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Gastrointestinal Cancer™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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Gastrointestinal Cancer Update

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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* utilizes 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

- Evaluate significant data presented at the ASCO 2010 Annual Meeting, and determine how the data may apply to the treatment of GI cancer.
- Summarize key findings from clinical studies of emerging therapeutic regimens for pancreatic and biliary tract cancer.
- Assess the role of molecular markers in optimizing therapeutic decisions for patients with early or advanced CRC.
- Communicate to patients with metastatic CRC the benefits and risks of existing and emerging anti-VEGF and anti-EGFR biologic therapy.
- Apply clinical trial results to integrate the use of chemotherapy with biologic agents, such as anti-HER2 and anti-VEGF agents, into the treatment of gastroesophageal cancer when appropriate.
- Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials.

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TABLE OF CONTENTS

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INTERVIEW

Axel Grothey, MD

Dr Grothey is Professor of Oncology in the Department of Medical Oncology at the Mayo Clinic in Rochester, Minnesota.

Tracks 1-14

Track 1 NCCTG-N0147 trial: Adjuvant FOLFOX6 with or without cetuximab for K-ras wild-type and mutant Stage II/III colorectal cancer (CRC)

Track 2 Molecular and pathologic features of Stage II and III colon cancer in studies used for the development of the Onco*type* DX® colon cancer Recurrence Score® (RS)

Track 3 Refining the identification of patients with high- versus low-risk Stage II colon cancer

Track 4 Neoadjuvant FOLFOX with or without bevacizumab, without radiation therapy, for locally advanced rectal cancer

Track 5 Clinical approach to maintenance therapy in metastatic CRC (mCRC)

Track 6 MRC COIN trial: Intermittent versus continuous first-line oxaliplatin/fluoropyrimidine chemotherapy with or without cetuximab for mCRC

Track 7 **Case discussion:** A 64-year-old man presents with a HER2-positive gastroesophageal adenocarcinoma with bilobe hepatic metastases

Track 8 HER2 testing, scoring and interpretation in gastric cancer (GC)

Track 9 Modification of the REAL2 regimen for HER2-positive GC: Trastuzumab, oxaliplatin and capecitabine

Track 10 **Case discussion:** A 68-year-old woman with a history of radiation therapy for cervical cancer presents with low-risk Stage II colon cancer, is enrolled on the observational arm of the ECOG-E5202 trial and develops locally advanced rectal cancer one and a half years later

Track 11 **Case discussion:** A 48-year-old man with T3N2b micro-satellite stable sigmoid colon cancer receives adjuvant FOLFOX6 and presents with an asymptomatic, 2.5-cm, right hepatic mass two years later

Track 12 Preoperative therapy for a patient with a solitary resectable CRC metastasis

Track 13 **Case discussion:** A 44-year-old woman with initially unresectable pancreatic cancer (PC) and hepatic metastases experiences a response to capecitabine/gemcitabine and undergoes a laparoscopic Whipple operation with hepatic wedge resections followed by consolidation chemoradiation therapy

Track 14 FOLFIRINOX in the treatment of advanced PC

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you explain the molecular and pathologic features of Stage II and Stage III colon cancer and how they may affect treatment?

DR GROTHEY: The debate has been long and ongoing in terms of whether Stage II and Stage III colon cancer are the same biologic disease. Is Stage II disease a step on the way to Stage III disease, or is it a distinct biologic entity? Data from the PETACC-3 adjuvant trial demonstrated distinct molecular parameters and alterations of gene profiles between Stage II and Stage III disease (Roth 2009). A recent study compared pathologic markers and the expression of 375 genes between patients with Stage II and Stage III disease (O'Connell 2010; [1.1]). The study led to the development of the 12-gene Onco*type* DX colon cancer assay and concluded that a high concordance in gene expression exists between Stage II and Stage III colon cancer.

This could imply that the biological difference between these tumors is not large in terms of their genetic makeup and their molecular expression patterns. However, many more genes could be responsible for the differences in biology between Stage II and Stage III disease. Even if only five genes were different, which was the case in this study, that could drive a different biology. I am not satisfied with simply studying a subset of genetic markers and saying that we see high concordance so the tumors are not different. Clinically, they behave differently, and a future genomewide analysis may tell us if the concordance is high or not between these tumors.

In the QUASAR analysis that evaluated the prognostic value of nodal assessment and the Onco*type* DX Recurrence Score (RS), more than 60 percent of patients did not present with adequate lymph node information, which can influence the risk discrimination with the RS (Gray 2010; [1.2]). At this time, if patients ask for it we order the Onco*type* DX assay, but it is primarily a prognostic tool, and the discrimination among low-, medium- and high-risk groups is not as strong as in breast cancer. The good news is that the developers of the Onco*type* DX assay are working with MOSAIC and NSABP-C-07 investigators to further refine the assay and develop another molecular marker for our more modern therapies.

