GICU | 2013 VOL 4 | ISSUE 2

Gastrointestinal Cancer™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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EDITOR

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2 Audio CDs
Monograph

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Gastrointestinal Cancer Update

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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 therapy for patients with metastatic CRC.
- Summarize key findings from clinical studies of emerging therapeutic regimens for pancreatic cancer, and use this information to guide treatment decision-making.
- Counsel patients with early GI stromal tumors about the potential benefits of adjuvant imatinib, and define an evidence-based duration of treatment.
- Evaluate therapeutic options for patients with imatinib- and sunitinib-resistant GI stromal tumors.
- 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 USA LLC, Novartis Pharmaceuticals Corporation, Regeneron Pharmaceuticals and Sanofi.

Last review date: August 2013; Release date: August 2013; Expiration date: August 2014

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EDITOR

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INTERVIEW

George D Demetri, MD

Dr Demetri is Professor of Medicine at Harvard Medical School and Senior Vice President of Experimental Therapeutics and Director of the Ludwig Center at Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-11

Select Excerpts from the Interview

Tracks 1, 3

DR LOVE: Would you provide an overview of recent advances in the diagnosis and treatment of gastrointestinal stromal tumors (GIST)?

DR DEMETRI: In 2000 GIST was initially characterized by the identification of the causative KIT mutation. This was the first and the most common driver mutation for GIST. Since then, patients live longer due to treatment with targeted tyrosine kinase inhibitors (TKIs). Many patients present with metastases, often in the abdomen, particularly the omentum, or the liver. The standard first-line therapy for metastatic GIST is imatinib, with objective responses achieved by two thirds of patients and an additional 20% with prolonged stable disease.

About 17% of the first set of patients diagnosed with GIST worldwide and treated with imatinib starting in 2000 have never discontinued therapy and are still being followed. Unfortunately, most patients aren't that lucky. For about 50%, the benefits from imatinib will wane with evidence of disease resistance after about 2 years. By year 5, another 40% of patients will experience disease progression. The degree of response or lack thereof from first presentation differs among patients.

DR LOVE: What is your treatment approach for patients with metastatic GIST who are experiencing systemic progression on first-line imatinib?

DR DEMETRI: It is important to emphasize that progression on imatinib does not automatically necessitate the administration of a second-line agent. So an interesting question is, what do you do if only one site of the disease is progressing? At this point we involve multidisciplinary consultation with an expert surgeon.

Our surgeons will evaluate whether only 1 lump is progressing and whether it would be easy to resect. If it is determined to be resectable without much disturbance to the vital structure of any organ and if the patient is eligible for surgery and has a good performance status, we will adopt that approach.

If the patient has progressive disease in multiple sites, the standard second-line therapy is sunitinib. Sunitinib has activity in patients with GIST progressing on imatinib. It has more side effects than imatinib and has a different spectrum of effects. Being a VEGFR TKI, it may cause high blood pressure. As such, many patients are reluctant to receive sunitinib.

Tracks 4-6

DR LOVE: Would you discuss the Phase III GRID trial, which led to the FDA approval of regorafenib for patients with advanced GIST?

DR DEMETRI: Like sunitinib, regorafenib is a VEGFR TKI and does not inhibit BCR-ABL. Regorafenib has a different binding kinetic to the mutant receptor. It is active in patients with progressive GIST after imatinib and sunitinib failure.

The Phase III GRID trial was the definitive international study of regorafenib versus placebo after progression on imatinib and sunitinib (Demetri 2013; [1.1]). The median progression-free survival for placebo was 0.9 months. Because crossover was allowed, most patients received regorafenib in 1 month or less. Regorafenib significantly controlled the disease even after 2 or more prior TKIs.

The median progression-free survival for regorafenib was 4.8 months, which seems short. The response rates for any agent after imatinib failure are low, and in this study not many patients experienced objective tumor shrinkage, which is dramatically different from durable stable disease, which was achieved by about 70% of patients. In GIST, locking the tumor into a static state controls the disease. The pain is reduced, but eventually other clones proliferate, resistance develops, symptoms occur and other therapies are needed. Based on the results of the GRID study, the FDA approved regorafenib as third-line therapy for TKI-resistant GIST.

DR LOVE: How do you sequence regorafenib for these patients?

DR DEMETRI: Our standard sequence is imatinib, sunitinib and then regorafenib. We do not know if regorafenib will be better in the second-line setting. Ongoing research suggests that patients may fare better if these agents are sequenced differently. We are currently trying to model the duration of therapy for each agent in cell lines and are excited about this hypothesis.

DR LOVE: In your experience, what are the main side effects of regorafenib?

DR DEMETRI: With GIST, we were used to multitargeted kinase inhibitors like sunitinib. The similarities between sunitinib and regorafenib are notable. Both are VEGFR and PDGFR TKIs that cause hand-foot syndrome, which is manageable and can be diagnosed before blisters occur. Symptom worsening can be prevented and

patients are able to continue treatment. In the GRID study, less than 6% of patients discontinued therapy with regorafenib due to side effects.

DR LOVE: How do you manage hand-foot syndrome?

