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Gastrointestinal Cancer™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Eric Van Cutsem, MD, PhD
David P Ryan, MD
Ghassan Abou-Alfa, MD
Dirk Arnold, MD

EDITOR

Neil Love, MD

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2 Audio CDs
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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

- Effectively apply the results of practice-changing clinical research to the selection and sequencing of chemobiologic regimens for patients with metastatic colorectal 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.
- 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.
- Use clinical and molecular biomarkers to optimize systemic treatment of gastric and gastroesophageal cancer.
- Communicate the benefits and risks of existing and emerging systemic therapeutic interventions to patients with advanced hepatocellular carcinoma.
- Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials.

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EDITOR

Neil Love, MD
Research To Practice
Miami, Florida

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and we will do our best to get them answered for you

Facebook.com/ResearchToPractice or Twitter @DrNeilLove

INTERVIEW

Eric Van Cutsem, MD, PhD

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

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Select Excerpts from the Interview

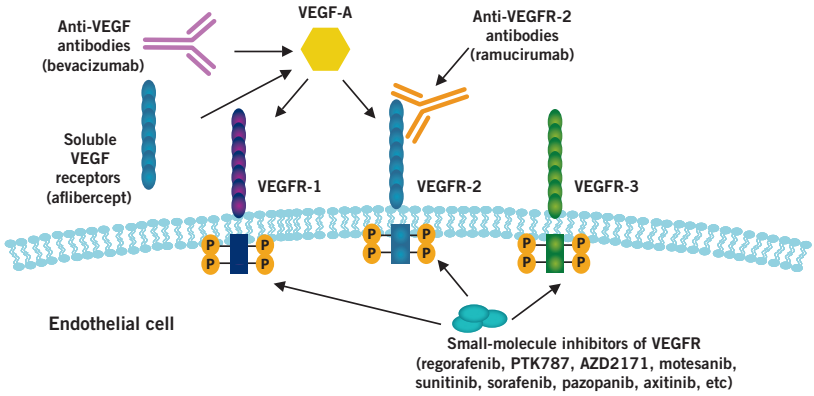
Tracks 1-4, 13-14

DR LOVE: Would you provide a brief overview of the mechanisms of action of some of the new anti-angiogenic agents under investigation in gastrointestinal cancer and how these compare to the mechanism of action of the anti-VEGF antibody bevacizumab (1.1)?

PROF VAN CUTSEM: We now have 3 novel angiogenesis inhibitors with evidence of activity, all with different mechanisms of action. Aflibercept is a fusion protein composed of parts of the different receptors (VEGFR-1 and VEGFR-2) that binds to and interferes with VEGF-A, VEGF-B and placental growth factor. Regorafenib is a

1.1

Agents Targeting the VEGF Pathway



Courtesy of John Mackey, MD.

novel multikinase inhibitor that mainly inhibits the action of VEGF through binding of VEGFR-2 and VEGFR-3.

Ramucirumab is a novel antibody that targets the VEGF receptor with broader activity. It doesn't bind to circulating VEGF as bevacizumab does. Whether that leads to a more profound clinical effect has yet to be shown in clinical trials.

DR LOVE: Would you summarize the results recently reported with each of these novel agents?

PROF VAN CUTSEM: Initial studies of ramucirumab were based on preclinical rationale, feasibility of the drug and knowledge that in gastric cancer blocking angiogenesis may be relevant (Spratlin 2010), so ramucirumab went directly to Phase III trials in gastric cancer. One ongoing Phase III trial is evaluating paclitaxel with or without ramucirumab for patients with metastatic gastric cancer (NCT01170663). An early-line trial with ramucirumab in gastric cancer is also ongoing.

Results from the Phase III CORRECT trial evaluating regorafenib in more than 700 patients with metastatic colorectal cancer (mCRC) with resistance to bevacizumab and anti-EGFR therapy were presented at the 2012 Gastrointestinal Cancers Symposium. The authors reported an improvement in survival for patients receiving regorafenib (Grothey 2012; [1.2]). So, in the continuum of care, having alternative anti-angiogenic agents may play an important role.

To my knowledge this is the first large trial in which a tyrosine kinase inhibitor has been studied as a single agent in patients with refractory CRC. The data are impressive because this patient population was optimally selected, needed to have clear indication of disease progression and needed to have been exposed to all agents available in colon cancer.

Our Phase III VELOUR study evaluated aflibercept versus placebo in combination with FOLFIRI as second-line therapy for patients with mCRC pretreated with oxaliplatin. All endpoints were met in this study. The primary endpoint was overall survival. The magnitude of benefit was not spectacular — median survival benefit was less than 2 months — but keep in mind that this was in the second-line setting. Improvements

1.2

CORRECT: A Phase III Trial of the Oral Multikinase Inhibitor 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 progression-free survival	1.9 mo	1.7 mo	0.49	<0.000001
Median overall survival	6.4 mo	5.0 mo	0.77	0.0052
Disease control rate	44.8%	15.3%	—	<0.000001

	Regorafenib + BSC (n = 500)		Placebo + BSC (n = 253)	
Select adverse events (AEs)	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Hand-foot skin reaction	46.6%	16.6%	7.5%	0.4%
Fatigue	47.4%	9.6%	28.1%	5.1%
Hypertension	27.8%	7.2%	5.9%	0.8%
Diarrhea	33.8%	7.2%	8.3%	0.8%
Rash/desquamation	26.0%	5.8%	4.0%	0%
Mucositis, oral	27.2%	3.0%	3.6%	0%
AEs leading to permanent treatment discontinuation	8.2%		1.2%	

* Standard therapies were required to include 5-FU, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if K-ras wild type).