1.1

Comparison of Molecular and Pathologic Features of Stage II and Stage III Colon Cancer in Four Large Studies

"Quantitative analysis by RT-PCR identified very similar expression in stage II and III disease for the vast majority of genes tested. Future studies should examine the clinical significance of differences identified between stage II and III, including MMR, grade, and a small number of individual genes."

O'Connell MJ et al. *Proc ASCO* 2010;**Abstract 3503**.

1.2

Correlation of Number of Nodes Examined and the 12-Gene Colon Cancer Recurrence Score with Recurrence in Patients with Stage II Colon Cancer from QUASAR

"No association between recurrence score (RS) and number of nodes examined or interaction between RS and nodes was observed ($p = 0.66$). Number of nodes examined and RS are independent predictors of recurrence in stage II colon cancer following surgery, and both should be considered when assessing individual recurrence risk."

Gray RG et al. Gastrointestinal Cancers Symposium 2010;**Abstract 331**.

DR LOVE: Are there any new developments in the management of Stage II disease?

DR GROTHEY: I believe in the past year we have better clarified high- and low-risk groups, to some extent. We have determined that patients with Stage II, T4 disease comprise a high-risk group with poor prognosis, and in my clinical practice, we are treating the disease similarly to Stage III disease. In addition, patients with MSI-high Stage II tumors — which are defective in DNA mismatch repair — should not receive adjuvant therapy because the outcome is excellent.

Track 4

DR LOVE: What are your thoughts on recent data on neoadjuvant chemotherapy without radiation therapy in locally advanced rectal cancer?

DR GROTHEY: This is an interesting research area. The current standard treatment for localized rectal cancer is neoadjuvant chemoradiation therapy prior to surgical resection. It is well acknowledged that radiation therapy is the more toxic component of this combined-modality treatment. Radiation therapy can particularly cause long-term side effects, and some of these patients may develop radiation proctitis, which could be difficult to manage and lead to constant pain, constant diarrhea and sphincter dysfunction.

A paradigm shift in this area would be to use highly systemically active chemotherapy alone, which would also provide local rectal control, and try to avoid radiation therapy. Two different pilot studies from the Memorial Sloan-Kettering Cancer Center (Schrag 2010; [1.3]; Cercek 2010) have

1.3

Pilot Study Evaluating FOLFOX/Bevacizumab without Radiation Therapy for Locally Advanced Rectal Cancer

Pathologic complete response	Clinical regression	Need for preoperative radiation therapy	R0 resection	Local recurrences	Distant recurrences
27%	100%	0%	100%	0%	10%

Schrag D et al. *Proc ASCO* 2010;**Abstract 3511**.

been presented, one using FOLFOX with bevacizumab and the other using FOLFOX without bevacizumab. Both of the studies showed that highly active systemic treatment can generate significant responses in primary tumors in the rectum. The pathologic complete remission rate for these patients was approximately 30 percent, which is comparable to 5-FU-based neoadjuvant chemoradiation therapy in this setting.

I believe that chemotherapy without radiation therapy is an interesting strategy that should be further explored. Both ACOSOG and the CALGB are proposing to test this prospectively in a multicenter setting.

The critical issue with this approach is ensuring adequate imaging before treatment. One must make sure that the eligible patient population is identified. T4 tumors should be excluded, and patients with T3N0 disease — and perhaps T3N1 disease — should be included. Those criteria encompass the bulk of patients with locally advanced rectal cancer. It would be ideal to be able to reduce the long-term morbidity of our treatment by avoiding radiation therapy, but we must have safeguards in place.

Track 5

DR LOVE: Would you discuss the issue of maintenance therapy for advanced colorectal cancer (CRC)?

DR GROTHEY: A large randomized Phase III study from Spain was presented at ASCO (Tabernero 2010; [1.4]). The question they asked was whether maintenance therapy with single-agent bevacizumab is noninferior to the continuation of chemotherapy/bevacizumab after initial induction with XELOX/bevacizumab in patients with CRC. Four hundred eighty patients were randomly assigned to six cycles of XELOX/bevacizumab followed by bevacizumab as maintenance therapy or six cycles of XELOX/bevacizumab followed by continuation of XELOX/bevacizumab.