DR DEMETRI: Our nurses utilize a number of unique emollients. The bottom line is, as long as patients are tuned in, it is a manageable side effect. Doctors need to understand the variability in the pharmacology of the 3 TKIs imatinib, sunitinib and regorafenib. Because of individual patient differences, a standard dose is not appropriate for every patient. It is important to personalize the dosing of these agents based on side effects and tolerability. ■

1.1

GRID: Results from a Phase III Trial of Regorafenib for Metastatic or Unresectable Gastrointestinal Stromal Tumor (GIST) Progressing Despite Prior Treatment with at Least Imatinib and Sunitinib

Efficacy	Regorafenib (n = 133)	Placebo (n = 66)	Hazard ratio	*p*-value
Median progression-free survival	4.8 mo	0.9 mo	0.27	<0.0001
Overall survival events	22%	26%	0.77	0.199
Disease control rate	52.6%	9.1%	—	<0.0001
	Regorafenib (n = 132)		**Placebo** (n = 66)	
Select adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hand-foot skin reaction	56%	20%	14%	0%
Hypertension	49%	24%	17%	3%
Diarrhea	40%	5%	5%	0%
Oral mucositis	38%	2%	8%	2%
Fatigue	39%	2%	27%	0%
Alopecia	24%	2%	2%	0%
Anorexia	21%	0%	8%	0%
Maculopapular rash	18%	2%	3%	0%
Nausea	16%	1%	9%	2%
Constipation	15%	1%	6%	0%
Myalgia	14%	1%	9%	0%

Conclusion: "The results of this study show that oral regorafenib can provide a significant improvement in progression-free survival compared with placebo in patients with metastatic GIST after progression on standard treatments… This is the first clinical trial to show benefit from a kinase inhibitor in this highly refractory population of patients."

Demetri GD et al. *Lancet* 2013;381(9863):295-302.

SELECT PUBLICATIONS

Demetri GD et al. **Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, phase 3 trial.** *Lancet* 2013;381(9863):295-302.

George S et al. **Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: A multicenter phase II trial.** *J Clin Oncol* 2012;30(19):2401-7.

Pisters PW et al; reGISTry Steering Committee. **A USA registry of gastrointestinal stromal tumor patients: Changes in practice over time and differences between community and academic practices.** *Ann Oncol* 2011;22(11):2523-9.

INTERVIEW

Johanna C Bendell, MD

Dr Bendell is Director of GI Oncology Research and Associate Director of the Drug Development Unit at Sarah Cannon Research Institute in Nashville, Tennessee.

Tracks 1-19

Select Excerpts from the Interview

Track 3

DR LOVE: The ToGA trial previously demonstrated a survival advantage with the addition of trastuzumab to chemotherapy for patients with HER2-positive advanced gastric cancer (GC). What other HER2-targeted therapies are currently under investigation in HER2-positive GC?

DR BENDELL: T-DM1 is currently under investigation as second-line therapy for advanced disease (2.1). We're excited about T-DM1 in GC as well as the data coming from studies of pertuzumab combined with trastuzumab. Additional ongoing studies are investigating anti-HER2 therapies in the first-line and locally advanced settings.

2.1

Select Ongoing Clinical Trials of HER2-Directed Therapies in Gastric Cancer (GC), Including Adenocarcinoma of the Gastroesophageal Junction (GEJ)

Trial ID	Phase	Treatment arms	Patient population
NCT01641939	III	• T-DM1 (3.6 mg/kg, q3wk) • T-DM1 (2.4 mg/kg, q1wk) • Taxane	Previously treated locally advanced or metastatic GC
NCT01774786	III	• Pertuzumab/trastuzumab/CT • Placebo/trastuzumab/CT	Chemotherapy and HER2-directed therapy-naïve metastatic GC or GEJ
NCT01702558	II	• T-DM1/capecitabine	Previously treated locally advanced or metastatic GC
NCT01191697	II	• Trastuzumab/CAPOX/bev	Metastatic GEJ

CT = chemotherapy; bev = bevacizumab

www.clinicaltrials.gov, June 2013.

Tracks 4-5

DR LOVE: Would you discuss the results of the Phase III REGARD trial evaluating second-line ramucirumab for metastatic GC or gastroesophageal junction cancer (Fuchs 2013; [2.2])?

DR BENDELL: Ramucirumab is a fully human monoclonal antibody directed against VEGFR-2. Whereas bevacizumab binds to the ligand, ramucirumab binds to the receptor. In the REGARD study, patients were randomly assigned to receive ramuci-

2.2

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	0.0473
Median progression-free survival	2.1 mo	1.3 mo	0.483	<0.0001
Response rate (CR + PR)	3.4%	2.6%	—	0.756
Select adverse events, Grade ≥3	**Ramucirumab** (n = 236)		**Placebo** (n = 115)	
Fatigue	6.4%		9.6%	
Hypertension	7.6%		2.6%	
Anemia	6.4%		7.8%	

CR = complete response; PR = partial response

Fuchs S et al. Gastrointestinal Cancers Symposium 2013;**Abstract LBA5**.

rumab or placebo. Improvements were observed in overall and progression-free survival with ramucirumab. A few years ago, data from the AVAGAST study of capecitabine/cisplatin with or without bevacizumab as first-line therapy for patients with GC reported no improvements in overall survival (Ohtsu 2011). However, on subgroup analysis, particularly of patients in the United States, a significant trend toward improvement in overall and progression-free survival was observed with bevacizumab.

