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Gastrointestinal Cancer™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Charles D Blanke, MD
Bert H O'Neil, MD
Steven R Alberts, 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 continually 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

- Utilize case-based learning to formulate individualized management strategies for GI cancer.
- Summarize key findings from clinical studies of emerging therapeutic regimens for pancreatic cancer, and utilize this information to guide treatment decision-making for patients.
- Assess the role of molecular markers in optimizing therapeutic decisions for patients with early or advanced CRC.
- Counsel patients with Stage II colon cancer about their individual risk of recurrence based on clinical, pathologic and genomic biomarkers, and consider adjuvant therapeutic options.
- Apply the results of new research when recommending neoadjuvant chemoradiation therapy to patients with locally advanced rectal cancer.
- Formulate a treatment plan for patients with primary CRC and liver-only metastases.
- Utilize clinical and molecular biomarkers to optimize the selection of systemic therapy for patients with gastric or gastroesophageal cancer.
- Communicate the benefits and risks of existing and emerging systemic interventions to patients with advanced hepatocellular carcinoma.

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INTERVIEW

Charles D Blanke, MD

Dr Blanke is Vice-President of Systemic Therapy at the BC Cancer Agency and Head of the Division of Medical Oncology at the University of British Columbia in Vancouver, British Columbia.

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Track 2 Long-term results from a Phase II study of standard- versus higher-dose imatinib for unresectable or metastatic, KIT-positive GIST

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Track 5 Sorafenib in advanced GIST

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DR LOVE: What are your thoughts on the SSGXVIII/AIO trial of adjuvant imatinib therapy for patients with operable gastrointestinal stromal tumors (GIST) with a high risk of recurrence?

DR BLANKE: This trial demonstrated a marked improvement in recurrence-free survival for 3 years versus 1 year of treatment, but the surprising observation from this study was the overall survival benefit (Joensuu 2011; [1.1]).

Previous studies, such as the ACOSOG-Z9001 trial, demonstrated a dramatic improvement in recurrence-free survival with 1 year of imatinib therapy but no overall survival benefit (DeMatteo 2009). Unfortunately as a result, some oncologists decided not to treat with adjuvant imatinib because they thought they could catch up at the metastatic stage.

The SSGXVIII/AIO trial provides 3 take-home messages. First, 3 years is the new gold standard for imatinib adjuvant therapy. Second, due to the overall survival benefit, it is no longer practicable to wait for patients to experience relapse. Last, whether adjuvant imatinib therapy is curative or whether it merely prolongs disease remission in these patients is yet to be determined.

This has important implications for determining if 3 years is the actual "magic number" or whether it is 5 or 10 years or whether these patients should undergo lifelong treatment, although this is a huge commitment for a patient who may already have been cured. In practice, I will continue adjuvant imatinib therapy beyond the 3-year treatment point if I can.

1.1

SSGXVIII/AIO: A Randomized Phase III Clinical Trial of 12 versus 36 Months of Adjuvant Imatinib Therapy for Patients with High-Risk Gastrointestinal Stromal Tumors

Outcome	**One-year arm** (%)	**Three-year arm** (%)	Hazard ratio	*p*-value
Five-year RFS	47.9	65.6	0.46	<0.0001
Five-year OS	81.7	92.0	0.45	0.019

RFS = recurrence-free survival; OS = overall survival

Joensuu H et al. *Proc ASCO* 2011;**Abstract LBA1**.

DR LOVE: Any other important new studies in the treatment of GIST?

DR BLANKE: I was involved with the B2222 trial that began patient enrollment about 10 years ago (von Mehren 2011). This was a randomized Phase II study of 400 versus 600 milligrams per day of imatinib for patients with KIT-positive, unresectable or metastatic GIST. Though not surprising, an interesting result from this study was a 35% 9-year overall survival rate, meaning

that a third of all patients were alive and well after almost a decade. Of importance is the result that few relapses occurred after about 5 to 6 years. This has important implications for how we survey patients in the future. It negates the need for quarterly or semiannual CTs, thereby resulting in less frequent patient monitoring and reduced exposure to radiation and IV dye.

DR LOVE: What about the role of sorafenib in advanced GIST?

DR BLANKE: Sorafenib is a multikinase inhibitor approved for the treatment of advanced renal cell carcinoma and unresectable hepatocellular carcinoma (HCC) and has also been "floating around" for a while in GIST therapy. Data at ASCO 2011 reported an approximate 70% tumor control rate without disease progression for about 5 months when sorafenib was administered as late-line therapy (Kindler 2011; [1.2]).

