infusion reactions.

2.1

Phase III Study of Second-Line FOLFIRI with or without Panitumumab (P) in Metastatic Colorectal Cancer (N = 1,186): Analysis According to K-ras Status

Wild-type K-ras (central review)

	FOLFIRI + P	FOLFIRI	Hazard ratio	*p*-value
ORR	35%	10%	—	<0.001
Median PFS	5.9 months	3.9 months	0.73	0.004

Mutant K-ras (central review)

	FOLFIRI + P	FOLFIRI	Hazard ratio	*p*-value
ORR	13%	14%	—	1.0
Median PFS	5.0 months	4.9 months	0.85	0.14

Peeters M et al. Gastrointestinal Cancers Symposium 2010;**Abstract 282**.

Track 13

DR LOVE: What do you generally use as first-line treatment for unresectable metastatic colon cancer?

DR BERLIN: My front-line choice is FOLFIRI and bevacizumab because patients usually receive their first regimen for the longest duration. Although FOLFIRI and FOLFOX both cause toxicities, the side effects more commonly observed with FOLFIRI, such as diarrhea and alopecia, are not cumulative, whereas the neuropathy that occurs more commonly with FOLFOX is (2.2).

Even with the OPTIMOX-type strategy of stopping and starting oxaliplatin to decrease the neuropathy and extend treatment, sooner or later patients experience neuropathy. For that reason, we favor FOLFIRI to avoid the cumulative toxicity until later in their treatment course. Quality of life is much more important now that patients are living longer.

DR LOVE: What has been your experience with bevacizumab in terms of tolerability and complications?

DR BERLIN: We participated in the original trial of IFL with or without bevacizumab — the Hurwitz trial — and in the ECOG-E3200 study in addition to a couple of other trials with bevacizumab (Hurwitz 2004; Giantonio 2007). We had a tough time discerning who was receiving bevacizumab based on side effects.

I believe bevacizumab is a well-tolerated drug. I tend to avoid using it for patients with high-risk factors for thromboembolic or arterial complications because that's a crucial issue. If a patient has a history of untreated angina or fairly severe coronary artery disease with stroke or heart attack, I'm much more cautious about using bevacizumab. ■

2.2

Phase IV Study of First-Line FOLFIRI with Bevacizumab in Metastatic Colorectal Cancer (N = 209)

Efficacy (intent-to-treat population)

	Duration	95% CI
Median progression-free survival	11.1 months	10.3-12.1 months
Median overall survival	22.2 months	20.5-25.9 months

CI = confidence interval

Sobrero A et al. *Oncology* 2009;77(2):113-9.

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Peeters M et al. **Randomized phase III study of panitumumab (pmab) with FOLFIRI versus FOLFIRI alone as second-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC): Patient-reported outcomes (PRO).** Gastrointestinal Cancers Symposium 2010;**Abstract 282**.

Sobrero A et al. **Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer.** *Oncology* 2009;77(2):113-9.

INTERVIEW

Andrew X Zhu, MD, PhD

Dr Zhu is Director of Liver Cancer Research at Massachusetts General Hospital Cancer Center and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-12

Track 1 Association between metabolic syndrome and hepatocellular carcinoma (HCC)

Track 2 Mechanism of action of sorafenib in HCC

Track 3 Phosphorylated extracellular signaling-related kinase (pERK) as a predictor of response to sorafenib in HCC

Track 4 Rationale for targeting angiogenesis pathways in HCC

Track 5 Activity and risks of bevacizumab in the treatment of HCC

Track 6 Trials of sorafenib after transarterial chemoembolization and in the adjuvant and post-transplant settings

Track 7 Use of sorafenib in patients with advanced Child-Pugh B HCC

Track 8 Treatment of elderly patients who have a good performance status with sorafenib

Track 9 Management of sorafenib-associated hand-foot syndrome

Track 10 **Case discussion:** A 65-year-old man with hepatitis C presents with Child-Pugh A HCC, pulmonary metastases and mediastinal lymphadenopathy

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Track 12 Current challenges in the prevention, screening and treatment of HCC

Select Excerpts from the Interview

Tracks 2-3, 6

DR LOVE: Can you discuss your research on ERK and response to sorafenib in hepatocellular carcinoma (HCC)?