A treatment-related issue that was seen on the continuation XELOX/bevacizumab arm was the development of Grade III or IV neurotoxicity associated with oxaliplatin in approximately 25 percent of the patients, which is unacceptable. A better trial design might have been to evaluate capecitabine/bevacizumab maintenance versus bevacizumab maintenance versus no maintenance, after initial induction chemotherapy with XELOX/bevacizumab. This combination is being evaluated in an ongoing German trial. I believe the continuation of oxaliplatin and the absence of a negative control arm are flaws that hamper and impair our interpretation of the data.

DR LOVE: Off protocol, how do you approach patients in this setting?

DR GROTHEY: I start with an oxaliplatin-based regimen, either FOLFOX or XELOX with bevacizumab. After eight cycles of FOLFOX or six cycles of XELOX, I discontinue the oxaliplatin component and continue the fluoropyrimidine and bevacizumab as maintenance therapy.

1.4

Phase III MACRO Trial: XELOX and Bevacizumab (Bev) Maintenance versus Bev Maintenance After Initial XELOX/Bev in Metastatic Colorectal Cancer

	XELOX/bev maintenance	Bev maintenance	Hazard ratio
Median PFS	10.4 months	9.7 months	1.11
Median OS	23.4 months	21.7 months	1.04

PFS = progression-free survival; OS = overall survival

Tabernero J et al. *Proc ASCO* 2010;**Abstract 3501**.

Track 8

DR LOVE: How are you approaching gastric cancer with respect to HER2 testing and the use of trastuzumab?

DR GROTHEY: HER2 testing in gastric cancer is not like testing in breast cancer because more tumor heterogeneity exists within different areas of the same tumor specimen. Pathologists want at least four biopsies to screen because of this heterogeneity. Also, immunohistochemistry (IHC) scoring for breast and gastric tumors is not aligned. There is a difference in what is considered 3+ or 2+ between breast cancer and gastric or gastroesophageal (GE) junction tumors.

In our practice, approximately 12 to 15 percent of gastric cancer cases have HER2 overexpression and approximately 15 to 20 percent of patients with GE junction adenocarcinomas test positive for HER2, and we add trastuzumab to chemotherapy for these patients. ■

SELECT PUBLICATIONS

Cercek A et al. **Complete pathologic response in the primary of rectal or colon cancer treated with FOLFOX without radiation.** *Proc ASCO* 2010;**Abstract 3649**.

Gray RG et al. **Correlation of number of nodes examined and the 12-gene colon cancer recurrence score with recurrence in stage II colon cancer patients from QUASAR.** Gastrointestinal Cancers Symposium 2010;**Abstract 331**.

O'Connell MJ et al. **Comparison of molecular and pathologic features of stage II and stage III colon cancer in four large studies conducted for development of the 12-gene colon cancer recurrence score.** *Proc ASCO* 2010;**Abstract 3503**.

Roth AD et al. **Correlation of molecular markers in colon cancer with stage-specific prognosis: Results of the translational study on the PETACC 3-EORTC 40993-SAKK 60-00 trial.** Gastrointestinal Cancers Symposium 2009;**Abstract 288**.

Schrag D et al. **Neoadjuvant FOLFOX-bev, without radiation, for locally advanced rectal cancer.** *Proc ASCO* 2010;**Abstract 3511**.

Tabernero J et al. **Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single-agent (s/a) BEV as maintenance therapy in patients (pts) with metastatic colorectal cancer (mCRC): The MACRO trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]).** *Proc ASCO* 2010;**Abstract 3501**.

INTERVIEW

Jaffer A Ajani, MD

Dr Ajani is Professor of Medicine in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-11

Track 1 Clinical research and practice implications of the ToGA trial of first-line chemotherapy/trastuzumab for HER2-positive advanced GC

Track 2 **Case discussion:** A man in his midforties with HER2-positive GC and multiple large pulmonary metastases receives 5-FU/oxaliplatin/docetaxel and bevacizumab/trastuzumab

Track 3 Selection of chemotherapy for patients with HER2-positive and HER2-negative GC

Track 4 AVAGAST trial: First-line capecitabine/cisplatin with bevacizumab or placebo for advanced GC

Track 5 Geographic and ethnic differences in the etiology of hepatocellular carcinoma (HCC)

Track 6 Investigational strategies to identify predictive biomarkers for bevacizumab in GC

Track 7 Therapeutic approach for patients with newly diagnosed GC

Track 8 Incidence and potential etiologic factors in gastroesophageal cancer

Track 9 Stem cells, chronic inflammation/injury and the development of cancer

Track 10 Challenges in developing anticancer therapy: Targeting proliferating cells, stem cells and the stroma

Track 11 Complexity of communication between primary and metastatic tumor cells

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the results of the ToGA trial, evaluating trastuzumab in HER2-positive gastric cancer?