Regorafenib, a later derivative of sorafenib, is another modestly promising agent in advanced GIST therapy. It is possible that one of these will eventually be moved up into the adjuvant setting as combination therapy or monotherapy.

1.2

Phase II Consortium Trial of Sorafenib for Patients with Imatinib (IM)- and Sunitinib (SU)-Resistant Gastrointestinal Stromal Tumors

	IM resistant (n = 6)	IM/SU resistant (n = 32)
Partial response	17%	13%
Stable disease	50%	56%
Disease control rate	67%	69%

Kindler HL et al. *Proc ASCO* 2011;**Abstract 10009**.

Tracks 15-16

DR LOVE: Anything presented at ASCO 2011 in gastric cancer (GC) that caught your attention?

DR BLANKE: Because intensifying cancer therapy in the metastatic GC setting may yield better outcomes, particularly with the addition of an anthracycline, in the CALGB-80101 adjuvant trial for patients with gastric or gastroesophageal junction adenocarcinoma 5-FU was administered during radiation therapy but then intensified systemically with epirubicin/cisplatin/5-FU (Fuchs 2011). The trial was slow to accrue and it was "stone cold negative" without a hint of benefit. Hence, 5-FU adjuvant therapy remains the standard used with radiation therapy in North America.

The Phase III CLASSIC trial, which evaluated capecitabine/oxaliplatin without radiation therapy for GC, reported a dramatic improvement in disease-free survival (Bang 2011). Although improvement has not yet been observed in overall survival, that may occur in time as a trend emerged toward statistical significance with a *p*-value of 0.0775.

DR LOVE: Have we seen new developments in advanced GC with regard to anti-HER2 treatment?

DR BLANKE: I consider HER2 testing to be a new standard procedure in GC. The ToGA trial results in advanced GC mandate trastuzumab treatment for patients with HER2-positive GC (Bang 2010; [1.3]). Considering it is being used in the metastatic setting, I will certainly treat with trastuzumab until disease progression. Unlike breast cancer, treatment with trastuzumab beyond disease progression in GC has garnered little enthusiasm, although this may be the right approach to take. ■

1.3

ToGA: Efficacy from a Phase III Study of the Addition of Trastuzumab to First-Line Chemotherapy for HER2-Positive Advanced Gastric or Gastroesophageal Junction Cancer

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

F = fluoropyrimidine (5-FU or capecitabine); C = cisplatin; T = trastuzumab

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

SELECT PUBLICATIONS

Bang YJ et al. **Adjuvant capecitabine and oxaliplatin for gastric cancer: Results of the phase III CLASSIC trial.** *Proc ASCO* 2011;**Abstract LBA4002**.

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

DeMatteo RP et al. **Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: A randomised, double-blind, placebo-controlled trial.** *Lancet* 2009;373(9669):1097-104.

Fuchs CS et al. **Postoperative adjuvant chemoradiation for gastric or gastroesophageal junction (GEJ) adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (CRT) compared with bolus 5-FU/LV before and after CRT: Intergroup trial CALGB 80101.** *Proc ASCO* 2011;**Abstract 4003**.

Joensuu H et al. **Twelve versus 36 months of adjuvant imatinib (IM) as treatment of operable GIST with a high risk of recurrence: Final results of a randomized trial (SSGXVIII/AIO).** *Proc ASCO* 2011;**Abstract LBA1**.

Kindler HL et al. **Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): Final results of a University of Chicago Phase II Consortium trial.** *Proc ASCO* 2011;**Abstract 10009**.

Von Mehren M et al. **Follow-up after 9 years (yrs) of ongoing, phase II B2222 trial of imatinib mesylate (IM) in patients (pts) with metastatic or unresectable KIT+ gastrointestinal stromal tumors (GIST).** *Proc ASCO* 2011;**Abstract 10016**.

INTERVIEW

Bert H O'Neil, MD

Dr O'Neil is Associate Professor and Director of the GI Oncology Clinical Research Program at UNC Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

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Track 2 Chemoembolization with or without sorafenib in unresectable HCC

Track 3 Side effects, dose reduction and supportive care measures with sorafenib

Track 4 Evaluation of novel agents in advanced HCC

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Track 6 **Case 7 discussion:** A 58-year-old man who has HCV-related HCC with portal vein thrombosis, thrombocytopenia and Child-Pugh A liver disease

Track 7 Use of yttrium-90 microspheres for patients with advanced HCC and portal vein thrombosis

Track 8 Perspective on the benefits of locoregional versus systemic therapy for advanced HCC

Track 9 Use of sorafenib among medical oncologists and hepatologists for HCC

Track 10 Capecitabine-based chemoradiation therapy for the preoperative treatment of rectal cancer

Track 11 NSABP-R-04 study: Impact of oxaliplatin in the preoperative multimodality treatment of rectal cancer

Track 12 Investigation of dual antibody therapy for patients with K-ras wild-type mCRC

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What criteria do you consider to determine which patients with HCC are appropriate for transplant as opposed to resection?