Grothey A et al. Gastrointestinal Cancers Symposium 2012;**Abstract LBA385**.

also were seen in response rate and prolongation of progression-free survival with the addition of aflibercept to a chemotherapy backbone (Van Cutsem 2011; [1.3]).

VEGF-related adverse events were not more pronounced with aflibercept compared to those previously reported with bevacizumab with regard to the frequency of hypertension, proteinuria and thrombosis. What was different compared to bevacizumab was that aflibercept increased the chemotherapy-related adverse events — stomatitis, diarrhea, neutropenia and fatigue. Those were more pronounced when aflibercept was combined with chemotherapy compared to chemotherapy alone (Van Cutsem 2011).

One third of the patients had received bevacizumab. In a subgroup analysis, we reported similar trends of benefit with the addition of aflibercept in the bevacizumab-pretreated population versus those not pretreated (Van Cutsem 2011). This raises some interesting questions: Is aflibercept more active than bevacizumab? Or is this the proof

1.3

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

Survival	FOLFIRI + aflibercept (n = 614)	FOLFIRI + placebo (n = 612)	Hazard ratio	*p*-value
Median progression-free survival	6.9 mo	4.7 mo	0.76	0.00007
Median overall survival	13.5 mo	12.1 mo	0.82	0.0032

Van Cutsem E et al. World Congress on Gastrointestinal Cancer 2011;**Abstract O-0024**.

or suggestion that postprogression continuation of an anti-angiogenic agent could be of benefit?

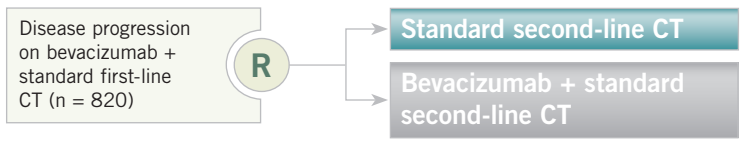
DR LOVE: Would you expand on that last question — the suggestion that postprogression continuation of anti-angiogenic therapy could provide benefit?

PROF VAN CUTSEM: Data from the BRiTE expanded access program published by Dr Axel Grothey have suggested that this approach is beneficial. This cohort study reported a prolongation in survival for patients receiving a second chemotherapy backbone and bevacizumab after disease progression on first-line therapy with a chemotherapy backbone and bevacizumab (Grothey 2008). However, these data do not provide hard scientific proof because this was not a randomized study.

A large prospective European trial is now under way evaluating continuation of bevacizumab beyond disease progression. More than 800 patients with CRC who had received first-line therapy with an oxaliplatin or irinotecan backbone and bevacizumab were eligible for this trial. Patients were randomly assigned to a different chemotherapy backbone and continuation of bevacizumab or no bevacizumab. The trial has a strong endpoint — overall survival – and should answer in an evidence-based fashion the question of whether bevacizumab should be continued after progression. Initial results are slated to be reported at ASCO 2012 (1.4). In view of the slightly higher toxicity reported with aflibercept compared to bevacizumab, this is going to be an important and relevant question in this setting and for our strategy in the treatment of CRC.

1.4

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



- **Primary endpoint:** Overall survival
- **Secondary endpoints:** Progression-free survival, overall response rate and safety
- **Status:** Completed, first data expected for ASCO 2012

Press release (January 26, 2012): "Bevacizumab-based regimen extends survival when continued beyond initial treatment in patients with metastatic colorectal cancer."

www.clinicaltrials.gov. Identifier NCT00700102, April 2012.

Tracks 10-11

DR LOVE: What new directions are we headed in regarding HER2-positive gastric cancer?

PROF VAN CUTSEM: No new data from large randomized trials have been reported since those from the ToGA trial, which evaluated the addition of trastuzumab to a chemotherapy backbone of 5-FU or capecitabine in combination with cisplatin (Bang 2010). The Phase III LOGIC trial is evaluating capecitabine/oxaliplatin with or

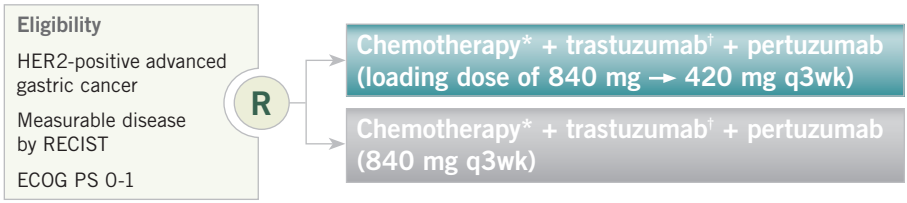
without lapatinib as first-line therapy for HER2-positive advanced gastric cancer. We now have also initiated a protocol combining trastuzumab with pertuzumab. We're performing a Phase I run-in because we're using a slightly different chemotherapy backbone — capecitabine/cisplatin. We don't expect any problems in Phase I, but we need to evaluate a few dose levels in this setting. Then the main part of this protocol will be a Phase II trial of capecitabine/cisplatin/trastuzumab in combination with pertuzumab for patients with HER2-positive advanced gastric cancer (1.5).