DR AJANI: The ToGA trial was conducted in a subset of patients with gastric cancer with HER2 overexpression, and it demonstrated that the addition of trastuzumab to chemotherapy prolonged both progression-free survival and overall survival, without causing significant toxicity (Bang 2010; [2.1, 2.2]). These data clearly suggest that patients with advanced gastric cancer, particularly those with moderately or well-differentiated tumors, should undergo testing for

2.1

ToGA: Efficacy Results from a Phase III Study of Adding Trastuzumab to First-Line Chemotherapy in HER2-Positive Advanced Gastric Cancer

	FC (n = 290)	FC + T (n = 294)	Hazard ratio	*p*-value
Overall survival	11.1 mo	13.8 mo	0.74	0.0046
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	0.53	<0.0001

F = fluoropyrimidine; C = cisplatin; T = trastuzumab

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

2.2

ToGA: Cardiac Adverse Events from a Phase III Study of Adding Trastuzumab to First-Line Chemotherapy in HER2-Positive Advanced Gastric Cancer

	FC (n = 290)	FC + T (n = 294)
Cardiac adverse events	6%	6%
Grade III or IV cardiac events	3%	1%
Cardiac failure	<1%	<1%

F = fluoropyrimidine; C = cisplatin; T = trastuzumab

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

HER2 status. However, it is apparent that in terms of HER2 testing, what is relevant in breast cancer may not necessarily apply directly in gastric cancer.

DR LOVE: What is known about the correlation between primary tumor location or gastric cancer subtype and the likelihood of HER2-positive status?

DR AJANI: In general, if the patient has a well-differentiated or moderately differentiated tumor, testing for HER2 status should immediately be considered.

An intestinal type of tumor, which is usually moderately or well differentiated and often located in the lower half of the stomach, is more likely to be HER2-positive than tumors located higher in the GI tract — the rate can be up to 20 percent. Moving proximally, toward the gastroesophageal junction, tumors tend to become poorly differentiated and tend not to be HER2-positive.

Track 3

DR LOVE: Which chemotherapy options would you consider to combine with trastuzumab?

DR AJANI: The ToGA trial demonstrated that the addition of trastuzumab to a fluoropyrimidine in combination with cisplatin prolongs survival and time to disease progression. However, I believe you can add trastuzumab to any chemotherapy combination that is effective in this setting.

I use a combination of docetaxel, oxaliplatin and capecitabine or fluorouracil. This combination appears to have a high response rate, and when you add trastuzumab, the response rates increase by an additional 10 percent.

DR LOVE: What about patients with gastric cancer with a HER2-negative tumor?

DR AJANI: Treatment for patients with HER2-negative status is a challenge. Off protocol, we use modified DCF or oxaliplatin with capecitabine. We don't have many choices. In the second-line setting I use irinotecan.

Only four drug classes are useful for patients with HER2-negative disease: fluoropyrimidines, platinum compounds, taxanes and camptothecin. If you use three of them for first-line treatment, only one remains for the second line. It is a difficult situation, and we haven't made much progress in this setting.

Tracks 4, 6

DR LOVE: Are any new research endeavors, agents or strategies promising in gastric cancer?

DR AJANI: An important trial to discuss is AVAGAST, which was an international front-line study for patients with advanced gastric cancer who were randomly assigned to receive a combination of capecitabine and cisplatin with bevacizumab or with placebo. Patients with the usual contraindications to bevacizumab — hypertension, bleeding tendency or wound infection — were excluded.

No significant difference was observed in the median survival of the experimental arm — 12.1 months — versus the control arm — 10.1 months, with a *p*-value of 0.1 (Kang 2010; [2.3]).

However, when the data are analyzed by geographic region, interesting effects are seen (2.4). In Asia, the difference between the control arm and the experimental arm was the narrowest, and it was largest in South America.

The difference between the arms in the European group was intermediate. Therefore, had the trial been conducted in Europe and the Americas, the results would have been significant.

Owing to these observations, additional testing will take place with blood and tissue samples from the AVAGAST trial. A second trial is under consideration and will be designed based on the subgroup analysis of AVAGAST to focus on certain populations in which bevacizumab may be beneficial. ■

2.3

Survival and Response of First-Line Capecitabine and Cisplatin (XP) with or without Bevacizumab (Bev) During the Phase III AVAGAST Trial for Patients with Advanced Gastric Cancer

Efficacy	XP + placebo N = 387	XP + bev N = 387	*p*-value
ORR	37%	46%	0.03
PFS	5.3 mo	6.7 mo	0.003

"While the primary endpoint was not met (median OS, HR 0.87; $p = 0.1002$), there was a significant improvement in PFS and ORR and an acceptable safety profile for bev + chemo in patients with advanced gastric cancer."