DR O'NEIL: Resection is not an option for patients with severe cirrhosis, even in those with small tumors. However, these patients may fall within the UNOS criteria for transplant — having either 1 lesion of 5 centimeters or less or 3 or fewer lesions of less than 3 centimeters in diameter. The long-term survival rate after transplant for patients with those criteria is about 80%, so it's quite an effective therapy.

By contrast, for a similar patient who is a candidate for resection, you're probably looking at more like a 40% to 50% long-term survival rate because of worsening of liver disease or development of new tumors elsewhere in the liver.

DR LOVE: For which patients do you consider local therapy as a bridge to transplant?

DR O'NEIL: For patients with borderline tumors — ie, those between 3½ and just smaller than 5 centimeters — we will often consider this approach. The procedure we prefer at our institution is embolization because it has good response rates. It allows the patient to stay on the transplant list without experiencing progression, and I believe it's a good way to care for that particular group of patients. Another option for some patients is ablation, although some concerns persist about tracked seeding when you perform ablation.

DR LOVE: What are your thoughts on the integration of sorafenib with chemoembolization?

DR O'NEIL: The answer to that question will come from the ECOG-E1208 study in which patients with unresectable HCC receive sorafenib prior to transarterial chemoembolization (TACE). Sorafenib is discontinued for a few days around the procedure but then resumed and continued until progression (2.1).

DR LOVE: Do you believe this strategy is reasonable outside a protocol setting?

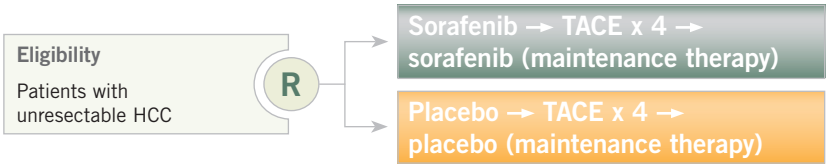
DR O'NEIL: That is a tough question. We perform embolization for different types of patients. One is the group of patients with unresectable tumors, such as tumors that are too large to ablate but are quite vascular. Some of those patients fare remarkably well with embolization. Some of my patients have undergone repeated embolizations for a number of years. I find it hard to imagine that such a patient would benefit much from concomitant sorafenib.

But some patients clearly don't respond well to embolization, and they end up receiving sorafenib relatively shortly thereafter. So you wonder if starting the sorafenib earlier, around the time of embolization, might benefit those patients.

Additionally, data suggest that when we perform an embolization, the tumor secretes VEGF in response to the hypoxia. Perhaps that might assist the

2.1

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

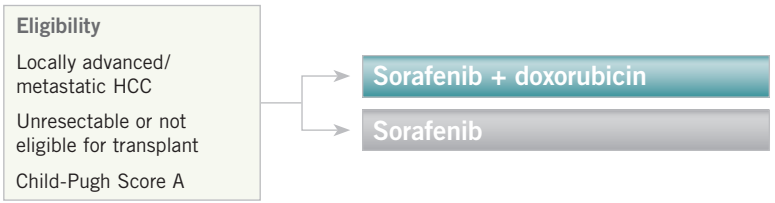


www.clinicaltrials.gov, October 2011.

2.2

Randomized Phase III Study Comparing Sorafenib and Doxorubicin to Sorafenib Alone in Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC)

Protocol ID: CALGB-80802 **Target Accrual:** 480 (Open)



www.clinicaltrials.gov, October 2011.

tumor's growth in the postembolization period, and maybe inhibiting VEGF signaling with sorafenib around the time of embolization might help. I believe we need more randomized data before we routinely adopt such an approach.

Track 4

DR LOVE: Are there any new encouraging research strategies in HCC?

DR O'NEIL: The CALGB has an interesting study evaluating the combination of doxorubicin and sorafenib (2.2) based on some Phase II data on this combination (Abou-Alfa 2010; [2.3]). Some people have limited enthusiasm for doxorubicin, given that it is an older agent and is a bit toxic, but I believe this is an important study that needs to be done.