DR ZHU: Sorafenib has clearly demonstrated improvement in overall survival in randomized Phase III studies in HCC (Llovet 2008; Cheng 2009; [3.1]). It targets tumor angiogenesis by inhibiting VEGF receptor, PDGF receptor and possibly Raf kinase (3.2). Information is limited as to whether its activity in HCC is secondary to inhibition of these known targets or to inhibition of some unidentified targets.

Preclinically, HCC cell lines with higher baseline levels of phosphorylated extracellular signaling-regulated kinase (ERK) seem to respond better to sorafenib inhibition. In addition, in retrospective analysis of tumors from the initial Phase II study of sorafenib in HCC, time to tumor progression was

longer for those with higher baseline levels of phosphorylated ERK (Abou-Alfa 2006).

DR LOVE: What exactly is ERK?

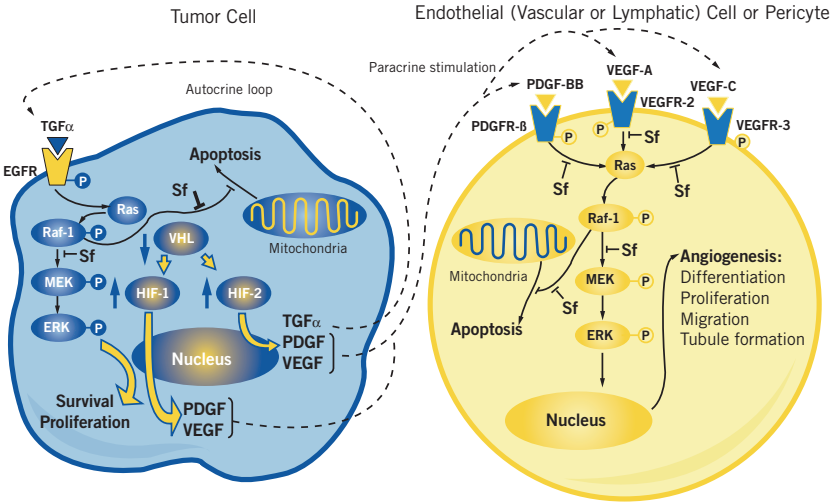
DR ZHU: ERK is a vertical signal transduction pathway through which signals are transmitted from the cell surface receptors to the nucleus (Kolch 2002). Many receptors, such as EGFR and insulin growth factor receptor, use this pathway to transmit signals. In cancer cells the ERK pathway is preferentially activated and in some situations may be constitutively active.

3.1 **Efficacy of Sorafenib in Phase III Studies in Hepatocellular Carcinoma**

	SHARP study[1]	Asia-Pacific study[2]
	Sorafenib versus placebo	Sorafenib versus placebo
Overall survival	**10.7 mo versus 7.9 mo**	**6.5 mo versus 4.2 mo**
Hazard ratio	0.69	0.68
p-value	<0.001	0.014
Time to disease progression	**5.5 mo versus 2.8 mo**	**2.8 mo versus 1.4 mo**
Hazard ratio	0.58	0.57
p-value	<0.001	<0.001
Response rate	**2% versus 1%**	**3.3% versus 1.3%**

[1] Llovet JM et al. *N Engl J Med* 2008;359(4):378-90; [2] Cheng AL et al. *Lancet Oncol* 2009;10(1):25-34.

3.2 **Putative Sorafenib Targeting of Tumor Cell Proliferation and Angiogenesis**



Reprinted with permission from Wilhelm SM et al. **Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling.** *Mol Cancer Ther* 2008;7(10):23129-40, figure 1.

Tracks 6-9

DR LOVE: What do we know about using sorafenib after conventional local treatment with surgery or transarterial chemoembolization (TACE)?

DR ZHU: The success in advanced disease has led to clinical trials of sorafenib for HCC in the adjuvant setting. Ongoing trials are evaluating sorafenib versus placebo in HCC after successful surgical resection, radiofrequency ablation or TACE. No definitive data are currently available on whether sorafenib improves the outcomes already achieved with local therapy.

