GICU | 2013 VOL 4 | ISSUE 3

Gastrointestinal Cancer™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

David J Kerr, CBE, MA, MD, DSc
Matthew Kulke, MD, MMSc
Peter C Enzinger, MD
Bert H O'Neil, MD

EDITOR

Neil Love, MD

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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

- 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 based on an evaluation of this information.
- Effectively apply the results of practice-changing clinical research to the selection and sequencing of chemobiologic regimens for patients with metastatic CRC.
- Summarize key findings from clinical studies of emerging and newly approved therapeutic regimens for patients with advanced pancreatic cancer, and use this information to guide treatment decision-making.
- Use clinical and molecular biomarkers to optimize the selection of systemic therapy for patients with gastric or gastroesophageal cancer.
- Educate patients with unresectable metastatic neuroendocrine tumors of the GI tract regarding approved and novel treatment approaches and their associated risks and benefits.
- 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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This activity is supported by educational grants from Astellas, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Genentech BioOncology, Genomic Health Inc, Lilly, Novartis Pharmaceuticals Corporation, Regeneron Pharmaceuticals and Sanofi.

Last review date: January 2014; Release date: January 2014; Expiration date: January 2015

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EDITOR

Neil Love, MD
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INTERVIEW

David J Kerr, CBE, MA, MD, DSc

Dr Kerr is Professor of Cancer Medicine at the University of Oxford in Oxford, United Kingdom.

Tracks 1-13

Select Excerpts from the Interview

Tracks 2-3, 6-7

DR LOVE: Would you comment on the role of the Onco*type* DX® Colon Cancer assay in the management of Stage II and Stage III disease?

DR KERR: We work closely with Norman Wolmark, and we codeveloped and validated the Onco*type* DX test with the NSABP. It does appear that when we evaluate patients with Stage III colon cancer, the Onco*type* DX assay provides useful discriminatory information (Yothers 2013; [1.1]).

It's not classically predictive, so it doesn't allow us to identify those patients who will be more or less responsive to a fluoropyrimidine. However, the huge advantage Onco*type* DX holds is that it can be delivered from paraffin-embedded tissue rather than from fresh or frozen tissue. I believe the Onco*type* DX assay is a beautiful piece of translational science.

1.1 **Validation of the Onco*type* DX 12-Gene Colon Cancer Recurrence Score (RS) in the Phase III NSABP-C-07 Study as a Predictor of Recurrence in Patients with Stage II and III Colon Cancer Treated with 5-FU/Leucovorin with or without Oxaliplatin**

		Five-year recurrence risk by RS	
		5-FU	5-FU + oxaliplatin
Stage II	Low RS	7%	12%
	Intermediate RS	8%	10%
	High RS	23%	9%
Stage IIIA/B	Low RS	19%	17%
	Intermediate RS	30%	19%
	High RS	43%	31%
Stage IIIC	Low RS	41%	38%
	Intermediate RS	48%	40%
	High RS	67%	59%

Conclusions: "The 12-gene Recurrence Score predicts recurrence risk in stage II and stage III colon cancer and provides additional information beyond conventional clinical and pathologic factors. Incorporating Recurrence Score into the clinical context may better inform adjuvant therapy decisions in stage III as well as stage II colon cancer."

Yothers G et al. *J Clin Oncol* 2013;[Epub ahead of print].

This group of investigators are utterly committed to validating their gene signatures to the highest level. And the more we understand about the biology of cancer, the better the care we can provide for our patients.

DR LOVE: What are your thoughts on the recently published report of a subanalysis of elderly patients and patients with Stage II colon cancer treated on the adjuvant MOSAIC trial of 5-FU in combination with leucovorin with or without oxaliplatin (Tournigand 2012)?

DR KERR: When they updated these results, no benefits were reported in high-risk Stage II colon cancer. So I agree with Robert Mayer that we cannot recommend the use of oxaliplatin in Stage II disease (Mayer 2012; Midgley 2013). We have no discriminates now that would allow us to define a group of patients who would experience any benefits whatsoever.

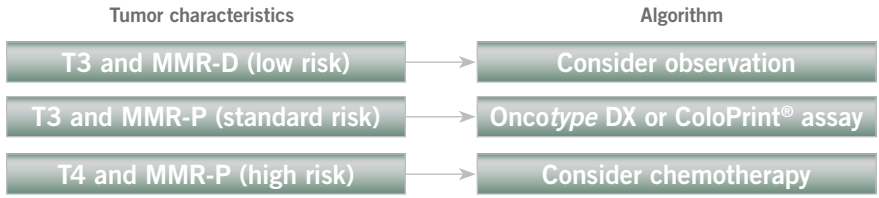
DR LOVE: Would you discuss the treatment algorithm you outlined in a recent publication (Kerr 2013; [1.2]) in terms of individualizing adjuvant therapy for patients with Stage II colon cancer?

DR KERR: We believe that with the degree of evidentiary support for the Onco*type* DX assay, a role exists for it in modern molecular pathology. When we performed a careful pathological review of all the specimens we'd collected from the QUASAR trial and conducted tight multivariate modeling with the Onco*type* DX assay against all these old pathologic variables — degree of differentiation, T3 versus T4 tumor staging, vascular and lymphatic invasion, et cetera — they all fell out at the bottom of the model. The factors that remained were Onco*type* DX Recurrence Score, T4 and MSI status. So for us in our new model, those were the 3 variables we believe we must take account of.