Differences in the epidemiology of GC worldwide have been discussed. In the United States, GC with much poorer prognosis tends to be present, which, for unknown reasons, appears to be more susceptible to anti-angiogenic agents. In the REGARD study, most patients received ramucirumab in North America. This may explain why the REGARD study was positive, whereas AVAGAST wasn't.

We're awaiting results from 2 other studies: The RAINBOW trial, which is evaluating second-line paclitaxel with or without ramucirumab, and a first-line Phase II study of FOLFOX with or without ramucirumab. Patients with metastatic gastroesophageal cancer definitely need more treatment options. Most patients don't make it to second-line therapy, and those who do have a poor survival of approximately 4 months. The availability of more agents should result in a better survival.

Tracks 15-16

DR LOVE: Given the new options for continued angiogenic inhibition after progression on first-line therapy, how do you approach the treatment of metastatic colorectal cancer (mCRC)?

DR BENDELL: The ARIES (Bendell 2012) and BRiTE (Grothey 2008) registrational trials initially investigated bevacizumab beyond progression, and benefits in the TML study (2.3) weren't as robust as those observed in ARIES or BRiTE. This suggests that doctors can select patients who are benefiting from anti-angiogenic therapy better than the trials. The patients who benefit from bevacizumab beyond first progression are those for whom up-front bevacizumab-based chemotherapy was beneficial and well tolerated. The decision for bevacizumab continuation as second-line therapy boils down to individual patient outcomes in the first line.

If a patient fared well with bevacizumab-based chemotherapy, such as FOLFOX, in the first-line setting, then I'm more inclined to continue bevacizumab with FOLFIRI into the second line. If a patient experienced rapid progression on first-line bevacizumab-based therapy, I may consider switching up the anti-angiogenic agent to something like afliber-

2.3

ML18147: Results from a Phase III Trial Evaluating the Addition of Bevacizumab (Bev) to Crossover Fluoropyrimidine-Based Chemotherapy (CT) for Patients with Metastatic Colorectal Cancer Experiencing Disease Progression on First-Line CT/Bev

Efficacy	CT + bev (n = 409)	CT (n = 410)	Hazard ratio	*p*-value
Median overall survival	11.2 mo	9.8 mo	0.81	0.0062
Median progression-free survival	5.7 mo	4.1 mo	0.68	<0.0001

Bennouna J et al. *Lancet Oncol* 2013;14(1):29-37.

cept. And, although it's good to now have regorafenib as an available option for mCRC, we are far from being able to identify those patients who might best benefit from it.

Aflibercept in combination with FOLFIRI improved overall and progression-free survival in the Phase III VELOUR trial (2.4). In my practice, the major side effect associated with aflibercept is asthenia. I also observe an increased incidence of diarrhea and neutropenia.

In terms of regorafenib, I have been seeing a patient for 5 years who had received all systemic chemotherapies. He also participated in 3 Phase I trials for patients with refractory disease. I was running out of options when regorafenib received FDA approval. I initiated treatment and was thrilled because after 2 cycles of regorafenib, his CEA level dropped, he experienced a minor response and he is currently tolerating it well. Like sorafenib, the major side effects of regorafenib are fatigue and hand-foot syndrome (2.5). For the latter, I recommend a urea-based cream thrice daily.

2.4

VELOUR: A Phase III Trial of Aflibercept versus Placebo in Combination with FOLFIRI as Second-Line Therapy for Metastatic Colorectal Cancer

Survival	FOLFIRI + aflibercept (n = 612)	FOLFIRI + placebo (n = 614)	Hazard ratio	*p*-value
Median progression-free survival	6.9 mo	4.7 mo	0.758	<0.0001
Median overall survival	13.5 mo	12.1 mo	0.817	0.0032

Select adverse events (Grades 3-4)	FOLFIRI + aflibercept (n = 611)	FOLFIRI + placebo (n = 605)
Neutropenia	36.7%	29.5%
Asthenic conditions	16.8%	10.6%
Diarrhea	19.3%	7.8%

Van Cutsem E et al. *J Clin Oncol* 2012;30(28):3499-506.

2.5

CORRECT: A Phase III Trial of Regorafenib with Best Supportive Care (BSC) versus Placebo with BSC for Patients with Metastatic Colorectal Cancer Who Experience Disease Progression After Standard Therapies

Efficacy	Regorafenib + BSC (n = 505)	Placebo + BSC (n = 255)	Hazard ratio	*p*-value
Median overall survival	6.4 mo	5.0 mo	0.77	0.0052
Median progression-free survival	1.9 mo	1.7 mo	0.49	<0.0001
Disease control rate	41.0%	15%	—	<0.0001
	Regorafenib + BSC (n = 500)		**Placebo + BSC** (n = 253)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Hand-foot skin reaction	47%	16.6%	8%	0.4%
Fatigue	47%	9.6%	28%	5.1%

Grothey A et al. *Lancet* 2013;381(9863):303-12.

Track 18

DR LOVE: What are your thoughts on the results of the Phase III MPACT study of gemcitabine with or without weekly *nab* paclitaxel for metastatic pancreatic cancer?