DR LOVE: What about the use of sorafenib in patients with HCC who also have hepatic dysfunction or for those who are elderly?

DR ZHU: The randomized SHARP study of sorafenib in HCC generally enrolled patients with preserved hepatic function. Data with sorafenib in patients with hepatic dysfunction are limited. Retrospective analyses have shown that the pharmacokinetic profile of sorafenib is comparable in Child-Pugh A and Child-Pugh B disease, and the toxicity profile is also similar within these subgroups, with the exception of hyperbilirubinemia, which is more common in patients with Child-Pugh B disease.

Sorafenib dose reduction may be considered up front for these patients. Patients with Child-Pugh C disease will likely succumb to cirrhosis rather than HCC, and sorafenib should not be considered for those patients. Regarding the elderly, my view is to consider concomitant comorbidities, hepatic function and physiologic age rather than chronologic age.

DR LOVE: What has been your experience with sorafenib-associated hand-foot syndrome?

DR ZHU: Vigilant monitoring — particularly in the first couple of weeks of sorafenib administration — and early intervention when symptoms are detected are the keys to managing hand-foot syndrome. Interventions may include dose reduction, use of topical creams to decrease inflammation and meticulous skin care, including appropriate footwear. With these practices, I have not encountered any patients who developed uncontrolled hand-foot syndrome. ■

SELECT PUBLICATIONS

Abou-Alfa GK et al. **Phase II study of sorafenib in patients with advanced hepatocellular carcinoma.** *J Clin Oncol* 2006;24(26):4293-300.

Cheng AL et al. **Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A Phase III randomised, double-blind, placebo-controlled trial.** *Lancet Oncol* 2009;10(1):25-34.

Kolch W et al. **The role of Raf kinases in malignant transformation.** *Expert Rev Mol Med* 2002;4(8):1-18.

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

Roberts LR. **Sorafenib in liver cancer — Just the beginning.** *N Engl J Med* 2008;359(4):420-2.

INTERVIEW

Eileen M O'Reilly, MD

Dr O'Reilly is Associate Attending for the GI Medical Oncology Service at Memorial Sloan-Kettering Cancer Center and Associate Professor of Medicine at Weill Medical College of Cornell University in New York, New York.

Tracks 1-12

Select Excerpts from the Interview

Track 2

DR LOVE: Would you discuss the RTOG-0848 trial, which is evaluating adjuvant gemcitabine with or without erlotinib followed by chemotherapy with or without radiation therapy as adjuvant treatment for patients with resected cancer in the head of the pancreas?

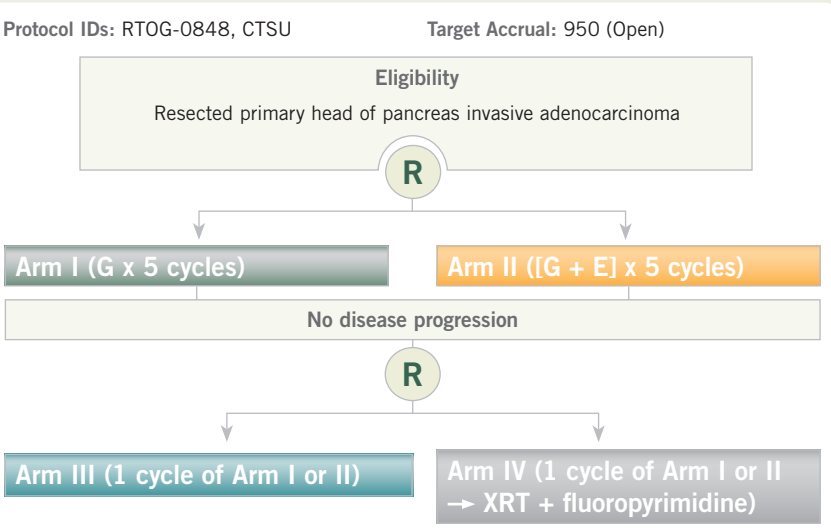
DR O'REILLY: An important question here, as in the locally advanced disease setting, is what is the role of chemoradiation therapy? It's widely agreed that it increases local control rates, but the effect on overall survival has yet to be definitively established in most people's opinions.