So with regard to the treatment of Stage II disease, in a patient with T4 status we'd be more inclined to offer chemotherapy. For patients whose tumors were MMR deficient,

1.2

Dr Kerr's Molecular Prognostic and Pathologic Algorithm for the Treatment of Resected Stage II Colon Cancer



T = tumor; MMR-D = mismatch repair deficient; MMR-P = mismatch repair proficient

Personal communication with David J Kerr, CBE, MA, MD, DSc August 2013; Kerr DJ, Shi Y. *Nat Rev Clin Oncol* 2013;10(8):429-30.

we'd be inclined to not offer chemotherapy because their 5-year survival rate will be around 90%. I don't believe we can do much better than that with chemotherapy.

In the middle, for the approximately 75% of patients who have T3 tumors that are MMR proficient, rather than deficient, then I believe something like Onco*type* DX, possibly an assay like ColoPrint, would offer useful additional information that would allow the treating physician and the patient to move toward saying, "I'm going to stick with surgery alone" or "I'm going to place my bets on more chemotherapy." It's a simple algorithm, but it's one that we're using in our hospital.

Track 5

DR LOVE: The 5-year follow-up data from the NSABP-C-08 trial were recently published and confirmed the initial findings that, even though there was a transient effect on disease-free survival, bevacizumab for 1 year with modified FOLFOX6 did not significantly prolong disease-free or overall survival in Stage II/III colon cancer (Allegra 2013). What are your thoughts on the role now of bevacizumab, if any, in this setting?

DR KERR: The adjuvant bevacizumab story in colon cancer appeared to be over after these results were originally presented. However, the trial did produce the observation that bevacizumab could be delivered safely in this setting (Allegra 2013; [1.3]), and we have now completed a large Phase III adjuvant trial called QUASAR 2 that is evaluating capecitabine alone versus capecitabine in combination with bevacizumab in Stage II and Stage III colon cancer.

This trial is a genome-wide association study, and we have identified a number of germline markers of toxicity for capecitabine. So I believe we have a relatively simple genetic test that will allow us to identify a priori those patients most at risk for Grade III and Grade IV toxicity.

We expect to have these data ready for next year's ASCO or ESMO meeting, so we'll see what the data show. I know that Norman Wolmark was keen to evaluate administering bevacizumab for a couple of years rather than for 1 year, and I believe some of these ideas are interesting — whether we end up pursuing those further with bevacizumab or with aflibercept.

1.3

Bevacizumab (Bev) in Stage II and III Colon Cancer: 5-Year Update of the Phase III NSABP-C-08 Trial Results

Efficacy	mFOLFOX6	mFOLFOX6 + bev	Hazard ratio	*p*-value
3-y DFS*	75.1%	77.9%	0.93	0.35
5-y overall survival	80.7%	82.5%	0.95	0.56
Select adverse events†	**mFOLFOX6**		**mFOLFOX6 + bev**	
Hypertension	0.6%		0.7%	
Pain	1.1%		1.1%	
Proteinuria	0.1%		0%	
ATE	0.1%		0.5%	
VTE	0.4%		0.2%	
Hemorrhage	0.3%		0.3%	

Conclusion: Bevacizumab for 1 year with modified FOLFOX6 does not significantly prolong DFS or OS in Stage II-III colon cancer. We observed no evidence of a detrimental effect of exposure to bevacizumab. A transient effect on disease-free survival was observed during bevacizumab exposure in the study's experimental arm.

* Exploratory analyses found that the effect of bevacizumab on DFS was different before and after a 1.25-year landmark (time-by-treatment interaction $p = 0.0001$). HR before the 15-month landmark strongly favored bevacizumab (HR, 0.61; $p = 0.0001$), whereas this benefit was entirely lost subsequently (HR, 1.19; $p = 0.059$).

† Grade ≥3 toxicities generally associated with bevacizumab during the 9-month period beginning 3 months after completion of all therapy

mFOLFOX6 = modified FOLFOX6; DFS = disease-free survival; ATE = arterial thrombotic event; VTE = venous thrombotic event

Allegra CJ et al. *J Clin Oncol* 2013;31(3):359-64.

We know that 80% of recurrences of colorectal cancer occur within the first 3 years after surgery. If we could lay down some "anti-angiogenic cover" during those 3 years, perhaps we'd be talking a different ballgame then. ■

SELECT PUBLICATIONS

Allegra CJ et al. **Bevacizumab in stage II-III colon cancer: 5-year update of the National Surgical Adjuvant Breast and Bowel Project C-08 trial.** *J Clin Oncol* 2013;31(3):359-64.

Kerr DJ, Shi Y. **Biological markers: Tailoring treatment and trials to prognosis.** *Nat Rev Clin Oncol* 2013;10(8):429-30.

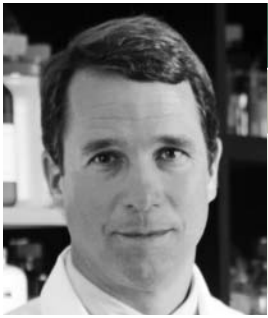
Mayer RJ. **Oxaliplatin as part of adjuvant therapy for colon cancer: More complicated than once thought.** *J Clin Oncol* 2012;30(27):3325-7.