DR BENDELL: This study showed that the *nab* paclitaxel/gemcitabine regimen is effective with overall and progression-free survival benefits (Von Hoff 2013; [2.6]). The MPACT study was conducted in a different patient population from the ACCORD-11 trial of FOLFIRINOX, which was conducted exclusively in France by investigators who understood and knew how to administer FOLFIRINOX. The ACCORD-11 study provided patients with growth factors and strong antiemetics and included adequate supportive care and dose reductions to manage toxicities.

DR LOVE: Typically, younger patients with metastatic pancreatic cancer are treated with FOLFIRINOX. Based on the results of the MPACT study, would you consider *nab* paclitaxel/gemcitabine as an option in this setting?

DR BENDELL: We were involved in the MPACT trial, but I would like to have more experience with *nab* paclitaxel/gemcitabine in terms of toxicities. The primary toxicities I observed were blood count issues, so I administered growth factors on occasion, not automatically as I do with FOLFIRINOX. I have also observed numbness, tingling and neuropathy but primarily hematologic toxicities. I would also like to get a personal feel for its efficacy compared to that of modified FOLFIRINOX. ■

2.6

MPACT: A Phase III Trial of Weekly *Nab* Paclitaxel (*nab*-P)/Gemcitabine (Gem) versus Gem Alone for Patients with Metastatic Pancreatic Cancer

Efficacy outcome	*nab*-P/Gem (n = 431)	Gem (n = 430)	Hazard ratio	*p*-value
Median OS	8.5 months	6.7 months	0.72	0.000015
Median PFS	5.5 months	3.7 months	0.69	0.000024
ORR (independent review)	23%	7%	—	1.1×10^{-10}
Grade ≥3 adverse events	***nab*-P/Gem** (n = 421)		**Gem** (n = 402)	
Neutropenia	38%		27%	
Leukopenia	31%		16%	
Fatigue	17%		7%	
Peripheral neuropathy	17%		<1%	

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

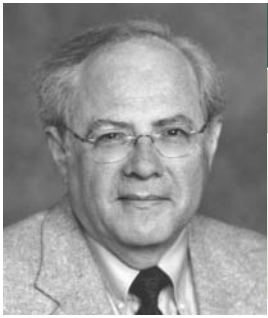
Von Hoff DD et al. Gastrointestinal Cancers Symposium 2013;**Abstract LBA148**.

SELECT PUBLICATIONS

Bendell JC et al. **Treatment patterns and clinical outcomes in patients with metastatic colorectal cancer initially treated with FOLFOX-bevacizumab or FOLFIRI-bevacizumab: Results from ARIES, a bevacizumab observational cohort study.** *Oncologist* 2012;17(12):1486-95.

Grothey A et al. **Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: Results from a large observational cohort study (BRiTE).** *J Clin Oncol* 2008;26(33):5326-34.

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.



INTERVIEW

Norman Wolmark, MD

Dr Wolmark is Chairman of the NSABP at Allegheny General Hospital in Pittsburgh, Pennsylvania and Professor of Human Oncology at the Drexel University College of Medicine in Philadelphia, Pennsylvania.

Tracks 1-8

Track 1 NSABP-C-07 study: Validation of the Onco*type* DX Colon Cancer assay RS as a predictor of recurrence risk in patients with Stage II and III colon cancer treated with 5-FU/leucovorin with or without oxaliplatin

Track 2 QUASAR: Validation study results for the Onco*type* DX Colon Cancer assay for prediction of recurrence risk in Stage II colon cancer

Track 3 Use of the Onco*type* DX RS to assist in tailoring treatment decisions for patients with early colon cancer

Track 4 Complexities in the use of adjuvant oxaliplatin for localized colon cancer

Track 5 Utility of the Onco*type* DX and ColoPrint assays

Track 6 Use of oxaliplatin in patients aged 70 or older

Track 7 Development of an Onco*type* DX Treatment Score for prediction of benefit with oxaliplatin

Track 8 NSABP-C-10: Results from a Phase II study evaluating mFOLFOX6 in combination with bevacizumab for patients with unresectable metastatic colon cancer and a synchronous asymptomatic primary tumor

Select Excerpts from the Interview

Tracks 1-3

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

DR WOLMARK: The QUASAR study prospectively validated the Onco*type* DX Recurrence Score as a predictor of recurrence risk for patients with Stage II colon cancer (Gray 2011). Patients were randomly assigned to surgery with or without fluoropyrimidine-based chemotherapy, excluding oxaliplatin. About 40% of the surgery-alone cohort fell into the low-risk category and had a 12% recurrence risk at 3 years. The intermediate-risk group had an 18% recurrence risk, whereas the high-risk group, which constituted about 25% of the study cohort, had a 22% recurrence risk. This study demonstrated that not all patients with Stage II disease are the same and that a spectrum can be categorized to reflect low, intermediate and high recurrence risk groups.

The NSABP-C-07 trial confirmed the value of the 12-gene Onco*type* DX Colon Cancer Recurrence Score as a predictor of recurrence risk in patients with Stage II and III colon cancer treated with 5-FU/leucovorin with or without the addition of oxaliplatin (O'Connell 2012; [3.1]). The Recurrence Score does not predict response to chemotherapy, but it was associated with outcome independent of other discriminates like nodal status and tumor grade.