An impressive improvement has already been reported with trastuzumab/pertuzumab and docetaxel in the HER2-positive breast cancer arena (Baselga 2012). Mechanistically, there are some explanations. Pertuzumab and trastuzumab bind to different epitopes of the HER2 receptor, but even keeping that fact in mind, the magnitude of the benefit with the combination was larger than what many expected. That's why it's important to also evaluate this combination in patients with HER2-positive gastric cancer. ■

1.5

Phase IIA Study Evaluating 2 Different Doses of Pertuzumab in Combination with Trastuzumab and Chemotherapy for HER2-Positive Advanced Gastric Cancer

Protocol ID: NCT01461057 **Target Accrual:** 30 (Open)



* Cisplatin 80 mg/m^2 on day 1 of each cycle in combination with capecitabine 1,000 mg/m^2 twice daily
† Loading dose 8 mg/kg for cycle 1; 6 mg/kg for subsequent cycles

www.clinicaltrials.gov, April 2012.

SELECT PUBLICATIONS

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

Baselga J et al. **Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.** *N Engl J Med* 2012;366(2):109-19.

Grothey A et al. **Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients (pts) with metastatic colorectal cancer (mCRC) who have progressed after standard therapies.** Gastrointestinal Cancers Symposium 2012;**Abstract LBA385**.

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.

Spratlin JL et al. **Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2.** *J Clin Oncol* 2010;28(5):780-7.

Tabernero J et al. **Results from VELOUR, a phase 3 study of aflibercept versus placebo in combination with FOLFIRI for the treatment of patients with previously treated metastatic colorectal cancer.** European Multidisciplinary Congress 2011;**Abstract 6LBA**.

Van Cutsem E et al. **Intravenous (IV) aflibercept versus placebo in combination with irinotecan/5-FU (FOLFIRI) for second-line treatment of metastatic colorectal cancer (MCRC): Results of a multinational phase III trial (EFC10262-VELOUR).** World Congress on Gastrointestinal Cancer 2011;**Abstract O-0024**.

INTERVIEW

David P Ryan, MD

Dr Ryan is Associate Chief of Hematology/Oncology and Clinical Director of the Tucker Gosnell Center for Gastrointestinal Cancers at Massachusetts General Hospital in Boston, Massachusetts.

Tracks 1-9

Track 1 Clinical experience with FOLFIRINOX in advanced pancreatic cancer (PC)

Track 2 Current role of FOLFIRINOX in the adjuvant and neoadjuvant settings

Track 3 Therapeutic options for patients with locally advanced PC

Track 4 Adjuvant chemotherapy with or without radiation therapy in PC

Track 5 RTOG-0848: Adjuvant gemcitabine with or without erlotinib followed by chemotherapy with or without radiation therapy for pancreatic adenocarcinoma

Track 6 Preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable ductal adenocarcinoma of the pancreatic head

Track 7 Second-line therapy options for patients with metastatic PC

Track 8 Clinical relevance of EGFR and K-ras status in the treatment of PC

Track 9 Investigating the role of early palliative care in patients with PC

Select Excerpts from the Interview

Tracks 1, 7

DR LOVE: What is the most common question you receive from oncologists regarding first-line therapy for patients with advanced pancreatic cancer?

DR RYAN: Oncologists want to know what our experience has been with FOLFIRINOX. I would say that you see durable responses with FOLFIRINOX that you rarely saw with gemcitabine (Conroy 2011; [2.1]). Patients experience tumor shrinkage and generally feel a lot better.

2.1

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

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

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

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

The problem with FOLFIRINOX is that it is difficult to administer safely. Patients become dehydrated quickly as a result of the underlying nausea, pain and anorexia. They don't eat and drink as much as they should and are not in great shape physically. If you are aggressive about hydration, you can generally get patients on a dose and a schedule with this regimen that's good for them.

We administer preemptive IV fluids, and it is also important to make sure that patients are taking both ondansetron and dexamethasone to prevent nausea. With ondansetron alone patients can experience some breakthrough nausea, so it's important to also administer dexamethasone. If that approach doesn't work, we quickly move to aprepitant.

DR LOVE: Do you administer FOLFIRINOX to older patients?

DR RYAN: Older patients have difficulty staying hydrated and dealing with pain and constipation issues. You need to be careful when administering FOLFIRINOX in this setting. We often start older patients out with FOLFOX and add irinotecan after ascertaining that they can tolerate FOLFOX.

DR LOVE: What are your thoughts on the use of erlotinib for patients with pancreatic cancer?