Midgley RS, Kerr DJ. **Adjuvant chemotherapy for stage II colon cancer: Less complicated than we thought.** *J Clin Oncol* 2013;31(12):1611.

O'Connell MJ et al. **Validation of the 12-gene colon cancer Recurrence Score result in NSABP C-07 as a predictor of recurrence in stage II and III colon cancer patients treated with 5FU/LV (5FU) and 5FU/LV + oxaliplatin (5FU+Ox).** *Proc ASCO* 2012;**Abstract 3512**.

Tournigand C et al. **Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: Subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial.** *J Clin Oncol* 2012;30(27):3353-60.

Yothers G et al. **Validation of the 12-gene colon cancer Recurrence Score in NSABP C-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin.** *J Clin Oncol* 2013;[Epub ahead of print].



INTERVIEW

Matthew Kulke, MD, MMSc

Dr Kulke is Director of the Program in Neuroendocrine and Carcinoid Tumors at Dana-Farber/Brigham and Women's Cancer Center and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-12

Select Excerpts from the Interview

Track 5

DR LOVE: What is known in terms of the spectrum of drug activity in pancreatic neuroendocrine tumors (NET) as opposed to carcinoid NET? If an agent is effective in one, will it be effective in the other?

DR KULKE: We don't know the answer to that question yet, though ongoing trials are attempting to address it. We know that the somatostatin analog octreotide can slow tumor progression in carcinoid NET, but we are not as sure about that in pancreatic neuroendocrine tumors. An ongoing trial called the CLARINET study is evaluating another somatostatin analog called lanreotide in gastroenteropancreatic NET, so we hope to have an answer soon. (Editor's note: Subsequent to this interview the results of the CLARINET study were presented at ESMO [2.1].)

DR LOVE: What about chemotherapy in carcinoid NET?

2.1

CLARINET: A Phase III Study of Lanreotide versus Placebo for Gastroenteropancreatic Neuroendocrine Tumors (NET)

	Lanreotide (n = 101)	Placebo (n = 103)	Hazard ratio (HR)	*p*-value
Median progression-free survival	Not reached	18 mo	0.47	0.0002

- After 2 years, 62% of patients who received lanreotide versus 22% of patients who received placebo had not experienced disease progression or died.
- A subgroup analysis showed a statistically significant benefit for patients with midgut NET (HR = 0.35; $p = 0.009$) and a benefit, though not statistically significant, for patients with pancreatic NET (HR = 0.58; $p = 0.064$).*

Caplin M et al. *Proc ECCO* 2013;**Abstract LBA3**. * Available at: **http://www.ipsen.com/wp-content/uploads/2013/09/PR-Results-Clarinet-ESMO.pdf**.

DR KULKE: Traditional chemotherapy — streptozocin or temozolomide — is not highly effective for most carcinoid tumors. Those agents, however, are effective in pancreatic neuroendocrine tumors.

DR LOVE: In a patient with progressive disease, what systemic therapies do you use in carcinoid NET other than octreotide, if any?

DR KULKE: Beyond octreotide we arrive rapidly in a fairly data-free zone, but methods that we talk about for a patient with hepatic-predominant disease, such as chemoembolization, can be effective in this setting. We also know that alpha interferon can be helpful and slow tumor progression in some cases. Everolimus, which is known to be effective in pancreatic NET, has also been evaluated in carcinoid tumors. The RADIANT-2 study suggested activity there (Pavel 2011), and a follow-up Phase III study called RADIANT-4 is now evaluating everolimus versus placebo in carcinoid NET to try to confirm the hints of activity that were observed in the first study (NCT01524783).

Tracks 3, 6

DR LOVE: Would you discuss the design and results of the PROMID study, which evaluated the effect of octreotide on tumor growth in patients with metastatic midgut NET?

DR KULKE: PROMID was a randomized study involving patients with locally inoperable or metastatic midgut NET. Patients were randomly assigned to receive either octreotide using the long-acting formulation at a dose of 30 mg or placebo. The trial reported a clear benefit in terms of time to tumor progression on the order of 14 months versus 6 months favoring octreotide, so octreotide seemed to slow tumor progression (Rinke 2009).

DR LOVE: Do any other somatostatin analogs have potential advantages compared to octreotide?

DR KULKE: Lanreotide is approved right now in Europe for carcinoid syndrome. It is a similar agent, although it is administered slightly differently. Octreotide LAR is administered using an IM injection in the gluteus muscle, which works but can be painful sometimes. Lanreotide can be self-administered as a deep subcutaneous injection. Efficacy is probably similar between the 2 agents.

DR LOVE: Do you observe any toxicity or side effects with octreotide?

DR KULKE: We typically see few side effects with octreotide. Patients sometimes develop a borderline elevated glucose level. It is fairly unusual that you need to institute treatment for that. You must watch out for biliary sludge. If the patient still has a gallbladder, a slightly higher risk of gallstones exists. If a patient already has borderline diabetes and they start octreotide, you do need to watch the blood glucose, and not uncommonly you'll need to start an oral hypoglycemic.