RTOG-0848, a relatively ambitious trial in terms of design, should provide some data in the adjuvant setting. This trial opened in January 2010 and

has a target accrual of more than 950 patients. The trial involves a two-fold randomization to gemcitabine with or without erlotinib and, perhaps the more important randomization in terms of implications for clinical practice, with or without chemoradiation therapy after the systemic therapy (4.1).

4.1

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



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

Track 9

DR LOVE: Would you discuss the relationship between SPARC expression and response to therapy among patients with advanced pancreatic cancer?

DR O'REILLY: Dan Von Hoff's Phase I/II data on the correlation of SPARC with response to gemcitabine and *nab* paclitaxel in advanced pancreatic cancer have garnered a lot of publicity (Von Hoff 2009). Many patients now inquire about whether they should have their tumors tested for the SPARC protein, what it means and whether they should receive gemcitabine/*nab* paclitaxel on or off study.

DR LOVE: Do we know enough to say that if patients have low or absent SPARC expression, they won't benefit?

DR O'REILLY: Patients with SPARC-positive disease benefited from gemcitabine/*nab* paclitaxel, but some patients with SPARC-negative disease also appeared to benefit (Von Hoff 2009). I don't believe one can make this

decision yet. These data must be further validated to determine whether this is a useful biomarker for this particular class of drugs. The *nab* paclitaxel and gemcitabine combination is now the subject of a Phase III trial in the advanced disease setting.

DR LOVE: What are your thoughts on whether *nab* paclitaxel is working directly against the tumor in addition to the stroma?

DR O'REILLY: Some people feel it's both, and that's perhaps one of the attractions — targeting both the profound desmoplastic stromal reaction that pancreatic adenocarcinoma can induce and the metastatic disease.

SPARC binding may be related both to the tumor and to the stroma, and it's possible that it acts as a delivery system for getting more drug into the tumor (4.2). ■

4.2

Nab Paclitaxel Targets Tumor Stroma and Results in High Efficacy in Combination with Gemcitabine Against Pancreatic Cancer Models

"To gain insight into the mechanisms underlying the high efficacy of [*nab* paclitaxel and gemcitabine], we treated 11 freshly generated pancreatic cancer xenografts from the Johns Hopkins PancXenoBank collection. Tumors treated with *nab* paclitaxel showed a marked decrement in the otherwise abundant fibrotic stroma characteristic of pancreatic cancer and present in control and gemcitabine only treated animals.

The elimination of the stroma resulted in marked cellular tumors and increased tumor vascularization and cell-vessel proximity. Consequently, the intratumoral concentration of gemcitabine increased by 3.7 fold in mice treated with *nab* paclitaxel and gemcitabine versus those receiving gemcitabine alone. We conclude that *nab* paclitaxel effectively eliminates pancreatic cancer stroma resulting in increased delivery of gemcitabine and high anti-tumor effects. Targeting tumor stroma appears a promising strategy in pancreatic cancer."

Maitra A et al. AACR-NCI-EORTC International Conference 2009;**Abstract C246**.

SELECT PUBLICATIONS

Garber K. **Stromal depletion goes on trial in pancreatic cancer.** *J Natl Cancer Inst* 2010;102(7):448-50.

Hosein PJ et al. **A phase II trial of *nab*-paclitaxel (NP) in patients with advanced pancreatic cancer (PC) who have progressed on gemcitabine (G)-based therapy.** *Proc ASCO* 2010;**Abstract 4120**.

Maitra A et al. ***Nab*-paclitaxel targets tumor stroma and results, combined with gemcitabine, in high efficacy against pancreatic cancer models.** AACR-NCI-EORTC International Conference 2009;**Abstract C246**.

Moore MJ et al. **Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group.** *J Clin Oncol* 2007;25(15):1960-6.