2.3

Sorafenib and Doxorubicin (S + D) versus Placebo and Doxorubicin (P + D) for Advanced Hepatocellular Carcinoma

	S + D (n = 47)	P + D (n = 49)	Hazard ratio	*p*-value
Median time to progression	6.4 months	2.8 months	0.50	0.02
Median overall survival	13.7 months	6.5 months	0.49	0.006
Median progression-free survival	6.0 months	2.7 months	0.54	0.006

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

Tracks 6-8

Case discussion

A 58-year-old man who has HCV-related HCC with portal vein thrombosis (PVT), thrombocytopenia and Child-Pugh A liver disease.

DR O'NEIL: This patient would have been a candidate for the SHARP trial evaluating sorafenib in HCC (Llovet 2008). For someone like him, the question right from the outset was, is it better to use regional therapy or start the patient on sorafenib, or should we do both? Without the data, I'm hesitant to do both.

This is one of those borderline areas in which little consensus is seen regarding the best treatment approach. We have several strategies for this type of patient. The patient was not eligible for transplant. His spleen was fairly large and his platelet count was about 38,000, so we were unable to perform a resection and were stuck with this localized but effectively incurable tumor.

This patient received treatment with yttrium-90 microspheres (Y-90). Y-90 is used quite a bit without any randomized data. A large case series study has shown an improvement in overall survival with Y-90 versus a regional therapy (Carr 2010), but no randomized data have been presented against any other form of therapy. One advantage of Y-90 is that it is safer to administer in the setting of PVT than chemoembolization. The reason is that although these are embolic particles, the number of particles in a treatment is designed to deliver a particular radiation dose but does not fully embolize the region.

With chemoembolization, if you have an issue with the portal vein and you embolize the artery, you effectively have no blood flow to that segment of the liver, which can result in complications. In bad cases, patients can experience complete necrosis of an area. They'll experience hepatocyte damage in that region, and some patients don't have enough liver reserve to tolerate that. This can result in liver failure. Chemoembolization can be performed. It's not an absolute contraindication. With the improved catheters of today, you can get to smaller portions of the liver. But most of us still consider a major PVT to be at least a relative contraindication to chemoembolization.

This patient's tumor was hard to measure, so we followed him for a few months with MRI. He had stable disease for quite some time but then eventually developed venous thrombosis and evidence of tumor involvement in the opposing lobe. This posed a dilemma: Do we keep chasing this with regional therapy or move to systemic therapy? My preference is to move to sorafenib in such cases, and he has now been receiving sorafenib for about 6 months. Because of the diffuse nature of the patient's tumor, we didn't expect to see much change. Portal vein thrombi tend to remain static. So in his case we're looking for lack of disease progression as a sign of benefit. He's tolerated sorafenib well with only minor hand-foot issues, for which we paused therapy without dose reduction. ■

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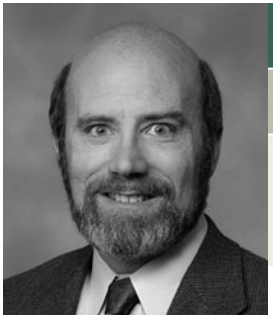
Abou-Alfa GK et al. **Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: A randomized trial.** *JAMA* 2010;304(19):2154-60.

Carr BI et al. **Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: A two-cohort study.** *Cancer* 2010;116(5):1305-14.

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



INTERVIEW

Steven R Alberts, MD

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

Tracks 1-13

Track 1 Association of K-ras G13D mutation with outcome in patients with mCRC treated with cetuximab

Track 2 Prognostic web-based models for Stage II and III colon cancer: A population- and clinical trials-based validation of Numeracy and Adjuvant! Online

Track 3 Utility of the Onco*type* DX colon cancer assay

Track 4 **Case 8 discussion:** A 58-year-old man with resected Stage III colon cancer had several postoperative surgical complications precluding adjuvant chemotherapy and developed small, resectable hepatic metastases 18 months later

Track 5 Determining resectability of liver-limited mCRC

Track 6 Conversion therapy in potentially resectable colorectal hepatic metastases

Track 7 Perioperative FOLFOX/bevacizumab for patients with potentially resectable CRC hepatic metastases

Track 8 Perioperative chemotherapy versus surgery alone for patients with resectable mCRC