Track 8

DR LOVE: What are the options for treatment for progressive pancreatic NET?

DR KULKE: The classic situation in which you should consider a targeted therapy is in a patient with fairly low-volume disease who is feeling well but clearly has evidence of tumor growth within 1 year. The 2 targeted therapies that have recently been approved for use in progressive advanced pancreatic neuroendocrine tumors are everolimus and sunitinib.

DR LOVE: Would you discuss the data supporting those 2 agents and how you weigh them in a situation like this?

DR KULKE: The data for both agents come from randomized placebo-controlled trials, and in both cases a clear improvement in progression-free survival was evident for patients who received the targeted agent versus patients who received placebo. Interestingly enough, the numbers were extremely close — approximately an 11-month progression-free survival for patients receiving the targeted agent and on the order of 5 months for patients who received placebo (2.2, 2.3).

The flip side of that is that objective responses with either agent are fairly low. The response rate in the sunitinib trial was 9%, and on the everolimus trial it was 5%. Realistically you will not see a great rate of tumor shrinkage if you are using these drugs.

2.2

RADIANT-3: Results from the Phase III Study of Everolimus for Advanced Pancreatic Neuroendocrine Tumors

Efficacy	**Everolimus** (n = 207)	**Placebo** (n = 203)	Hazard ratio	*p*-value
Median progression-free survival	11.0 mo	4.6 mo	0.35	<0.001
Median overall survival	Not reached	Not reached	1.05	0.59
	Everolimus (n = 204)		**Placebo** (n = 203)	
Select adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Stomatitis	64%	7%	17%	0%
Fatigue	31%	2%	14%	<1%
Anemia	17%	6%	3%	0%
Pneumonitis	17%	2%	0%	0%
Hyperglycemia	13%	5%	4%	2%
Thrombocytopenia	13%	4%	<1%	0%

Yao JC et al. *N Engl J Med* 2011;364(6):514-23.

2.3

Results from a Phase III Trial of Sunitinib Malate for Patients with Advanced or Metastatic, Well-Differentiated Pancreatic Neuroendocrine Tumors

Efficacy	**Sunitinib** (n = 86)	**Placebo** (n = 85)	Hazard ratio	*p*-value
Median progression-free survival	11.4 mo	5.5 mo	0.42	<0.001
Median overall survival	Not reached	Not reached	0.41	0.02
Objective response rate	9.3%	0%	—	0.007
	Sunitinib (n = 83)		**Placebo** (n = 82)	
Select adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Diarrhea	59%	5%	39%	2%
Nausea	45%	1%	29%	1%
Fatigue	32%	5%	27%	8%
Neutropenia	29%	12%	4%	0%
Hypertension	26%	10%	5%	1%
Hand-foot syndrome	23%	6%	2%	0%

Raymond E et al. *N Engl J Med* 2011;364(6):501-13.

In deciding between the 2 agents, probably one of the biggest factors is simply evaluating the patient, considering some of the comorbidities and seeing which one might be a better fit for that specific patient.

The side effects for both agents have been well described because they are both used for other indications also. Sunitinib is a tyrosine kinase inhibitor, so expect to see some of the classic side effects, such as hypertension, perhaps a slightly higher bleeding risk and in rare cases some hepatic toxicity.

With everolimus, patients may have side effects like mild mucositis. One of the rare but potentially more concerning side effects is pulmonary toxicity and infiltrates. So if the patient has any underlying lung disease, you might not want to start with everolimus.

One of the great things about having both of these available, at least in comparison to the more traditional chemotherapy, is how well tolerated they are. We have observed some quality-of-life issues in patients with renal cell carcinoma receiving sunitinib, which initially had been administered on a different dosing schedule. The dosing schedule that was used previously was 50 mg per day for 4 weeks, followed by 2 weeks off. We observed some fatigue associated with that. The dosing schedule that was used in the neuroendocrine trial was 37.5 mg continuously, which seemed to be much better tolerated without nearly as much fatigue (Raymond 2011; [2.3]). ■

SELECT PUBLICATIONS

Pavel ME et al. **Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): A randomised, placebo-controlled, phase 3 study.** *Lancet* 2011;378(9808):2005-12.

Rinke A et al; PROMID Study Group. **Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID Study Group.** *J Clin Oncol* 2009;27(28):4656-63.

INTERVIEW

Peter C Enzinger, MD

Dr Enzinger is Director of the Center for Esophageal and Gastric Cancer and Assistant Professor of Medicine at Harvard Medical School's Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-17

Select Excerpts from the Interview

Tracks 1, 8

DR LOVE: What is your approach to the treatment of advanced gastric and gastroesophageal (GE)-junction cancer?

DR ENZINGER: Therapy for gastric cancer continues to be difficult, primarily because the available agents are not very effective. We're still stuck with platinum/5-FU with or without epirubicin. Added to the complexity is whether radiation therapy is of benefit. Radiation oncologists push for radiation therapy extending down the esophagus to the GE junction, even into the proximal stomach. I do believe that radia-

tion therapy can provide additional benefit to patients who are healthy, and platinum agents probably prevent resistance to 5-FU, particularly in terms of lung metastases, but we must find better therapies for these patients. Particularly for patients with HER2-positive disease, trastuzumab and its successors will have a significant impact. I believe we'll see a difference in the near future.