DR RYAN: A Canadian group reported that the addition of erlotinib to gemcitabine improves survival by several weeks compared to gemcitabine alone (Moore 2007). A publication in *Cancer* from the same Canadian group evaluated the K-ras mutation status of patients on their study (de Cunha Santos 2010). Although the authors didn't report a statistically significant difference between K-ras wild-type cases and those with K-ras mutations, my own interpretation of that study is that a signal was definitely present — patients with K-ras wild-type disease had a fairly good hazard ratio if they received erlotinib compared to those who did not. I do not administer erlotinib to patients with K-ras mutation-positive disease, but for those with K-ras wild-type disease, I certainly consider it.

Tracks 4-6

DR LOVE: Is there anything new and notable in adjuvant treatment of pancreatic cancer?

DR RYAN: The second most common question I receive in the pancreatic cancer arena has to do with the use of radiation therapy and whether it provides sufficient benefit. There's a divide between Europe and North America.

The Europeans have moved away from using chemoradiation therapy. Results were disappointing in randomized controlled studies. An ESPAC study did not report a benefit to chemoradiation therapy administered after resection of pancreatic cancer (Neoptolemos 2004). In fact, outcomes seemed to be a little worse. It is difficult to deliver upper gastrointestinal tract chemoradiation therapy — patients don't like it and get sick, and the older the patient is, the sicker he or she becomes. Hence, in Europe they administer 6 months of gemcitabine-based chemotherapy alone.

In North America there is a lot of attention to the risk of local recurrence. Chemoradiation therapy reduces the locoregional recurrence rate. If we had better systemic therapy, we would see an improvement in survival. Hence, we still include chemoradiation in adjuvant therapy for pancreatic cancer.

An ongoing cooperative group study led by RTOG is attempting to address this divide. Patients receive adjuvant gemcitabine with or without erlotinib followed by randomization to either further gemcitabine with or without erlotinib or gemcitabine with or without erlotinib with added chemoradiation therapy (2.2).

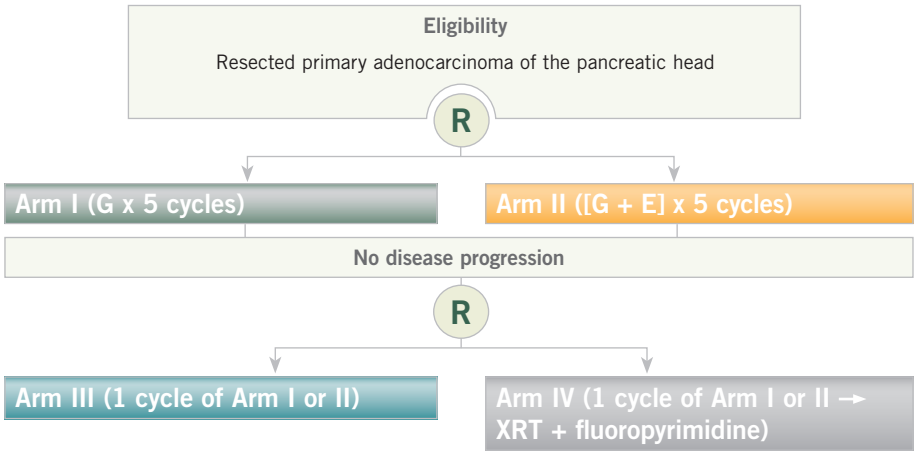
Part of the problem in our approach in the United States is that postoperative chemoradiation therapy is difficult to administer and to tolerate. We prefer to deliver preoperative chemoradiation therapy because it is easier to tolerate. We have been experimenting on protocol with neoadjuvant capecitabine and proton beam therapy (5-times-5 fraction) (Hong 2011).

The advantage of using protons is that you can paint in the dose and avoid exposure in normal tissues, thus reducing toxicity. We use capecitabine as a radiation sensitizer for 2 weeks, patients go to surgery and after surgery we administer gemcitabine. ■

2.2

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

Protocol ID: RTOG-0848 **Target Accrual:** 950 (Open)



NCI Physician Data Query, April 2012; **www.rtog.org**.

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Da Cunha Santos G et al. **Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: National Cancer Institute of Canada Clinical Trials Group Study PA.3.** *Cancer* 2010;116(24):5599-607.

Hong TS et al. **Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head.** *Int J Radiat Oncol Biol Phys* 2011;79(1):151-7.

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

Neoptolemos JP et al. **A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer.** *N Engl J Med* 2004;350(12):1200-10.

INTERVIEW

Ghassan Abou-Alfa, MD

Dr Abou-Alfa is Assistant Attending at Memorial Sloan-Kettering Cancer Center and Assistant Professor at Weill Medical College at Cornell University in New York, New York.