DR LOVE: Although the QUASAR study showed that the Onco*type* DX assay was not predictive of benefit from chemotherapy, it seems that you can determine an absolute benefit from chemotherapy and differentiate patients who will have, for example, a 3% absolute relapse risk reduction and others with an 8% benefit. Can you comment on this aspect?

DR WOLMARK: This is definitely true of the QUASAR study and gets to the crux of how the algorithm can be applied. The proportional reductions in risk of recurrence with chemotherapy were similar across the range of Recurrence Scores. However, a patient with a low likelihood of recurrence has a smaller absolute benefit from chemotherapy than one with a high risk of recurrence.

It is noteworthy that in the NSABP-C-07 trial we can make the same observation. Even though the hazard ratio for the addition of oxaliplatin was similar across groups, patients in the low-risk cohort obtain little benefit from the use of oxaliplatin. The NSABP-C-07 study provides objective data to determine what the absolute benefit of adjuvant oxaliplatin will be to guide treatment decisions.

3.1

Validation of the Onco*type* DX Colon Cancer Recurrence Score (RS) in the Phase III NSABP-C-07 Study as a Predictor of Recurrence in Patients with Stage II and Stage 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: "RS predicts recurrence risk in Stage II and III colon cancer, capturing underlying biology and providing risk information beyond conventional factors. RS is not predictive of relative benefit of oxaliplatin added to adjuvant 5-FU but enables better discrimination of absolute oxaliplatin benefit as a function of risk. For certain patients with Stage IIIA/B disease, the finding of low RS (<30), and thus low recurrence risk and low absolute oxaliplatin benefit, may not justify the risk of potential toxicity from adding oxaliplatin."

O'Connell M et al. *Proc ASCO* 2012;**Abstract 3512**.

Tracks 4-5

DR LOVE: We presented a poster at the 2013 Gastrointestinal Cancers Symposium on the results from a survey of 102 US-based oncologists regarding the use of adjuvant oxaliplatin in 408 patients with Stage II and III colon cancer. Surprisingly, there was a high rate of oxaliplatin use for patients with Stage IIB disease and elderly patients, aged 70 and older, with Stage III colon cancer (Love 2013; [3.2]). What are your thoughts about usage of adjuvant oxaliplatin?

DR WOLMARK: I believe that the use of oxaliplatin for Stage II colon cancer can be challenged based on the data from the QUASAR and NSABP-C-07 studies. Patients at high risk derive a greater benefit from oxaliplatin whether they have Stage II or Stage III disease. So the risk must be considered in addition to whether the patient has Stage II or Stage III colon cancer. Even though the relative recurrence risk across the entire continuous variable for the addition of oxaliplatin is the same, the absolute benefit varies dramatically from low-risk to high-risk groups.

Oxaliplatin is an effective agent in the adjuvant setting for colon cancer. However, it's associated with neurotoxicity, and around 15% to 20% of patients have some residual neurotoxicity. So we have to be mindful of that. If a patient at high risk was reluctant to take oxaliplatin, I would try to convince him or her to take it as part of the regimen. However, in the low-risk group, where the absolute benefit is much smaller, one can justify not administering oxaliplatin based on the results of the NSABP-C-07 study.

DR LOVE: Does the Onco*type* DX Colon Cancer assay have a role outside a protocol setting?

DR WOLMARK: I believe this assay has a role outside a research setting. The Onco*type* DX 21-gene assay is used for more than 60% of women with node-negative, ER-positive breast cancer in the United States and has led to a decrease in the use of adjuvant chemotherapy in this population. In colon cancer we've seen reluctance to embrace the Onco*type* DX assay, which has been validated and confirmed, provides prognostic information and is useful in making treatment decisions. ■

3.2

Is Adjuvant Oxaliplatin Overused in Colon Cancer? 408 Cases from the Practices of 102 Oncologists

	Stage II (N = 306)					Stage III (N = 102)	
Adjuvant treatment	T2 N = 16	T3 N = 229	T4 N = 61	Age <70 N = 200	Age ≥70 N = 106	Age <70 N = 84	Age ≥70 N = 18
None	12 **75%**	142 **62%**	5 **8%**	78 **39%**	81 **76%**	1 **1%**	1 **6%**
5-FU	1 **6%**	11 **5%**	3 **5%**	11 **5%**	4 **4%**	0 **0%**	0 **0%**
Capecitabine	2 **13%**	32 **14%**	13 **21%**	31 **16%**	16 **15%**	4 **5%**	1 **6%**
Oxaliplatin/ fluoropyrimidine	1 **6%**	44 **19%**	40 **66%**	80 **40%**	5 **5%**	79 **94%**	16 **88%**

Love N et al. Gastrointestinal Cancers Symposium 2013;**Abstract 479**.

SELECT PUBLICATIONS

Gray RG et al. **Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer.** *J Clin Oncol* 2011;29:4611-9.

Kelley RK, Venook AP. **Prognostic and predictive markers in stage II colon cancer: Is there a role for gene expression profiling?** *Clin Colorectal Cancer* 2011;10(2):73-80.

Love N et al. **Is adjuvant oxaliplatin (Ox) overutilized in colon cancer (CC)? 408 cases from the practices of 102 oncologists.** Gastrointestinal Cancers Symposium 2013;**Abstract 479**.