Track 9 **Case 9 discussion:** A 56-year-old woman with T3N0M0 colon cancer with a focal area of lymphovascular invasion, 0 of 47 positive lymph nodes and no MMR deficiencies has an Onco*type* DX Recurrence Score® of 20

Track 10 Perspective on the utility of Onco*type* DX for patients with Stage II colon cancer

Track 11 BRAF V600E mutation as a potential therapeutic target in CRC

Track 12 **Case 10 discussion:** A 63-year-old man with a T3 rectal tumor and nodal involvement receives neoadjuvant capecitabine and radiation therapy followed by adjuvant FOLFOX

Track 13 Use of radiation therapy in upper rectal cancer

Select Excerpts from the Interview

Track 1

DR LOVE: What are your thoughts about recent data suggesting a possible benefit from anti-EGFR antibodies in patients with a G13D K-ras mutation?

DR ALBERTS: A recent article in *JAMA* reported on this specific K-ras mutation. Patients with metastatic colorectal cancer and G13D still seem to

respond to EGFR inhibitors (de Roock 2010; [3.1]), and it was also reported in a presentation at ASCO 2011 that this subgroup benefits from cetuximab (Tejpar 2011). These data raise the point that when we're doing K-ras testing, we need to be aware of specific subgroups as to not exclude a patient population from potential therapeutic benefit. Although the proportion of patients with the K-ras mutation who have this G13D subtype is small — it represents roughly 20% of mutations — we certainly don't want to deprive them of the opportunity to receive an EGFR inhibitor.

Given these findings, we performed a retrospective analysis of patients who received cetuximab on our NCCTG-N0147 trial. Our results indicated no benefit in the adjuvant setting within the group of patients with the K-ras G13D mutation who received cetuximab (Alberts 2011).

3.1

Association of K-ras G13D Mutation with Outcome for Patients with Chemotherapy-Refractory Metastatic Colorectal Cancer Treated with Any Cetuximab-Based Therapy

	K-ras mutation		
	K-ras G13D mutation (n = 45)	**Other K-ras mutations** (n = 265)	**K-ras wild type** (n = 464)
Median overall survival	7.6 months Reference	5.7 months HR* = 0.50; $p = 0.005$	10.1 months HR* = 0.94; $p = 0.79$
Median progression-free survival	4.0 months Reference	1.9 months HR* = 0.51; $p = 0.004$	4.2 months HR* = 1.10; $p = 0.66$

* Hazard ratios are expressed for comparison of K-ras G13D mutation versus other status.

De Roock W et al. *JAMA* 2010;304(16):1812-20.

Tracks 3, 9-10

DR LOVE: What are your thoughts about the Onco*type* DX colon cancer assay?

DR ALBERTS: The Onco*type* DX assay for colon cancer was designed using a similar paradigm as for breast cancer. Retrospective analyses of large databases were performed to select genes that would provide a better understanding of which patients with Stage II colon cancer are more likely to experience relapse after surgery and who might benefit from adjuvant therapy if that risk of relapse is high enough.

The Onco*type* DX colon cancer assay focuses on patients at intermediate risk based on other clinical parameters. It is not meant for patients at high risk and also excludes patients with deficiency in mismatch repair who have a low risk of recurrence. So you're left with that group in between with an approximate 10% to 30% risk of recurrence. If we're going to administer chemotherapy,

we'd want to focus on that higher end of the spectrum. This assay is meant to help clarify where a patient fits along that spectrum.

Although the breast assay does provide some information about potential benefit with chemotherapy, the colon Onco*type* DX assay doesn't do so directly. We are unfortunately left with information derived from the NSABP-C-07 and MOSAIC trials to determine within that subgroup of patients who were enrolled with Stage II colon cancer how much benefit they gained from chemotherapy overall. We can then apply that to the risk of recurrence based on the Onco*type* DX colon assay and derive some potential benefit for a patient from those pieces of information.

The colon assay became available recently, and oncologists are still trying to understand how it fits into their daily practice and whether it changes their decision-making when they meet with a patient with Stage II colon cancer.

DR LOVE: Do you have any patients for whom you have used the Onco*type* DX colon assay?

DR ALBERTS: I used it for a young woman who had average-risk Stage II colon cancer. Due to her young age, the surgeon strongly recommended that she receive chemotherapy to ensure that the disease didn't recur, but other than focal lymphovascular invasion, no other risk factors suggested she would benefit from chemotherapy. We discussed the potential use of the Onco*type* DX assay. She agreed and the result came back as a Recurrence Score of 20, which translates to a risk of recurrence of about 13% (Kerr 2009; [3.2]).