Tracks 1-12

Track 1 Treatment algorithm for hepatocellular carcinoma (HCC)

Track 2 Use of the remove-avoid-apply-report model for management of sorafenib-related hand-foot syndrome in HCC

Track 3 Common sorafenib-related toxicities in HCC

Track 4 Use of sorafenib in advanced Child-Pugh B HCC

Track 5 GIDEON study: A global investigation of therapeutic decisions by oncologists and hepatologists on the use of sorafenib in the management of HCC

Track 6 Termination of a Phase III trial of sorafenib versus sunitinib in advanced HCC due to sunitinib-associated safety concerns

Track 7 Investigation of anti-angiogenic strategies in the treatment of HCC

Track 8 Improving survival outcomes for patients with HCC

Track 9 Efficacy of erlotinib/bevacizumab and ongoing evaluation of this combination versus sorafenib as first-line therapy in advanced HCC

Track 10 Common risk factors for HCC

Track 11 Key clinical research issues in biliary cancer

Track 12 Perspective on the use of adjuvant systemic therapy for HCC and risk of recurrence after liver resection

Select Excerpts from the Interview

Track 2

DR LOVE: What new developments have been reported in the management of side effects of systemic therapy for hepatocellular carcinoma (HCC)?

DR ABOU-ALFA: Without question one of the big challenges has been the management of side effects associated with sorafenib. The most common side effect is hand-foot syndrome. The second most common side effect is diarrhea, and the third is fatigue.

Dr Mario Lacouture at our institution has developed the remove, avoid, apply and report (RAAR) model that ensures that any potential skin damage is managed before treatment with sorafenib. RAAR recommends removing any calluses and allowing the skin to be well healed and not dry; avoiding items that can cause skin abrasion such as chemicals, hot water or scrubbing; applying moisturizers and taking pain medications, as needed; and most important, reporting all signs and symptoms immediately (Gish 2010; Lacouture 2008; [3.1]).

We pride ourselves at Memorial Sloan-Kettering Cancer Center that our patients do not develop hand-foot syndrome that is worse than Grade 2 because they receive clear

instructions after they start therapy. Within 2 to 3 days we are on the telephone with them and we are in the clinic within 7 days so we can circumvent any issue that may arise.

3.1 **The RAAR Model for Management of Sorafenib-Related Hand-Foot Skin Reactions**

Remove	calluses and hyperkeratotic regions
Avoid	factors that may aggravate the condition, such as sunlight, direct friction, hot water, constrictive footwear and cleaning products containing strong chemicals
Apply	moisturizers and cold packs
Report	signs of hand-foot skin reaction early

Gish RG et al. *Gastroenterol Hepatol* (NY) 2010;6(9 Suppl 16):1-16; Lacouture ME et al. *Oncologist* 2008;13(9):1001-11.

Tracks 6, 9

DR LOVE: What promising novel agents are under investigation in HCC?

DR ABOU-ALFA: Some anti-angiogenic agents are still in the running and are generating interest. Sunitinib is out, however, based on some disappointing results recently reported by Ann-Lii Cheng at ASCO. That Phase III study demonstrated a higher median overall survival with sorafenib as compared to sunitinib in patients with advanced HCC (Cheng 2011; [3.2]). However, this study was interesting because it was able to reproduce results reported with sorafenib in the Phase III SHARP trial, which compared sorafenib to placebo (Llovet 2008).

DR LOVE: What do we know about bevacizumab in HCC?

DR ABOU-ALFA: Bevacizumab has been studied extensively and appears to have some activity in HCC, but bleeding concerns are not to be ignored (Siegel 2008). Nonetheless, the addition of an anti-angiogenic agent to an EGFR inhibitor such as cetuximab or erlotinib may allow the combination to work synergistically.

The report from a single-arm study of a median overall survival of 15.7 months with bevacizumab/erlotinib in advanced HCC was impressive (Thomas 2009), making the Phase II study of bevacizumab/erlotinib versus sorafenib an appropriate scientific approach (3.3).

3.2 **Phase III Study* of Sunitinib versus Sorafenib in Advanced Hepatocellular Carcinoma**

	Sunitinib	Sorafenib	Hazard ratio	*p*-value
Median overall survival,				
ITT population (n = 530, 544)	7.9 mo	10.2 mo	1.30	0.0010
Asian regions (n = 402, 410)	7.7 mo	8.8 mo	1.21	0.0171
Ex-Asian regions (n = 127, 134)	9.3 mo	15.1 mo	1.64	0.0036

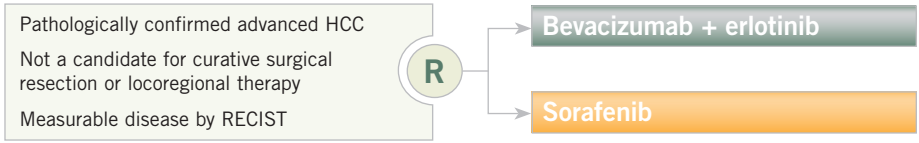
* Study was halted due to higher incidence of serious adverse events with sunitinib.

Cheng A et al. *Proc ASCO* 2011;**Abstract 4000**.

3.3

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

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



www.clinicaltrials.gov, April 2012.

Track 11

DR LOVE: Would you discuss the biology of biliary tract cancers and your approach to treating these diseases?