DR LOVE: Would you discuss your treatment algorithm for patients with HER2-negative versus HER2-positive gastric or esophageal cancer?

DR ENZINGER: I believe at least 3 lines of therapy are active in esophageal or gastric cancer. Platinum/5-FU with or without epirubicin remains front-line treatment, and if the tumor is HER2-positive you would consider adding trastuzumab in place of the epirubicin.

In the second line a taxane-based therapy is appropriate. In patients with significant disease burden or symptoms I recommend a weekly docetaxel/cisplatin/irinotecan combination, which has a high response rate and works well in refractory disease. In patients with lower disease burden who are less symptomatic, weekly single-agent docetaxel or paclitaxel is reasonable. Every 3-week therapy is probably more effective, but it's also more toxic. Finally, if you don't use irinotecan in the second line, that's a third line option by itself or in combination with cisplatin, 5-FU or FOLFIRI.

Track 4

DR LOVE: Getting back to the issue of chemoradiation therapy, would you comment on how this disease is managed in the community and how well the treatment is tolerated?

DR ENZINGER: In the past, we used cisplatin/5-FU/radiation therapy for esophageal and GE junction cancer followed by surgery, but it is a toxic regimen. Half of the patients ended up being hospitalized, and the majority of patients were unable to receive the third cycle of cisplatin/5-FU. Some were too weak to proceed to surgery.

3.1

CROSS Study: Neoadjuvant Chemoradiation Therapy (CRT)* for Esophageal or Gastroesophageal-Junction Cancer

Efficacy	**CRT + surgery** (n = 178)	**Surgery alone** (n = 188)	Hazard ratio	*p*-value
Median overall survival	49.4 months	24.0 months	0.657	0.003
Adverse events†	**CRT + surgery** (n = 171)		**Surgery alone** (n = 186)	
Pulmonary complications	46%		44%	
Cardiac complications	21%		17%	
Chylothorax	10%		6%	
Anastomotic leakage	22%		30%	

* Weekly carboplatin/paclitaxel; † During neoadjuvant CRT and after surgery

The most common major hematologic toxic effects in the CRT + surgery group were leukopenia (6%) and neutropenia (2%); the most common major nonhematologic toxic effects were anorexia (5%) and fatigue (3%).

Van Hagen P et al. *N Engl J Med* 2012;366(22):2074-84.

That brings us to the CROSS study, which was a well-powered trial that reported a survival benefit in both adenocarcinoma and squamous cell carcinoma. Moreover, it used a regimen that most doctors in the community will have no trouble administering — neoadjuvant paclitaxel/carboplatin and radiation therapy (van Hagen 2012; [3.1]). Unlike with cisplatin/5-FU, almost all patients make it through this regimen. Some patients experience fatigue, but we do not see any significant hematologic toxicities. It's a well-tolerated regimen that delivers the patient back to the surgeon intact.

Track 5

DR LOVE: What are your thoughts on the REGARD trial and ramucirumab in advanced gastric or GE junction cancer?

DR ENZINGER: The REGARD trial reported a significant improvement in overall survival for patients who received an anti-angiogenesis agent (Fuchs 2013; [3.2]). All of the patients received platinum/5-FU therapy up front and then were randomly assigned to best supportive care or ramucirumab. The results indicated a significant improvement in overall survival and progression-free survival with hardly any toxicity. So in addition to the nearly positive AVAGAST study with bevacizumab in combination with chemotherapy (Ohtsu 2011) and the positive REGARD trial, I believe anti-angiogenesis therapy will play a significant role in this disease in the future.

3.2

REGARD: A Phase III, Randomized, Double-Blind Trial of Ramucirumab and Best Supportive Care (BSC) versus Placebo and BSC as Second-Line Therapy for Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Efficacy	Ramucirumab (n = 238)	Placebo (n = 117)	Hazard ratio	Log-rank *p*-value
Median overall survival	5.2 mo	3.8 mo	0.776	0.047
Median progression-free survival	2.1 mo	1.3 mo	0.483	<0.0001
Objective response rate	3%	3%	—	0.76
Select adverse events, Grade ≥3	**Ramucirumab** (n = 236)		**Placebo** (n = 115)	
Fatigue	6%		10%	
Hypertension	8%		3%	
Anemia	6%		8%	

Fuchs CS et al. *Lancet* 2013;S0140-6736(13)61719-5.

Tracks 14-15

DR LOVE: Would you discuss the PRODIGE 4/ACCORD 11 trial data on the use of FOLFIRINOX versus gemcitabine (Conroy 2011; [3.3]) and also the MPACT trial results with *nab* paclitaxel and gemcitabine versus gemcitabine alone (Von Hoff 2013; [3.3]) for metastatic pancreatic cancer?