She decided not to pursue chemotherapy unless the Recurrence Score came back indicating a high risk of recurrence. She is now being followed periodically for any evidence of recurrence.

3.2

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

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

* With surgery alone

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

Track 8

DR LOVE: Would you comment on the important issue of preoperative systemic therapy for patients with colorectal cancer and resectable liver metastases?

DR ALBERTS: The question remains, does a benefit exist to perioperative versus postoperative chemotherapy in this setting? Part of the thought process has been that if we administer perioperative chemotherapy, then we're immediately gaining control of any metastatic disease either within or outside the liver and that ultimately should lead to better outcomes versus immediately taking patients to surgery and delaying the use of chemotherapy until they recover.

A European trial seemed to show a benefit to perioperative chemotherapy (Nordlinger 2008). An ongoing NSABP trial should help clarify this issue in a group of patients at somewhat higher risk (3.3).

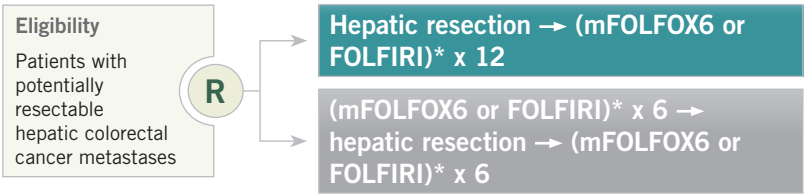
DR LOVE: What is your typical approach to a patient who presents with a single, easily resectable metastasis?

DR ALBERTS: For patients a year or more out from adjuvant therapy with a solitary metastasis, I tend to refer them directly to the surgeon and encourage proceeding to surgery. For a patient at higher risk with either multiple metastases, even if it's 3 or 4 metastases in 1 lobe or somebody who experiences relapse shortly after adjuvant therapy, I believe it's important to show that you can establish control of the disease prior to proceeding to surgery. ■

3.3

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

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



* Dependent upon prior exposure to oxaliplatin

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

NSABP Protocol Summaries, March 2011.

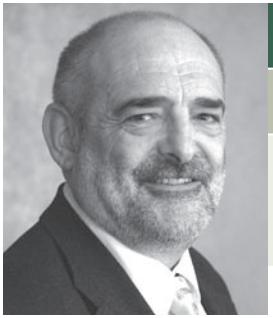
SELECT PUBLICATIONS

Alberts SR et al. **Influence of KRAS and BRAF mutational status and rash on disease-free survival (DFS) in patients with resected stage III colon cancer receiving cetuximab (Cmab): Results from NCCTG N0147.** *Proc ASCO* 2011;**Abstract 3607**.

De Roock W et al. **Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab.** *JAMA* 2010;304(16):1812-20.

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

Tejpar S et al. **Influence of KRAS G13D mutations on outcome in patients with metastatic colorectal cancer (mCRC) treated with first-line chemotherapy with or without cetuximab.** *Proc ASCO* 2011;**Abstract 3511**.



INTERVIEW

Jean-Yves Douillard, MD, PhD

Dr Douillard is Professor of Medical Oncology and Director of Clinical and Translational Research at ICO R Gauducheau in Saint Herblain, France.

Tracks 1-12

Track 1 Defining therapeutic goals in the treatment of mCRC in the era of bevacizumab, cetuximab and panitumumab

Track 2 Immediate surgery versus perioperative systemic therapy for patients with CRC liver metastases

Track 3 Conversion therapy with FOLFIRI and bevacizumab or cetuximab prior to resection of CRC hepatic metastases

Track 4 Treatment decision-making for patients with Stage II colon cancer

Track 5 Novel therapeutic strategies involving fucosylated EGFR antibodies in mCRC

Track 6 Management of synchronous asymptomatic primary colon cancer and mCRC

Track 7 Epirubicin/cisplatin/capecitabine for patients with gastroesophageal cancer

Track 8 Implications of the ToGA trial of first-line chemotherapy/trastuzumab for advanced HER2-positive GC

Track 9 Transarterial chemoembolization with or without sorafenib in HCC

Track 10 Approach to initial dosing of sorafenib in HCC

Track 11 Use of FOLFIRINOX in early and advanced-stage pancreatic cancer

Track 12 Current preoperative and adjuvant treatment approach to rectal cancer

Select Excerpts from the Interview

Track 4

DR LOVE: The use of adjuvant therapy for Stage II colon cancer has long been controversial. Would you discuss your treatment decision-making process in that situation?