DR ABOU-ALFA: Even though the biology may differ, bile duct and gallbladder cancers are often lumped together. The ABC-02 trial previously reported that gemcitabine in combination with cisplatin improves survival versus gemcitabine alone (Valle 2010; [3.4]), and this combination is currently the standard for patients with advanced biliary cancers. Interestingly enough, that approach has been evolving because we see a tolerance issue with regard to how much cisplatin can be administered. This has given rise to an interest in combination therapies. I am currently involved in a study evaluating gemcitabine/cisplatin and sorafenib for patients with advanced biliary tract cancers (NCT00919061). Data from this study should be published soon. ■

3.4

UK ABC-02 Trial: Gemcitabine (Gem) with or without Cisplatin (Cis) for Patients with Advanced or Metastatic Biliary Tract Cancer

	Gem (n = 206)	Gem + Cis (n = 204)	Hazard ratio	*p*-value
Median overall survival	8.1 mo	11.7 mo	0.64	<0.001
Median progression-free survival	5.0 mo	8.0 mo	0.63	<0.001

Valle J et al. *N Engl J Med* 2010;362(14):1273-81.

SELECT PUBLICATIONS

Cheng A et al. **Phase III trial of sunitinib (Su) versus sorafenib (So) in advanced hepatocellular carcinoma (HCC).** *Proc ASCO* 2011;**Abstract 4000**.

Gish RG et al. **Integrating recent data in managing adverse events in the treatment of hepatocellular carcinoma.** *Gastroenterol Hepatol* (NY) 2010;6(9 Suppl 16):1-16.

Lacouture ME et al. **Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib.** *Oncologist* 2008;13(9):1001-11.

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

Siegel AB et al. **Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma.** *J Clin Oncol* 2008;26(2):2992-8.

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

Valle J et al. **Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer.** *N Engl J Med* 2010;362(14):1273-81.

INTERVIEW

Dirk Arnold, MD

Dr Arnold is Director of the Hubertus Wald Tumor Center at University Cancer Center Hamburg in Hamburg, Germany.

Tracks 1-12

Track 1 Utility of Onco*type* DX and ColoPrint® assays for patients with Stage II colon cancer

Track 2 Investigation of refined imaging techniques to identify patients with rectal cancer who can avoid preoperative radiation therapy

Track 3 Use of oral versus intravenous fluoropyrimidines in neoadjuvant chemoradiation therapy for rectal cancer

Track 4 K-ras status and treatment decision-making regarding first-line therapy for mCRC

Track 5 Selection of pre- versus postoperative therapy for patients with potentially resectable, hepatic-only, K-ras wild-type mCRC

Track 6 FOLFOX versus FOLFOX/bevacizumab versus FOLFOX/panitumumab as preoperative treatment for patients with resectable liver metastases from K-ras wild-type CRC

Track 7 Survival advantage with the addition of aflibercept to FOLFIRI in the Phase III VELOUR trial

Track 8 Side-effect profile and future directions with aflibercept in mCRC

Track 9 Consideration of bevacizumab beyond disease progression in patients with mCRC

Track 10 Viewpoint on the CORRECT trial results with regorafenib for the treatment of refractory mCRC

Track 11 Treatment algorithm for synchronous primary and metastatic CRC

Track 12 Perspective on future directions in the treatment of CRC

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss your treatment decision-making process when considering adjuvant therapy for a patient with Stage II colon cancer?

DR ARNOLD: Without chemotherapy, a subset of patients with Stage II disease have a worse prognosis than those with Stage III disease, whereas another group of patients with Stage II disease have a high likelihood of being cured.

The tools we currently have to help identify these patient groups are clinical risk factors and molecular information from single markers and complex gene arrays. The problem is that the information we obtain from clinical and molecular markers is only prognostic. We need predictive markers to inform us about which patients might benefit from a distinct treatment.

The Onco*type* DX assay provides additional information in terms of predicting the patient's prognosis with surgery alone. However, it tells us nothing about the relative benefit of 5-FU treatment (Gray 2011; [4.1]).

DR LOVE: I understand that no genomic assay is currently available in the colon cancer setting that can identify a group of patients with greater or lesser relative risk reduction as the Onco*type* DX assay does in patients with ER-positive, HER2-negative breast cancer. But if you evaluate the results of the article recently published in the *Journal of Clinical Oncology* analyzing the QUASAR trial of single-agent 5-FU versus surgery alone, it appears that the relative risk reduction with chemotherapy in the various risk categories is about the same. Thus you can attain a quantitative projected absolute benefit, although it's a fairly narrow range (Gray 2011).

DR ARNOLD: It is, and I believe this holds true. The relative risk reduction allows you to calculate an absolute risk reduction. I agree with the accompanying editorial in which Dr Al Benson recommends using the Onco*type* DX assay in patients who have adverse clinical pathologic factors (Benson 2011).

DR LOVE: Outside a research setting, how do you treat Stage II disease?

DR ARNOLD: My decision is based on clinical information. Only a small percentage of patients who are at a high clinical risk of recurrence should receive an oxaliplatin-based combination because of the lack of benefit and adverse effects of oxaliplatin. 5-FU as a single agent or capecitabine should be considered for other patients.

Once the patient is at a certain intermediate risk — when the tumor is well differentiated — we consider treating with 5-FU. The patients are informed that the absolute benefit of a 5-FU-based treatment will be between 3% and 7%.