DR ENZINGER: The MPACT study was one of the largest studies ever conducted in this disease, so the survival advantage was statistically significant even though it was only approximately 1.8 months. It was interesting for me to realize that now we have another active agent in this disease. Many of us were using taxanes in the third line,

3.3

Phase III Studies of FOLFIRINOX or *Nab* Paclitaxel (*Nab*-p)/Gemcitabine (Gem) versus Gem Alone in Metastatic Pancreatic Cancer

PRODIGE 4[1]	Gem	FOLFIRINOX	Hazard ratio	*p*-value
ORR	9.4%	31.6%	Not reported	<0.001
Median PFS	3.3 months	6.4 months	0.47	<0.001
Median OS	6.8 months	11.1 months	0.57	<0.001
MPACT[2]	Gem	*Nab*-p/Gem	Hazard ratio	*p*-value
ORR*	7%	23%	—	1.1×10^{-10}
Median PFS*	3.7 months	5.5 months	0.69	0.000024
Median OS	6.7 months	8.5 months	0.72	0.000015

* By independent review

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

[1] Conroy T et al. *N Engl J Med* 2011;364(19):1817-25; [2] Von Hoff DD et al. Gastrointestinal Cancers Symposium 2013;**Abstract LBA148**.

so now the question is, was this simply a large study powered to detect a small difference or is this agent better than a regular taxane? Both studies used gemcitabine as the comparator arm, and toxicity and survival were similar.

We all know not to conduct cross-study comparisons, but if you were to indirectly evaluate *nab* paclitaxel versus FOLFIRINOX by normalizing the 2 arms by creating a ratio, the response rate with *nab* paclitaxel is similar to that with FOLFIRINOX. However, FOLFIRINOX seems to yield better results in terms of survival, with a longer progression-free and overall survival in comparison to gemcitabine/*nab* paclitaxel.

Since the data were presented I've used *nab* paclitaxel in patients with refractory disease and am considering it for those who are not strong enough to receive FOLFIRINOX. Patients who have locally unresectable disease can tolerate this aggressive treatment.

I would also use FOLFIRINOX in patients who we're trying to take to surgery and those who want neoadjuvant therapy but not for those with unresectable metastatic disease. FOLFOX or, alternatively, gemcitabine/*nab* paclitaxel, one followed by the other, is a reasonable compromise for these patients.

In terms of specific toxicities, you observe more neutropenia and febrile neutropenia with FOLFIRINOX. However, patients experience less peripheral neuropathy with FOLFIRINOX although *nab* paclitaxel/gemcitabine causes more fatigue. In practice, I've found anorexia to be a problem with gemcitabine/*nab* paclitaxel. But overall, patients tell me that they prefer gemcitabine/*nab* paclitaxel to FOLFIRINOX. ■

SELECT PUBLICATIONS

Fuchs CS et al. **Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial.** *Lancet* 2013;S0140-6736(13)61719-5.

Ohtsu A et al. **Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: A randomized, double-blind, placebo-controlled phase III study.** *J Clin Oncol* 2011;29(30):3968-76.

Van Hagen P et al. **Preoperative chemoradiotherapy for esophageal or junctional cancer.** *N Engl J Med* 2012;366(22):2074-84.

INTERVIEW

Bert H O'Neil, MD

Dr O'Neil is Professor of Medicine and Director of the Phase I and GI Malignancies Programs at Indiana University Simon Cancer Center in Indianapolis, Indiana.

Tracks 1-8

Track 1	Anti-angiogenic therapies for advanced hepatocellular carcinoma (HCC)	Track 5	Investigation of bevacizumab-based therapies in advanced HCC
Track 2	Results of a Phase III trial of sorafenib versus sunitinib in advanced HCC	Track 6	Mechanism of action of ramucirumab in HCC
Track 3	Combination of sorafenib with chemo-therapy or TACE for advanced HCC	Track 7	Potential roles of mTOR, MET and checkpoint inhibitors in HCC
Track 4	Use of sorafenib in patients with HCC and Child-Pugh B versus Child-Pugh C disease	Track 8	Therapeutic options for patients with sorafenib-refractory advanced HCC

Select Excerpts from the Interview

Tracks 2, 4

DR LOVE: Would you discuss the results of the Phase III trial of sunitinib versus sorafenib for patients with advanced hepatocellular carcinoma (HCC) and why we observe differences in outcomes between these 2 tyrosine kinase inhibitors?

DR O'NEIL: Considering what we observed in renal cell cancer, it was a surprise to many of us that sorafenib would come out so much ahead of sunitinib in this trial (Cheng 2013; [4.1]). The investigators were hoping that sunitinib would be better, but that was clearly not the case.

These are complicated drugs, and they have nonoverlapping tyrosine kinase targets. I'd love to know which targets are responsible. Candidates for sorafenib are RAF, CRAF or perhaps mutant BRAF, and although we haven't seen much of it in HCC, some RAF-driven mechanisms may be at work in this disease. It's difficult to pin everything on RAF because we have studied MEK inhibitors, and we published the first MEK inhibitor study in HCC and didn't see much activity (O'Neil 2011).

DR LOVE: What is your approach to the role and dosing of sorafenib for patients with HCC and Child-Pugh B versus Child-Pugh C disease?