DR DOUILLARD: In low-risk Stage II disease I see no reason to administer adjuvant chemotherapy. The benefit is minimal, and if chemotherapy is administered, it is generally capecitabine or IV 5-FU. But again, the benefit is nonsignificant for overall survival and minimal for recurrence-free survival and the agents are toxic.

In high-risk Stage II disease I have no doubt that patients should receive adjuvant chemotherapy — the question is whether they should receive FOLFOX or 5-FU only.

A marker we could use is microsatellite instability (MSI). Because patients with so-called MSI-high disease generally have a better prognosis, they don't benefit from adjuvant 5-FU. They may benefit from oxaliplatin, but oxaliplatin as a single agent has almost no activity. So these cases should be discussed individually using a multidisciplinary approach. We also have to evaluate histoprognostic factors, microemboli and T4 for a high risk of recurrence. It is a difficult recommendation, and it depends on the individual patient profile.

Several gene profiles have been identified, one of which is the Onco*type* DX colon cancer assay. The technologies used for these gene profile assays vary. They are not yet standardized or routinely available, but I believe that's where the future lies.

Track 11

DR LOVE: What are your thoughts on the use of FOLFIRINOX in early and advanced-stage pancreatic cancer?

DR DOUILLARD: We have shown in France that FOLFIRINOX may almost double median survival in the metastatic setting (Conroy 2011; [4.1]), but this is not a regimen for everyone because it is toxic. If the patient has a good performance status, has not lost too much weight and is not too old, FOLFIRINOX is an option.

The key toxicity of oxaliplatin is neuropathy. Even when the treatment duration is not long, many patients experience neuropathy. We also see myelosuppression and diarrhea, so we often have to dose adapt, educate the patients and monitor them carefully.

If a patient cannot receive FOLFIRINOX we still have gemcitabine as an option, but it's clearly not satisfactory. The most interesting approach, which is now in a clinical trial, is the use of FOLFIRINOX preoperatively for patients with unresectable pancreatic tumors and no metastases. The response rate is high with tumor shrinkage, so more patients go on to surgery.

4.1

Efficacy of FOLFIRINOX versus Gemcitabine as First-Line Therapy for Metastatic Pancreatic Cancer

	FOLFIRINOX	Gemcitabine
Median overall survival	11.1 months	6.8 months
Median progression-free survival	6.4 months	3.3 months
Objective response rate	31.6%	9.4%

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

The other option for patients with resectable disease up front is adjuvant FOLFIRINOX. I have used this approach for 1 patient, but patients with resectable pancreatic cancer are rare. In the adjuvant setting I try to administer the regimen for 6 months, but often after 2 to 3 cycles dose adaptations are needed.

Track 12

DR LOVE: What is your current treatment approach to rectal cancer?

DR DOUILLARD: We have established that the sequence should be preoperative chemoradiation therapy followed by surgery after a 6-week interval and then adjuvant chemotherapy. It's important to have an idea of the effect of chemoradiation therapy on the tumor itself, which you won't see if you operate the week after the end of the radiation therapy.

The question is, however, what type of chemotherapy should be used in combination with the radiation therapy? Most of the studies I've seen that added oxaliplatin to 5-FU or capecitabine were inconclusive (Aschele 2011). The pathologic complete response rate was a bit higher in the German CAO/ARO/AIO-94 trial, although in another trial it was not significant (Roedel 2011; Roh 2011). I am not convinced that the addition of oxaliplatin to 5-FU is a breakthrough in the adjuvant treatment of colon and rectal cancer. The toxicity of oxaliplatin in the long term has to be considered. I believe the best combination remains a fluoropyrimidine with radiation therapy for 5 weeks.

DR LOVE: How do you choose between fluoropyrimidines in rectal cancer, both in the preoperative setting and as adjuvant therapy?

DR DOUILLARD: Studies have demonstrated that we can administer capecitabine instead of 5-FU and the outcome is exactly the same (Hofheinz 2011). Patients prefer that approach more in rectal cancer and colon cancer, so that is what I do. ■

SELECT PUBLICATIONS

Aschele C et al. **Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: Pathologic results of the STAR-01 randomized phase III trial.** *J Clin Oncol* 2011;29(20):2773-80.

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

Hofheinz R et al. **Capecitabine (cape) versus 5-fluorouracil (5-FU)-based (neo)adjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC): Long-term results of a randomized, Phase III trial.** *Proc ASCO* 2011;**Abstract 3504**.