Von Hoff DD et al. **SPARC correlation with response to gemcitabine (G) plus *nab*-paclitaxel (*nab*-P) in patients with advanced metastatic pancreatic cancer: A phase I/II study.** *Proc ASCO* 2009;**Abstract 4525**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the ToGA trial recruitment, what percent of patients with gastric cancer had HER2 overexpression?**
   a. Five percent
   b. 10 percent
   c. 20 percent
   d. 35 percent
   e. 50 percent

2. **In the ToGA trial, symptomatic cardiac adverse events occurred at a similar rate in the patients who received trastuzumab versus those who did not receive trastuzumab.**
   a. True
   b. False

3. **Which of the following management strategies has shown a survival advantage in potentially resectable gastric cancer?**
   a. Adjuvant therapy with oral S-1
   b. Perioperative chemotherapy
   c. Adjuvant chemoradiation therapy
   d. All of the above

4. **In the QUASAR study, which validated the Onco*type* DX assay for a genomic signature of Stage II colon cancer recurrence, scores were established for recurrence risk between __ and __ percent.**
   a. 12, 22
   b. Eight, 40
   c. 15, 50

5. **The QUASAR study demonstrated that the Onco*type* DX colon cancer assay was predictive of chemotherapy benefit for patients with Stage II colon cancer.**
   a. True
   b. False

6. **Maitra and colleagues reported that *nab* paclitaxel targets tumor stroma and, in combination with gemcitabine, has significant activity in pancreatic cancer models.**
   a. True
   b. False

7. **In the Phase III study of second-line FOLFIRI with or without panitumumab in metastatic colorectal cancer, reported by Peeters and colleagues, significant improvement was evident in which of the following parameters with the addition of panitumumab?**
   a. Objective response rate and progression-free survival for patients with wild-type K-ras tumors
   b. Objective response rate and progression-free survival for patients with mutant K-ras tumors

8. **In the Skin Toxicity Evaluation Protocol with Panitumumab (STEPP), which evaluated the effects of preemptive versus reactive treatment of skin toxicities associated with EGFR inhibitors, the incidence of Grade II or higher skin toxicities during the treatment period was more than 50 percent lower in the preemptive group than in the reactive group.**
   a. True
   b. False

9. **Sorafenib targets tumor cell proliferation and angiogenesis in HCC by inhibition of the following:**
   a. VEGF receptor
   b. PDGF receptor
   c. Raf kinase
   d. All of the above

10. **The Phase III RTOG-0848 trial is evaluating adjuvant _____ with or without erlotinib followed by chemotherapy with or without radiation therapy for patients with resected pancreatic cancer.**
    a. Bevacizumab
    b. Gemcitabine
    c. *Nab* paclitaxel

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 2, 2010

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
ToGA trial of chemotherapy/trastuzumab for HER2-positive advanced gastric cancer	4 3 2 1	4 3 2 1
Clinical trials of adjuvant chemotherapy and bevacizumab or cetuximab for colon cancer	4 3 2 1	4 3 2 1
QUASAR study of the Onco*type* DX assay for Stage II colon cancer	4 3 2 1	4 3 2 1
First-line chemotherapy and bevacizumab or cetuximab for metastatic colorectal cancer	4 3 2 1	4 3 2 1
RTOG-0848: Adjuvant gemcitabine with or without erlotinib followed by chemotherapy with or without radiation therapy for head of pancreas adenocarcinoma	4 3 2 1	4 3 2 1
Clinical investigation of the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib and gemcitabine in advanced pancreatic cancer	4 3 2 1	4 3 2 1
Clinical use of sorafenib in advanced HCC	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:.....

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 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:

- Apply the results of emerging clinical research to the best-practice management of GI cancer originating within (CRC) and outside of (non-CRC) the colon and rectum. . . . . 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
- Communicate the benefits and risks of existing and emerging anti-VEGF and anti-EGFR biologic therapy to patients with metastatic CRC. . . . . 4 3 2 1 N/M N/A
- Evaluate data on novel combination regimens for advanced pancreatic cancer. . . . . 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 cancer. . . . . 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)

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 faculty and editor for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Eric Van Cutsem, MD, PhD	4 3 2 1	4 3 2 1
Jordan D Berlin, MD	4 3 2 1	4 3 2 1
Andrew X Zhu, MD, PhD	4 3 2 1	4 3 2 1
Eileen M O'Reilly, 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:

.....

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Professional Designation:

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

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GICU210

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Gastrointestinal Cancer™

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