If all the patient wants to know is if his or her risk level is at 3% or at 7%, I would consider ordering a genomic assay. This area is becoming more complicated, however. We primarily order the Onco*type* DX assay, but there is also ColoPrint and another test called Predictor-C, which was reported at ASCO last year (Adams 2011; Tan 2011).

4.1

QUASAR/Onco*type* DX Results: Assessment of Recurrence Risk for Patients with Stage II Colon Cancer

Recurrence risk group	Range of Recurrence Score®	Surgery alone (proportion of patients)	Kaplan-Meier estimate of of recurrence risk at 3 years with surgery alone
Low (n = 311)	<30	43.7%	12%
Intermediate (n = 218)	30-40	30.7%	18%
High (n = 182)	≥41	25.6%	22%

Methods: Study analyzed relationship between the Recurrence Score (RS) and risk of recurrence in patients treated with surgery alone and between Treatment Score (TS) and benefits of adjuvant fluoropyrimidine chemotherapy.

Conclusions: The continuous 12-gene RS has been validated in a prospective study for assessment of recurrence risk in patients with Stage II colon cancer after surgery and provides prognostic value that complements T stage and MMR. The TS was not predictive of chemotherapy benefit.

Gray RG et al. *J Clin Oncol* 2011;29(35):4611-9.

DR LOVE: If you opt to administer a fluoropyrimidine, how do you decide between 5-FU and capecitabine?

DR ARNOLD: In patients who have no contraindications we administer capecitabine. In younger patients we do everything to achieve a cure and the acceptance of 5-FU-based treatment is higher. Oxaliplatin may also be an option for younger patients, but its long-term toxicity must be considered.

Track 4

DR LOVE: What is currently known about K-ras testing, and which patients might benefit from an EGFR antibody?

DR ARNOLD: K-ras testing is standard for decision-making regarding first-line treatment. K-ras mutation is a predictive marker for not using an EGFR antibody. Initial decision-making should be based on the clinical situation and depends on the intensity of treatment needed. FOLFIRI/cetuximab has a higher intensity and higher response rate and is the standard approach for patients in need of a high response rate. For the majority of asymptomatic patients FOLFOX and bevacizumab are alternatives. The aim is to prolong progression-free survival and to prevent unnecessary toxicity.

Analyses of data from the CRYSTAL and the OPUS trials report that patients with the K-ras G13D mutation might benefit from treatment with an EGFR antibody (Tejpar 2011; [4.2]). Because these are retrospective studies, one should be cautious. The only situation in which I would consider an EGFR antibody is for patients with the K-ras G13D mutation whose disease is progressing after treatment with FOLFIRI.

4.2 **Influence of K-ras G13D Mutations on Outcomes in Patients with Metastatic Colorectal Cancer Treated with First-Line Chemotherapy (CT) with and without Cetuximab (Cet)**

	N	Response (%)		PFS (mo)		OS (mo)	
		CT	CT + Cet	CT	CT + Cet	CT	CT + Cet
K-ras wild type	845	38.5	57.3	7.6	9.6	19.5	23.5
Odds ratio/HR *p*-value		2.17 <0.0001		0.66 <0.0001		0.81 0.0063	
K-ras G13D	83	22.0	40.5	6.0	7.4	14.7	15.4
Odds ratio/HR *p*-value		2.41 0.0748		0.60 0.1037		0.80 0.37	
K-ras other mutations	450	43.8	30.5	8.5	6.4	17.7	15.5
Odds ratio/HR *p*-value		0.56 0.0037		1.42 0.0069		1.14 0.1964	

PFS = progression-free survival; OS = overall survival; HR = hazard ratio

Tejpar S et al. *Proc ASCO* 2011;**Abstract 3511**.

Track 6

DR LOVE: Do you ever use biologic agents along with chemotherapy in the neoadjuvant setting for patients with potentially resectable liver-only metastases?

DR ARNOLD: Patients with clearly resectable liver metastases have the best prognosis, with a 5-year survival rate of 25% to 37% (Adson 1984; Fong 1999). Targeted agents or combination chemotherapy could be a consideration, especially in the preoperative setting.

However, most patients with resectable metastases are not receiving treatment preoperatively but in the adjuvant setting, and we do not know if these agents provide benefit in that setting. Disappointing results from Stage III trials leave me skeptical about bevacizumab and cetuximab.

DR LOVE: Outside a research setting, do you treat resectable liver metastases preoperatively?

DR ARNOLD: I treat most of these cases preoperatively. The exceptions are patients with 1 or 2 small liver metastases. If you can get good access with surgery, I would proceed with surgery first. In patients with 2 or more metastases or with large metastases that might make surgery difficult, I would consider preoperative treatment.

I offer most patients FOLFOX with or without bevacizumab, depending on the size of the tumor. If the tumor is clearly resectable, we limit treatment to chemotherapy to avoid unnecessary toxicity.

DR LOVE: What is your treatment approach when a patient's disease is borderline resectable and your goal is to "convert" the patient to being eligible for resection?

DR ARNOLD: Patients in this setting with K-ras wild-type disease are ideal candidates for EGFR-based treatment with either FOLFOX/panitumumab or FOLFIRI/cetuximab.