Roedel C et al. **Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: First results of the German CAO/ARO/AIO-04 randomized phase III trial.** *Proc ASCO* 2011;**Abstract LBA3505**.

Roh MS et al. **The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04.** *Proc ASCO* 2011;**Abstract 3503**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III SSGXVIII/AIO trial of 12 months versus 36 months of adjuvant imatinib therapy for patients with high-risk GIST reported a statistically significant improvement in 5-year overall survival with 36 months of imatinib therapy.**
   a. True
   b. False
2. **Which of the following improved in the ToGA trial with the addition of trastuzumab to chemotherapy for HER2-positive advanced GC?**
   a. Overall survival
   b. Overall response rate
   c. Progression-free survival
   d. All of the above
3. **Phase II trial data presented at ASCO 2011 in patients with imatinib- and sunitinib-resistant GIST reported a disease control rate of 68% upon treatment with sorafenib.**
   a. True
   b. False
4. **The Phase III ECOG-E1208 study is evaluating TACE with or without _____ for patients with unresectable HCC.**
   a. Imatinib
   b. Sunitinib
   c. Sorafenib
5. **A Phase II trial evaluating sorafenib with doxorubicin versus placebo with doxorubicin for patients with advanced HCC reported an improvement in _____ with the combination.**
   a. Median time to disease progression
   b. Median overall survival
   c. Median progression-free survival
   d. All of the above
6. **Reports from 2 retrospective analyses observed an association between the presence of K-ras G13D mutation and survival benefit in patients with metastatic colorectal cancer treated with cetuximab.**
   a. True
   b. False
7. **The Onco*type* DX colon cancer assay is able to define a Recurrence Score as a predictor of recurrence risk for patients with Stage II colon cancer.**
   a. True
   b. False
8. **A patient with Stage II colon cancer with an Onco*type* DX colon cancer assay Recurrence Score of 42 is considered to be at ____ risk of relapse.**
   a. Low
   b. Intermediate
   c. High
9. **In a recent French study by Conroy and colleagues, investigators reported no improvement in overall survival for patients who received FOLFIRINOX compared to those who received gemcitabine.**
   a. True
   b. False
10. **Results from the German CAO/ARO/AIO-94 trial indicate that the addition of oxaliplatin to 5-FU-based chemoradiation therapy is associated with increased pathologic complete response rates compared to 5-FU alone for patients with locally advanced rectal cancer.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 2, 2011

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

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

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

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal	BEFORE	AFTER
Roles of capecitabine and oxaliplatin in chemoradiation therapy for rectal cancer	4 3 2 1	4 3 2 1
HER2-directed therapies in GC management	4 3 2 1	4 3 2 1
TACE with or without sorafenib in unresectable HCC	4 3 2 1	4 3 2 1
Influence of K-ras G13D mutations on outcome for patients with metastatic colorectal cancer treated with cetuximab	4 3 2 1	4 3 2 1
Role of the Onco*type* DX assay and other prognostic models in early-stage colon cancer	4 3 2 1	4 3 2 1
Duration and dose of imatinib in GIST	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No If no, please explain: .....

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

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

If you intend to implement any changes in your practice, please provide 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:

- Utilize case-based learning to formulate individualized management strategies for GI cancer. . . . . 4 3 2 1 N/M N/A
- Summarize key findings from clinical studies of emerging therapeutic regimens for pancreatic cancer, and utilize this information to guide treatment decision-making for patients. . . . . 4 3 2 1 N/M N/A
- Assess the role of molecular markers in optimizing therapeutic decisions for patients with early or advanced CRC. . . . . 4 3 2 1 N/M N/A
- Counsel patients with Stage II colon cancer about their individual risk of recurrence based on clinical, pathologic and genomic biomarkers, and consider adjuvant therapeutic options . . . . . 4 3 2 1 N/M N/A
- Apply the results of new research when recommending neoadjuvant chemoradiation therapy to patients with locally advanced rectal cancer. . . . . 4 3 2 1 N/M
- Formulate a treatment plan for patients with primary CRC and liver-only metastases. . . . . 4 3 2 1 N/M N/A
- Utilize 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
- 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

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

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

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

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

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

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

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Charles D Blanke, MD	4 3 2 1	4 3 2 1
Bert H O'Neil, MD	4 3 2 1	4 3 2 1
Steven R Alberts, MD	4 3 2 1	4 3 2 1
Jean-Yves Douillard, MD, PhD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:

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

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

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UPDATE

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