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

Kang Y et al. *Proc ASCO* 2010;**Abstract LBA4007**.

2.4

Efficacy of First-Line Treatment with Capecitabine and Cisplatin (XP) with Bevacizumab (Bev) or Placebo According to Geographic Region During the Phase III AVAGAST Trial for Patients with Advanced Gastric Cancer

	XP + placebo	XP + bev	Change	HR; 95% CI
OS, median (mo)				
Asia	12.1	13.9	1.8	0.97; 0.75-1.25
Europe	8.6	11.1	2.5	0.85; 0.63-1.14
America	6.8	11.5	4.7	0.63; 0.43-0.94
PFS, median (mo)				
Asia	5.6	6.7	1.1	0.92; 0.74-1.14
Europe	4.4	6.9	2.5	0.71; 0.54-0.93
America	4.4	5.9	1.5	0.65; 0.46-0.93

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

Kang Y et al. *Proc ASCO* 2010;**Abstract LBA4007**; Kang Y. Presentation. ASCO 2010.

SELECT PUBLICATIONS

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

Jørgensen JT. **Targeted HER2 treatment in advanced gastric cancer.** *Oncology* 2010;78(1):26-33.

Kang Y et al. **AVAGAST: A randomized, double-blind, placebo-controlled, phase III study of first-line capecitabine and cisplatin plus bevacizumab or placebo in patients with advanced gastric cancer (AGC).** *Proc ASCO* 2010;**Abstract LBA4007**.

Wainberg ZA et al. **Lapatinib, a dual EGFR and HER2 kinase inhibitor, selectively inhibits HER2-amplified human gastric cancer cells and is synergistic with trastuzumab in vitro and in vivo.** *Clin Cancer Res* 2010;16(5):1509-19.

Yan B et al. **A study of HER2 gene amplification and protein expression in gastric cancer.** *J Clin Pathol* 2010;63(9):839-42.

INTERVIEW

Malcolm J Moore, MD

Dr Moore is Professor of Medicine and Pharmacology at the University of Toronto, Chief of Medicine and Head of the Division of Medical Oncology/Hematology at Princess Margaret Hospital and Director of the Bras Family Drug Development Program in Toronto, Ontario.

Tracks 1-8

Track 1	PRODIGE 4/ACCORD 11 trial: FOLFIRINOX versus gemcitabine as first-line therapy for metastatic PC
Track 2	Identification of prognostic factors in PC
Track 3	Systematic review of Phase II trials in PC to improve outcomes in Phase III studies
Track 4	Effect of smoking status on erlotinib pharmacokinetics, toxicity and the ability to dose escalate in advanced PC
Track 5	K-ras wild type as a predictor of benefit from erlotinib in PC
Track 6	Emerging clinical and translational studies of nanoparticle albumin-bound (*nab*) paclitaxel in advanced PC
Track 7	Key palliative management issues — pain, thromboembolism and gastric outlet obstruction — in PC
Track 8	Survival advantage with gemcitabine/cisplatin compared to gemcitabine alone in advanced or metastatic biliary tract cancer

Select Excerpts from the Interview

Track 1

DR LOVE: What are your thoughts about the French trial evaluating FOLFIRINOX versus gemcitabine as front-line treatment of advanced pancreatic cancer (Conroy 2010)?

DR MOORE: This is an important study from a clinical practice point of view as it demonstrates the value of an intensive chemotherapy regimen in advanced pancreatic cancer. This is a paradigm shift in this disease, in which we've always thought of using relatively nonaggressive chemotherapy.

Considering how many negative studies we have seen in pancreatic cancer, this is a dramatically positive and successful Phase III study demonstrating a more than four-month improvement in median survival.

The survival rate with gemcitabine was 6.8 months, which is fairly typical of this disease, and on the FOLFIRINOX arm it was 11.1 months (Conroy 2010; [3.1]). This is a substantial improvement that is beyond what we have observed with any other regimen in pancreatic cancer.

3.1

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

	Gemcitabine	FOLFIRINOX	Hazard ratio	*p*-value
ORR	9.4%	31.6%	Not reported	0.0001
PFS	3.3 mo	6.4 mo	0.47	<0.0001
OS	6.8 mo	11.1 mo	0.57	<0.0001

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

Conroy T et al. *Proc ASCO* 2010;**Abstract 4010**.