DR LOVE: How would you compare chemotherapy with bevacizumab to chemotherapy with panitumumab in patients with K-ras wild-type tumors?

DR ARNOLD: Response rates and tumor shrinkage are greater with the panitumumab regimen. An interesting trial from the EORTC will evaluate the efficacy of FOLFOX alone, FOLFOX in combination with bevacizumab and FOLFOX in combination with panitumumab as perioperative treatment for patients with resectable liver metastases from K-ras wild-type CRC (NCT01508000). This trial will shed light on the biologic activity of these agents in patients with metastases to the liver. ■

SELECT PUBLICATIONS

Adams H et al. **Independent validation of a prognostic classifier (Predictor-C) in a set of 292 patients with colorectal cancer of UICC stage II.** *Proc ASCO* 2011;**Abstract 3558**.

Adson MA et al. **Resection of hepatic metastases from colorectal cancer.** *Arch Surg* 1984;119(6):647-51.

Benson AB et al. **Path toward prognostication and prediction: An evolving matrix.** *J Clin Oncol* 2011;29(35):4599-601.

Fong Y et al. **Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases.** *Ann Surg* 1999;230(3):309-18.

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(35):4611-9.

Tan IB et al. **Genetics: An 18-gene signature (ColoPrint®) for colon cancer prognosis.** *Nat Rev Clin Oncol* 2011;8(3):131-3.

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**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III CORRECT trial of regorafenib in combination with best supportive care (BSC) versus placebo in combination with BSC for patients with mCRC whose disease progressed on standard therapies reported statistically significant improvements in _____ for patients who received regorafenib.**
   a. Median progression-free survival
   b. Median overall survival
   c. Disease control rate
   d. All of the above

2. **Results from the Phase III VELOUR trial indicate that the addition of aflibercept to FOLFIRI is associated with increased progression-free survival and overall survival compared to FOLFIRI alone as second-line therapy for patients with mCRC.**
   a. True
   b. False

3. **The Phase III ML18147 trial is evaluating the addition of _____ to crossover fluoropyrimidine-based chemotherapy for patients with mCRC experiencing disease progression on a first-line chemotherapy/bevacizumab combination.**
   a. Aflibercept
   b. Bevacizumab
   c. Cetuximab

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

5. **The Phase III RTOG-0848 trial is evaluating adjuvant gemcitabine with or without _____ followed by chemotherapy with or without radiation therapy for patients with resected pancreatic cancer.**
   a. Bevacizumab
   b. Erlotinib
   c. Nanoparticle albumin-bound (*nab*) paclitaxel

6. **A prospective randomized Phase II study (NCT00881751) will compare the combination of _____ to sorafenib as first-line therapy for advanced HCC.**
   a. Bevacizumab and erlotinib
   b. Bevacizumab and cetuximab
   c. Bevacizumab and sorafenib

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. **An EORTC trial will evaluate the efficacy of FOLFOX alone, FOLFOX in combination with bevacizumab and FOLFOX in combination with _____ as perioperative treatment for patients with resectable liver metastases from K-ras wild-type CRC.**
   a. Cetuximab
   b. Panitumumab
   c. Both of the above

9. **Analyses of data from the CRYSTAL and the OPUS trials reported an association between the presence of K-ras G13D mutation and survival benefit in patients with mCRC treated with cetuximab.**
   a. True
   b. False

10. **Based on the RAAR model, patients receiving sorafenib for HCC should have calluses and hyperkeratotic regions removed prior to initiating therapy in order to mitigate the risk of hand-foot skin syndrome.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 1, 2012

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
Available research data (BRiTE, VELOUR) and ongoing trials evaluating continued anti-VEGF therapy for patients with mCRC whose disease has progressed on chemotherapy/bevacizumab	4 3 2 1	4 3 2 1
RTOG-0848 study: Adjuvant gemcitabine with or without erlotinib followed by chemotherapy with or without radiation therapy for pancreatic adenocarcinoma	4 3 2 1	4 3 2 1
Novel agents targeting angiogenesis in the treatment of gastrointestinal cancers	4 3 2 1	4 3 2 1
FOLFIRINOX dosing in the treatment of advanced pancreatic cancer	4 3 2 1	4 3 2 1
Data supporting the utility of molecular markers (MMR, Onco*type* DX, ColoPrint) in guiding treatment planning for Stage II colon cancer	4 3 2 1	4 3 2 1
Management of sorafenib-related hand-foot syndrome in advanced HCC	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No

If no, please explain:.....

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:

- Effectively apply the results of practice-changing clinical research to the selection and sequencing of chemobiologic regimens for patients with metastatic colorectal 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
- 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
- Use clinical and molecular biomarkers to optimize systemic treatment of gastric and gastroesophageal cancer. . . . . 4 3 2 1 N/M N/A
- Communicate the benefits and risks of existing and emerging systemic therapeutic 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)

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Eric Van Cutsem, MD, PhD	4	3	2	1	4	3	2	1
David P Ryan, MD	4	3	2	1	4	3	2	1
Ghassan Abou-Alfa, MD	4	3	2	1	4	3	2	1
Dirk Arnold, 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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