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**.

INTERVIEW

Ghassan Abou-Alfa, MD

Dr Abou-Alfa is Associate Professor at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-11

Track 1 Critical assessment of local treatment modalities in hepatocellular carcinoma (HCC)

Track 2 Results from a Phase II trial of Bead Block® microspheres versus doxorubicin-eluting beads for arterial embolization of HCC

Track 3 Response assessment and complications associated with chemoembolization of HCC

Track 4 Transarterial chemoembolization with or without sorafenib in HCC

Track 5 Survival advantage with the addition of sorafenib to doxorubicin for advanced HCC

Track 6 Use of sorafenib in patients with HCC and Child-Pugh B disease

Track 7 Management of sorafenib-associated hand-foot syndrome

Track 8 Investigation of anti-angiogenic agents in HCC

Track 9 Heterogeneity of biliary tract cancers and opportunities for development of novel treatments

Track 10 **Case discussion:** A 78-year-old patient presents with abdominal pain and is diagnosed with HCC and bone metastases

Track 11 CALGB-80802: A Phase III trial of sorafenib alone versus sorafenib/doxorubicin for advanced HCC

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: What are your thoughts on the use of chemoembolization versus systemic therapy for patients with advanced hepatocellular carcinoma (HCC)?

DR ABOU-ALFA: Embolization or transarterial chemoembolization (TACE) is used for patients with extensive liver disease, tumors with close proximity to blood vessels or those that are unresectable. Systemic therapy with sorafenib would be recommended for patients with metastatic disease or unresectable local disease that is not amenable to therapy with embolization or TACE or for patients for whom prior therapy has failed.

Several years ago studies by Llovet (Llovet 2002) and Lo (Lo 2002) reported a survival benefit with TACE versus best supportive care, but it applied to relatively small disease in the liver. Notably, the study by Llovet and colleagues was discontinued early and the benefit of bland embolization versus best supportive care could not be determined.

Bland embolization has evolved with time, and we now try to achieve embolization to stasis to block off all the blood supply to the tumor. At the 2013 Gastrointestinal Cancers Symposium our group presented a randomized Phase II trial comparing bland embolization to chemoembolization with drug-eluting beads (Brown 2013; [4.1]). This

was probably the first study that directly compared chemoembolization to embolization. The most common side effect was postembolization syndrome, which is a classic syndrome of fever, pain and elevated liver function test results. As expected, certain side effects related to doxorubicin were observed on the chemoembolization arm.

The study reported no difference between the 2 arms, calling into question the addition of chemotherapy to embolization. The median overall survival for embolization versus chemoembolization was 16.6 and 19.6 months, respectively, which is much shorter than what was previously reported. Nowadays, we are expanding the scope of embolization to larger lesions, and that may account for the shorter survival. We may have to expand the role of systemic therapy to include not only patients with metastatic disease but also those with locally advanced disease that is beyond the scope of embolization.

DR LOVE: What are your thoughts on the combination of sorafenib with TACE for the treatment of HCC?

DR ABOU-ALFA: Recently, the large, randomized, Phase II SPACE trial reported no improvement in outcome with the addition of sorafenib to TACE for patients with HCC (Lencioni 2012). The combination of sorafenib and TACE is being further evaluated in 2 ongoing studies, ECOG-E1208 (NCT01004978) and TACE-2 (NCT01324076). Currently the data do not support the use of anti-angiogenic therapy after embolization.

4.1

Results from a Randomized Phase II Trial of Bead Block Microspheres versus Doxorubicin-Eluting Beads for Arterial Embolization of Hepatocellular Carcinoma

- This Phase II study reported that doxorubicin-eluting beads did not improve response rate, median time to disease progression, progression-free survival or overall survival.
- The addition of doxorubicin to the beads did not increase toxicity or compromise safety.
- The authors contend that the results from this study call into question added benefit of chemotherapy for embolization of hepatocellular carcinoma.

Brown KT et al. Gastrointestinal Cancers Symposium 2013;**Abstract 143**.

Tracks 5-7

DR LOVE: Would you discuss the combination of doxorubicin and sorafenib for patients with advanced HCC?

DR ABOU-ALFA: We investigated the combination of sorafenib with doxorubicin versus doxorubicin/placebo in the first-line setting for patients with advanced HCC. The study reported a significant improvement in overall survival for the doxorubicin/sorafenib arm, with a median survival of 13.7 months compared to 6.5 months for doxorubicin/placebo (Abou-Alfa 2010; [4.2]). The results with doxorubicin alone were expected, but the study raised the question of possible synergy between doxorubicin and sorafenib that could account for the 13.7-month median survival versus 10.7 months, which is what is reported for sorafenib.