Tracks 4-5

DR LOVE: Would you discuss your paper on the effect of smoking status on the pharmacokinetics of erlotinib in pancreatic cancer (Renouf 2010; [3.2])?

DR MOORE: We conducted a study of erlotinib in pancreatic cancer and wanted to determine whether smoking status predicts for toxicity and metabolism. We saw clear evidence that patients who were smokers metabolized the drug more rapidly, and the maximum tolerated dose in current smokers is considerably higher than the nonsmoking counterparts or the ex-smokers.

This suggests the possibility of a need to start with a higher dose of erlotinib for smokers. Of note, current smokers had the highest rate of metabolism and ex-smokers had an intermediate rate, though still higher than the nonsmokers.

For patients who are actively smoking, one should consider starting erlotinib at 150 mg a day, with a plan to escalate the drug quickly if a rash or other toxicity is not seen.

In our practice, we perform K-ras testing because the benefits of erlotinib are modest in an unselected population, much as you would see if you used trastuzumab in an unselected population of patients with breast cancer. Though we do not have definitive data on K-ras in pancreatic cancer yet, I believe this will be important because in CRC, EGFR inhibitors work effectively with wild-type K-ras only. In pancreatic cancer, wild-type K-ras

3.2

Analysis of Smoking Status on Erlotinib Pharmacokinetics, Toxicity and Ability to Dose Escalate in a Phase II Study of Advanced Pancreatic Cancer

"Smoking status is associated with erlotinib plasma concentrations, and was predictive of toxicity and ability to dose escalate in this study. Differential upfront dosing of erlotinib in pancreatic cancer based on smoking status should be further evaluated."

Renouf DJ et al. *Proc ASCO* 2010;**Abstract 4056**.

is present probably in approximately 20 percent of tumors. In our experience, the benefit seems to be much greater in this subgroup of K-ras wild-type disease. We are moving into an era when a number of different options are now available for advanced disease, and I see some value in testing patients for K-ras. Larger studies are exploring that, and we should have a definitive answer within one to two years.

Track 6

DR LOVE: What are your thoughts on nanoparticle albumin-bound (*nab*) paclitaxel in pancreatic cancer?

DR MOORE: The data presented from the Phase II study (Von Hoff 2009; [3.3]) are interesting, and the combination of *nab* paclitaxel and gemcitabine is currently being investigated in a Phase III study. This is an easy regimen to administer and has good tolerability.

DR LOVE: Would you comment on the translational work on SPARC and the potential mechanism of action of antitumor therapy?

DR MOORE: The most relevant issue for pancreatic cancer is that we have a poor sense of how drugs are delivered to the tumors. We know that the tumors are poorly vascularized, and the present vasculature is abnormal. In addition, the sclerotic stroma is quite dense. One school of thought is that the reason chemotherapy has not been effective is because the delivery of the drug into the tumor is extraordinarily poor. SPARC is secreted protein, acidic and rich in cysteine. Its function is not completely understood, and the association with efficacy is still somewhat speculative. ■

3.3

SPARC Correlation with Response to *Nab* Paclitaxel and Gemcitabine in Patients with Advanced Pancreatic Cancer

"The combination of *nab*-paclitaxel and gemcitabine was generally well tolerated and had substantial enough antitumor activity in patients with pancreatic cancer to warrant a phase III clinical trial. SPARC+ status in these patients was associated with higher response rate and longer progression free survival."

Von Hoff DD et al. *Proc ASCO* 2009;**Abstract 4525**.

SELECT PUBLICATIONS

Conroy T et al. **Randomized phase III trial comparing FOLFIRINOX (F: 5FU/leucovorin [LV], irinotecan [I], and oxaliplatin [O]) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): Preplanned interim analysis results of the PRODIGE 4/ACCORD 11 trial.** *Proc ASCO* 2010;**Abstract 4010**.

Renouf DJ et al. **An analysis of the effect of smoking status on erlotinib pharmacokinetics (PKs), toxicity, and ability to dose escalate in a phase II study of erlotinib in advanced pancreatic cancer (PC).** *Proc ASCO* 2010;**Abstract 4056**.

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

INTERVIEW

Al B Benson III, MD

Dr Benson is Professor of Medicine and Associate Director for Clinical Investigators at the Robert H Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois.