DR O'NEIL: Because we don't have many other options, physicians have tended to treat somewhat outside of the criteria of the SHARP trial (Llovet 2008). In the GIDEON study the median survival for the patients with Child-Pugh B disease was only approximately 5 months (Marrero 2011). We can't say without a randomization whether that would be worse without sorafenib, but if you're a purist you can argue that it's a poor

4.1

Phase III Study* Evaluating Whether Sunitinib was Superior or Equivalent to Sorafenib in Advanced Hepatocellular Carcinoma

	Sunitinib	Sorafenib	Hazard ratio	Two-sided *p*-value
Median overall survival, ITT population (n = 530, 544)	7.9 mo	10.2 mo	1.30	0.0014
Asian regions (n = 402, 410)	7.7 mo	8.8 mo	1.21	NR
Ex-Asian regions (n = 128, 134)	9.3 mo	15.1 mo	1.64	NR
	Sunitinib (n = 526)		**Sorafenib** (n = 542)	
Select adverse events	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	50.8%	29.7%	17.3%	3.6%
Hand-foot syndrome	44.3%	13.3%	60.9%	21.3%
Neutropenia	36.5%	25.7%	4.6%	2.2%
Anemia	35.9%	9.3%	11.3%	4.0%
Fatigue	32.7%	6.3%	21.0%	3.9%
Leukopenia	31.7%	13.2%	7.9%	0.2%
Nausea	24.7%	1.1%	17.3%	0.9%

* Study was halted because of higher incidence of serious adverse events with sunitinib
ITT = intention to treat; NR = not reported

Cheng AL et al. *J Clin Oncol* 2013;31(32):4067-75.

survival rate with treatment and perhaps these patients would be better off without the side effects.

However, it's difficult to tell a patient, "No, we have absolutely nothing for you," and I believe that if patients understand what the side effects are and would rather try it, many of us would offer sorafenib. I draw the line at Child-Pugh C disease, but with Child-Pugh B disease we see a large range of outcomes, and some patients should have the opportunity to receive therapy.

Track 7

DR LOVE: Are you excited about any other agents or strategies under evaluation in HCC?

DR O'NEIL: I believe that c-MET inhibitors have generated the most excitement recently (Venepalli 2013). Data indicate that patients with c-MET-positive tumors have a somewhat worse prognosis. When they receive a c-MET inhibitor, they fare better.

Phase III studies are now ongoing — I believe tivantinib is the "first one out of the gate," but several other c-MET inhibitors are being studied, as are a couple of different antibodies, including onartuzumab (MetMAb) and rilotumumab. It will be interesting to see which of these strategies emerge as more effective. This mechanism will be intriguing over the next few years.

Immunotherapy has been effective in the adjuvant setting for HCC (Hui 2009). HCC is behind other tumors in terms of newer immunotherapeutic strategies such as PD-1 or PD-L1 inhibitors, but I'm hopeful that those will be broadly active and that we'll see some new developments in that space soon.

Track 8

DR LOVE: What are some of the most frequent questions oncologists ask about HCC?

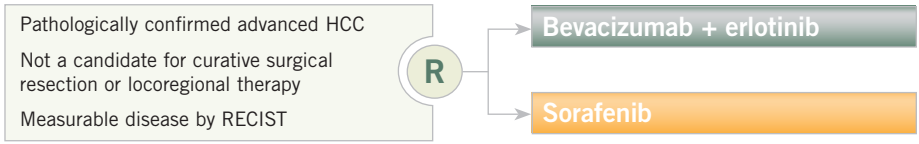
DR O'NEIL: What comes up the most is, "What do I do with a patient whose disease has progressed while he or she was receiving sorafenib?" I believe the options in that case include chemotherapy. We observe responses to chemotherapy occasionally, although I believe we don't have much proof that it improves survival. For a young patient with no other options, capecitabine, CAPOX or GEMOX can be considered.

Some investigators have also been interested in using bevacizumab/erlotinib, even though that combination regimen has not been subjected to Phase III studies yet. I believe that's an option for patients who don't have access to a trial, because the results from the single-arm Phase II study were compelling (Thomas 2009). Objective responses were clearly observed, in addition to an interesting median overall survival. A randomized Phase II study comparing bevacizumab/erlotinib to sorafenib has been ongoing for some time now, and we are looking forward to seeing the data (NCT00881751; [4.2]).

I have used bevacizumab/erlotinib sparingly outside of a trial setting. When I can, I enroll patients with sorafenib-refractory disease on clinical trials, but in the absence of such studies that's one of the options I have chosen. Perhaps 1 or 2 of my patients have benefited clinically from this regimen. It's not a home run, and in most patients with sorafenib-refractory disease for whom we've tried this regimen, we have not observed responses. ■

4.2 **Randomized Phase II Trial of Bevacizumab and Erlotinib Compared to Sorafenib as First-Line Therapy for Patients with Advanced Hepatocellular Carcinoma (HCC)**

Protocol ID: NCT00881751 **Target Accrual:** 120 (Open)



www.clinicaltrials.gov, November 2013.

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Hui D et al. **A randomized, controlled trial of postoperative adjuvant cytokine-induced killer cells immunotherapy after radical resection of hepatocellular carcinoma.** *Dig Liver Dis* 2009;41(1):36-41.

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

Marrero JA et al. **Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib (GIDEON) second interim analysis in more than 1,500 patients: Clinical findings in patients with liver dysfunction.** *Proc ASCO* 2011;**Abstract 4001**.

O'Neil BH et al. **Phase II study of the mitogen-activated protein kinase 1/2 inhibitor selumetinib in patients with advanced hepatocellular carcinoma.** *J Clin Oncol* 2011;29(17):2350-6.