That question is being addressed by the CALGB-80802 study, which is the first NCI-sponsored Phase III trial in HCC in the United States. This trial comparing

4.2

Randomized Phase II Trial of Doxorubicin (Dox) in Combination with Sorafenib versus Dox Alone for Advanced Hepatocellular Carcinoma

Survival	Dox + sorafenib (n = 47)	Dox + placebo (n = 49)	Hazard ratio	*p*-value
Median time to progression	6.4 mo	2.8 mo	0.5	0.02
Median overall survival	13.7 mo	6.5 mo	0.49	0.006
Median progression-free survival	6.0 mo	2.7 mo	0.54	0.006

Select adverse events (Grade 3 or 4)	Dox + sorafenib (n = 47)	Dox + placebo (n = 49)
Any adverse event	63.8%	60.4%
Constitutional symptoms	6.4%	6.3%
Fatigue	6.4%	6.3%
Dermatologic	10.6%	0%
Hand-foot skin reaction	6.4%	0%
Gastrointestinal	21.3%	18.8%
Hematologic	44.7%	50.1%
Infection	0%	8.3%
Pain	6.4%	0%

Abou-Alfa GK et al. *JAMA* 2010;304(19):2154-60.

doxorubicin and sorafenib to sorafenib alone for patients with locally advanced or metastatic HCC is ongoing (4.3).

At the 2012 Gastrointestinal Cancers Symposium we presented data from a retrospective study evaluating the addition of doxorubicin to sorafenib therapy in 14 patients for whom sorafenib had failed (Abou-Alfa 2012). It is intriguing that in comparison to historical controls the median survival almost doubled with second-line doxorubicin/sorafenib after failure of sorafenib. A Phase II study, due to start soon, will further investigate the addition of doxorubicin to sorafenib after failure to respond to sorafenib in the first line.

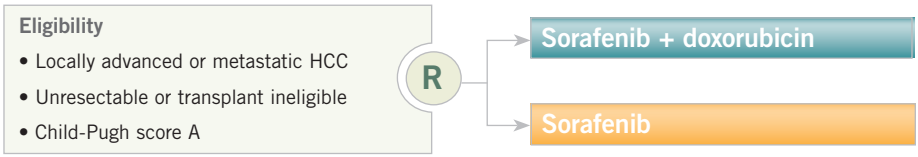
DR LOVE: What are the recommendations for sorafenib use in patients with HCC who have Child-Pugh B disease?

DR ABOU-ALFA: A retrospective analysis of data from a Phase II study evaluating sorafenib in patients with Child-Pugh B disease and advanced HCC reported a

4.3

CALGB-80802: A Phase III Study of Sorafenib with or without Doxorubicin for Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC)

Protocol ID: NCT01015833 **Target accrual:** 480



www.clinicaltrials.gov, July 2013.

worsening of liver function on sorafenib therapy (Abou-Alfa 2011). The CALGB-60301 trial evaluated the safety of sorafenib in patients with advanced hepatic or renal dysfunction (Miller 2009). The dose-limiting toxicity was an increase in bilirubin, which occurred more frequently in the patients with elevated bilirubin at baseline. The study made recommendations regarding the starting sorafenib dose in these patients.

Patients with bilirubin levels of 1.5 times the upper limit of normal or lower should receive the full dose of sorafenib — 400 mg BID. Patients with bilirubin levels of 1.5 to 3 times the upper limit of normal should receive half that dose — 200 mg BID. For patients with bilirubin levels more than 3 times the upper level of normal, no safe dose has been reported. For patients with albumin levels less than 2.5 mg/dL, regardless of the bilirubin level, sorafenib should be administered at 200 mg daily. These recommendations are not adopted by everyone. I use these guidelines because bilirubin levels can escalate quickly in a patient with Child-Pugh B disease who is receiving sorafenib.

DR LOVE: Are you concerned about administering sorafenib to elderly patients or those with poor performance status?

DR ABOU-ALFA: I'm not concerned about administering sorafenib to elderly patients with a good performance status. A poor performance status could be related to liver function in a patient with cirrhosis and would argue against sorafenib use in some cases.

DR LOVE: How do you manage the hand-foot skin reaction associated with sorafenib?

DR ABOU-ALFA: A large Phase II study evaluated the prophylactic effect of a urea-based cream on the hand-foot skin reaction associated with sorafenib in advanced HCC (Ren 2012). The study reported that the urea-based cream reduced the incidence and severity of hand-foot skin reaction. However, there were some caveats to the study with regard to how the assessments were performed and the fact that the study was not blinded. Hand-foot syndrome is still not completely understood and remains an active area of research. ■

SELECT PUBLICATIONS

Abou-Alfa GK et al. **Retrospective review of doxorubicin plus sorafenib as second-line therapy in hepatocellular carcinoma (HCC).** Gastrointestinal Cancers Symposium 2012;**Abstract 298**.

Abou-Alfa GK et al. **Safety and efficacy of sorafenib in patients with hepatocellular carcinoma (HCC) and Child-Pugh A versus B cirrhosis.** *Gastrointest Cancer Res* 2011;4(2):40-4.

Brown KT et al. **A randomized single blind controlled trial of beads versus doxorubicin-eluting beads for arterial embolization of hepatocellular carcinoma (HCC).** Gastrointestinal Cancers Symposium 2013;**Abstract 143**.

Lencioni R et al. **Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermediate-stage hepatocellular carcinoma (HCC): Phase II, randomized, double-blind SPACE trial.** Gastrointestinal Cancers Symposium 2012;**Abstract LBA154**.

Llovet JM et al. **Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial.** *Lancet* 2002;359(9319):1734-9.

Lo CM et al. **Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma.** *Hepatology* 2002;35(5):1164-71.