Tracks 1-11

Track 1 **Case discussion:** A 75-year-old man with Stage II colon cancer and a CEA level of 14 ng/mL undergoes a right hemicolectomy and elects no further therapy until the appearance of three liver lesions and an increase in CEA level to 54 ng/mL one year later

Track 2 Monitoring the pace of disease after neoadjuvant systemic therapy when assessing the resectability of hepatic metastases

Track 3 Treatment algorithm for mCRC

Track 4 EGFR antibody-associated dermatologic toxicity

Track 5 Treatment approach for patients with resectable hepatic-only metastases

Track 6 Chemotherapy/bevacizumab as conversion therapy for potentially resectable mCRC

Track 7 **Case discussion:** A 53-year-old man with chronic hepatitis C is diagnosed with HCC and undergoes bridge radioembolization therapy prior to liver transplantation and treatment with bortezomib/doxorubicin on the ECOG-E6202 study

Track 8 Liver transplantation for patients with hepatitis C and/or cirrhosis

Track 9 Sorafenib alone or in combination with chemotherapy for advanced HCC

Track 10 Chemoembolization with or without sorafenib in unresectable HCC

Track 11 Evaluation of biologic agents in the adjuvant setting for gastrointestinal cancer

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: For a patient with newly diagnosed metastatic CRC, do you order K-ras testing and consider an EGFR antibody, or do you generally go with bevacizumab in the first line?

DR BENSON: We obtain K-ras at the time of diagnosis for metastatic disease and also for patients with high-risk Stage III disease. I emphasize to patients that we have options for first-line therapy. I review the two dominant chemotherapy platforms — FOLFOX and FOLFIRI — and then I discuss the role of biologic agents, both bevacizumab and an anti-EGFR approach. We discuss the potential risks and toxicities. I don't believe we have a good way to choose

one EGFR antibody rather than another. In our part of the country, we tend not to see the cetuximab reaction, so some patients in our group receive cetuximab and some receive panitumumab.

DR LOVE: Is there a difference between the two antibodies in terms of dermatologic toxicity, and how do you approach the dermatologic issues?

DR BENSON: We have not seen much of a difference between the two agents in terms of rash. We have been fortunate in working with Mario Lacouture, who has established an algorithm for patients receiving anti-EGFR therapy (Lacouture 2010; [4.1]).

When we are ready to initiate one of these agents, we refer patients to dermatology, and they work together in terms of interventions, such as doxycycline and topical measures. Patients appreciate the interaction with dermatology, and I believe it has made a difference in helping to avoid some of the more severe skin reactions we have seen in the past. I have seen far fewer cases of severe skin reactions since participating in this program.

4.1

Skin Toxicity Evaluation Protocol with Panitumumab (STEPP): A Preemptive Skin Treatment Regimen

Preemptive treatment regimen is begun on day -1 (one day before the first panitumumab dose) and continued through week 6:

- Skin moisturizer daily AM on face, hands, feet, neck, back and chest
- Sunscreen on exposed skin areas before going outdoors
- Topical steroid daily in PM on face, hands, feet, neck, back and chest
- Doxycycline 100 mg twice per day

Lacouture ME et al. *J Clin Oncol* 2010;28(8):1351-7.

Tracks 9-10

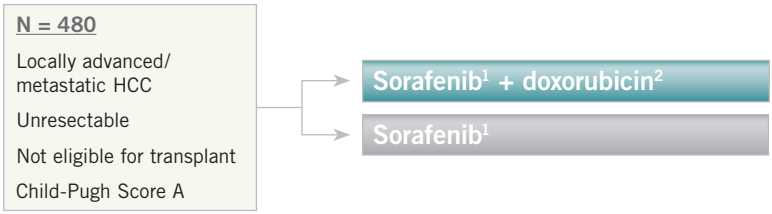
DR LOVE: Where are we headed in terms of clinical research for advanced hepatocellular carcinoma (HCC)?

DR BENSON: With single-agent sorafenib, we see a clear benefit in terms of progression-free survival and overall survival (Llovet 2008). Building on initial Phase II data with sorafenib and doxorubicin, a Phase III Intergroup trial sponsored by the CALGB is comparing sorafenib with doxorubicin to sorafenib alone for HCC (4.2).

Additional investigative approaches include chemoembolization with or without sorafenib in addition to sorafenib with or without chemoembolization. Because of the concern about potential toxicity with chemoembolization while receiving sorafenib, patients initially start with sorafenib and then receive chemoembolization without sorafenib. Once they have recovered from the chemoembolization, then they resume the sorafenib.

4.2

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

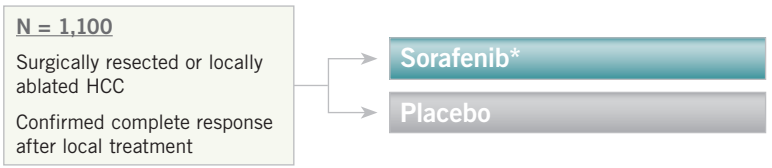


[1] Sorafenib is administered orally twice daily until disease progression or unacceptable toxicity.
[2] Doxorubicin is administered on day one, every 21 days, for a maximum of six cycles in the absence of disease progression or unacceptable toxicity.

www.clinicaltrials.gov. Identifier NCT01015833.