Thomas MB et al. **Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma.** *J Clin Oncol* 2009;27(6):843-50.

Venepalli NK, Goff L. **Targeting the HGF-cMET axis in hepatocellular carcinoma.** *Int J Hepatol* 2013;2013:341636.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Data evaluating patients enrolled in the Phase III NSABP-C-07 trial confirmed that the Onco*type* DX 12-gene Colon Cancer Recurrence Score predicts recurrence risk for patients with Stage II and Stage III colon cancer.**
   a. True
   b. False

2. **Five-year follow-up data from the NSABP-C-08 trial evaluating the addition of bevacizumab to modified FOLFOX for Stage II/III colon cancer reported a statistically significant disease-free or overall survival advantage for patients receiving bevacizumab.**
   a. True
   b. False

3. **The Phase III QUASAR 2 trial is evaluating capecitabine with or without _____ as adjuvant therapy for patients with Stage II or Stage III colorectal cancer.**
   a. Aflibercept
   b. Bevacizumab
   c. Both a and b
   d. Neither a nor b

4. **In the Phase III RADIANT-3 trial of everolimus for patients with advanced pancreatic neuroendocrine tumors, which of the following side effects were associated with everolimus?**
   a. Hyperglycemia
   b. Anemia
   c. Stomatitis
   d. Pneumonitis
   e. All of the above
   f. None of the above

5. **A Phase III trial of sunitinib malate versus placebo for patients with advanced or metastatic well-differentiated pancreatic neuroendocrine tumors demonstrated a statistically significant increase in progression-free survival with sunitinib.**
   a. True
   b. False

6. **The ongoing Phase III RADIANT-4 trial (NCT01524783) is evaluating _____ versus placebo for patients with carcinoid neuroendocrine tumors.**
   a. Everolimus
   b. Octreotide
   c. Sunitinib
   d. All of the above

7. **The Phase III REGARD trial evaluating ramucirumab/best supportive care versus placebo/best supportive care as second-line therapy for metastatic gastric or GE junction cancer demonstrated a small but statistically significant improvement in _____ with ramucirumab.**
   a. Overall survival
   b. Progression-free survival
   c. Both a and b
   d. Neither a nor b

8. **Patients with esophageal or GE-junction cancer who received neoadjuvant chemoradiation therapy in combination with surgery on the CROSS study experienced a statistically significant increase in overall survival without significant hematologic toxicities compared to those who received surgery alone.**
   a. True
   b. False

9. **An ongoing randomized Phase II study (NCT00881751) is comparing the combination of _____ to sorafenib as first-line therapy for patients with advanced HCC.**
   a. Bevacizumab and cetuximab
   b. Bevacizumab and erlotinib
   c. Bevacizumab and sorafenib

10. **A Phase III trial of sorafenib versus sunitinib for patients with advanced HCC was halted because of the higher incidence of serious adverse events with sunitinib.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 3, 2013

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 1 — 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
QUASAR 2: An international Phase III study of capecitabine with or without bevacizumab as adjuvant therapy for Stage II or III CRC	4 3 2 1	4 3 2 1
Tolerability of neoadjuvant paclitaxel/carboplatin in combination with RT for esophageal or GE-junction cancer (CROSS trial)	4 3 2 1	4 3 2 1
MPACT: Results from a Phase III study of *nab* paclitaxel in combination with gemcitabine versus gemcitabine alone for metastatic adenocarcinoma of the pancreas	4 3 2 1	4 3 2 1
Therapeutic options for sorafenib-refractory advanced HCC	4 3 2 1	4 3 2 1
Efficacy of somatostatin analogs — octreotide and lanreotide — in neuroendocrine tumors	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
☐ 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 1 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:

- 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 based on an evaluation of this information. . . . . 4 3 2 1 N/M N/A
- Effectively apply the results of practice-changing clinical research to the selection and sequencing of chemobiologic regimens for patients with metastatic CRC. . . . . 4 3 2 1 N/M N/A
- Summarize key findings from clinical studies of emerging and newly approved therapeutic regimens for patients with advanced pancreatic cancer, and use this information to guide treatment decision-making. . . . . 4 3 2 1 N/M N/A
- Use clinical and molecular biomarkers to optimize the selection of systemic therapy for patients with gastric or gastroesophageal cancer. . . . . 4 3 2 1 N/M N/A
- Educate patients with unresectable metastatic neuroendocrine tumors of the GI tract regarding approved and novel treatment approaches and their associated risks and benefits. . . . . 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

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Additional comments about this activity:

.....

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☐ Yes, I am willing to participate in a follow-up survey.

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

PART 2 — Please tell us about the faculty and editor for this educational activity

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

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David J Kerr, CBE, MA, MD, DSc	4 3 2 1	4 3 2 1
Matthew Kulke, MD, MMSc	4 3 2 1	4 3 2 1
Peter C Enzinger, MD	4 3 2 1	4 3 2 1
Bert H O'Neil, 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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This activity is supported by educational grants from Astellas, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Genentech BioOncology, Genomic Health Inc, Lilly, Novartis Pharmaceuticals Corporation, Regeneron Pharmaceuticals and Sanofi.

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Last review date: January 2014
Release date: January 2014
Expiration date: January 2015
Estimated time to complete: 3 hours

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