Miller A et al. **Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301.** *J Clin Oncol* 2009;27(11):1800-5.

Ren Z et al. **A randomized controlled phase II study of the prophylactic effect of urea-based cream on the hand-foot skin reaction associated with sorafenib in advanced hepatocellular carcinoma.** *Proc ASCO* 2012;**Abstract 4008**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III GRID trial of regorafenib/best supportive care versus placebo/best supportive care demonstrated a statistically significant improvement in _____ with regorafenib for patients with metastatic and/or unresectable GIST after disease progression on at least imatinib and sunitinib.**
   a. Overall survival
   b. Progression-free survival
   c. Disease control rate
   d. Both b and c
   e. All of the above

2. **_____ is a side effect commonly associated with regorafenib therapy for patients with metastatic and/or unresectable GIST after disease progression on at least imatinib and sunitinib.**
   a. Hand-foot skin reaction
   b. Hypertension
   c. Diarrhea
   d. Maculopapular rash
   e. All of the above

3. **_____ is a TKI that targets both VEGFR and PDGFR but not BCR-ABL in the treatment of advanced GIST.**
   a. Regorafenib
   b. Imatinib
   c. Sunitinib
   d. Nilotinib
   e. Both a and c
   f. All of the above

4. **The Phase III REGARD trial evaluating ramucirumab/best supportive care versus placebo/best supportive care as second-line therapy for patients with metastatic gastric or gastroesophageal junction adenocarcinoma demonstrated a statistically significant improvement in progression-free survival with ramucirumab.**
   a. True
   b. False

5. **The Phase III MPACT trial of gemcitabine with or without weekly *nab* paclitaxel for patients with metastatic adenocarcinoma of the pancreas demonstrated a statistically significant improvement in _____ with the addition of *nab* paclitaxel.**
   a. Progression-free survival
   b. Overall survival
   c. Overall response rate
   d. All of the above

6. **The Phase III TML trial evaluating the addition of bevacizumab to crossover fluoropyrimidine-based chemotherapy versus chemotherapy alone for patients with mCRC experiencing disease progression on first-line chemotherapy/bevacizumab demonstrated a statistically significant improvement in _____ with the addition of bevacizumab.**
   a. Overall survival
   b. Progression-free survival
   c. Both a and b
   d. Neither a nor b

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

8. **The QUASAR study, which prospectively validated the Onco*type* DX Recurrence Score as a predictor of recurrence risk for patients with Stage II colon cancer, reported that patients in the low-risk category had a _____ recurrence risk at 3 years with surgery alone.**
   a. ≥50%
   b. 12%
   c. 0%

9. **A randomized Phase II trial of doxorubicin in combination with sorafenib versus doxorubicin alone for patients with advanced HCC demonstrated a significant improvement in _____ with the doxorubicin/sorafenib combination therapy.**
   a. Median progression free-survival
   b. Median overall survival
   c. Both a and b

10. **A recent Phase II study by Brown and colleagues comparing embolization to chemoembolization with doxorubicin-eluting beads reported no difference in median overall survival between the 2 arms.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 2, 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
MPACT: Results from a Phase III study of weekly *nab* paclitaxel in combination with gemcitabine versus gemcitabine alone for metastatic adenocarcinoma of the pancreas	4 3 2 1	4 3 2 1
Validation of the Onco*type* DX Colon Cancer assay Recurrence Score as a predictor of recurrence for patients with Stage II and III colon cancer treated with 5-FU/leucovorin with or without oxaliplatin on the NSABP-C-07 trial	4 3 2 1	4 3 2 1
Efficacy and tolerability of ramucirumab as second-line therapy for metastatic gastric or gastroesophageal junction cancer (REGARD trial)	4 3 2 1	4 3 2 1
Results of the Phase III GRID trial of regorafenib for patients with imatinib- and sunitinib-resistant GIST	4 3 2 1	4 3 2 1
New options for continued anti-angiogenic treatment — aflibercept, bevacizumab beyond progression, regorafenib — after disease progression on first-line therapy for mCRC	4 3 2 1	4 3 2 1
Survival advantage with the addition of sorafenib to doxorubicin for 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: .....

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 therapy for patients with metastatic CRC. . . . . 4 3 2 1 N/M N/A
- Summarize key findings from clinical studies of emerging therapeutic regimens for pancreatic cancer, and use this information to guide treatment decision-making. . . . . 4 3 2 1 N/M N/A
- Counsel patients with early GI stromal tumors about the potential benefits of adjuvant imatinib, and define an evidence-based duration of treatment. . . . . 4 3 2 1 N/M N/A
- Evaluate therapeutic options for patients with imatinib- and sunitinib-resistant GI stromal tumors. . . . . 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 2 — 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			
George D Demetri, MD	4	3	2	1	4	3	2	1
Johanna C Bendell, MD	4	3	2	1	4	3	2	1
Norman Wolmark, MD	4	3	2	1	4	3	2	1
Ghassan Abou-Alfa, 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 USA LLC, Novartis Pharmaceuticals Corporation, Regeneron Pharmaceuticals and Sanofi.

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Last review date: August 2013
Release date: August 2013
Expiration date: August 2014
Estimated time to complete: 3 hours

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