4.3

STORM: A Randomized Phase III Trial of Adjuvant Sorafenib in Hepatocellular Carcinoma (HCC)



* Sorafenib is administered orally twice daily until disease recurrence or unacceptable toxicity or other criteria for withdrawal are met.

www.clinicaltrials.gov. Identifier NCT00692770.

DR LOVE: Is there a role for sorafenib for HCC in the adjuvant setting?

DR BENSON: There definitely is an interest and also an ongoing study (4.3). What we have learned in colon cancer is that the only way we will be able to intelligently use biologic agents in the adjuvant setting is to understand how a biologic agent interacts in a population with microcellular disease rather than in people who have measurable disease as we see in advanced-disease trials. ■

SELECT PUBLICATIONS

Lacouture ME et al. **Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer.** *J Clin Oncol* 2010;28(8):1351-7.

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **According to a study by Gray and colleagues, Recurrence Score and number of lymph nodes examined are independent predictors of recurrence in Stage II colon cancer after surgery.**
   a. True
   b. False
2. **Which of the following is correct regarding neoadjuvant FOLFOX/bevacizumab without radiation therapy in locally advanced rectal cancer?**
   a. Leads to a complete pathologic complete remission in approximately 30 percent of patients
   b. Results in a high local failure rate after surgery
3. **Which of the following improved in the ToGA trial with the addition of trastuzumab to chemotherapy for HER2-positive advanced gastric cancer?**
   a. Overall survival
   b. Overall response rate
   c. Progression-free survival
   d. All of the above
4. **The ToGA trial used the following methods to define HER2 status:**
   a. IHC
   b. FISH
   c. Both a and b
5. **In the Phase III AVAGAST study for patients with advanced gastric cancer, the addition of bevacizumab to capecitabine and cisplatin resulted in significant improvements in _____.**
   a. Overall survival
   b. Progression-free survival
   c. Response rate
   d. Both a and b
   e. Both b and c
6. **Which of the following is improved in the Phase III trial comparing FOLFIRINOX to gemcitabine for advanced pancreatic cancer?**
   a. Response rate
   b. Progression-free survival
   c. Overall survival
   d. All of the above
7. **Which of the following is correct regarding erlotinib and smoking status in pancreatic cancer?**
   a. Maximum tolerated dose of erlotinib is higher in smokers than in nonsmokers
   b. Maximum tolerated dose of erlotinib is lower in smokers than in nonsmokers
   c. Maximum tolerated dose of erlotinib is similar in smokers and nonsmokers
8. **A comparison of preemptive treatment versus reactive treatment for dermatological toxicity associated with anti-EGFR antibodies has shown _____.**
   a. Improvement with preemptive treatment for Grade II or higher skin toxicities
   b. Less quality-of-life impairment with preemptive treatment
   c. Both a and b
9. **Which of the following approaches are being investigated in clinical trials in HCC?**
   a. Sorafenib versus sorafenib and doxorubicin in locally advanced or metastatic HCC
   b. Chemoembolization with or without sorafenib
   c. Adjuvant sorafenib in resected or locally ablated HCC
   d. All of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 3, 2010

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

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

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

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

	BEFORE	AFTER
Management of anti-EGFR-associated dermatologic toxicity	4 3 2 1	4 3 2 1
Biomarkers for patients with high-risk Stage II colon cancer	4 3 2 1	4 3 2 1
Neoadjuvant FOLFOX with or without bevacizumab and without radiation therapy for locally advanced rectal cancer	4 3 2 1	4 3 2 1
HER2 testing and interpretation in gastric cancer	4 3 2 1	4 3 2 1
Role of maintenance bevacizumab in Stage IV CRC	4 3 2 1	4 3 2 1
Nongemcitabine-based regimens in metastatic pancreatic cancer	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No

If no, please explain:.....

.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Evaluate significant data presented at the ASCO 2010 Annual Meeting, and determine how the data may apply to the treatment of GI cancer. . . . . 4 3 2 1 N/M N/A
- Summarize key findings from clinical studies of emerging therapeutic regimens for pancreatic and biliary tract cancer. . . . . 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
- Communicate to patients with metastatic CRC the benefits and risks of existing and emerging anti-VEGF and anti-EGFR biologic therapy. . . . . 4 3 2 1 N/M N/A
- Apply clinical trial results to integrate the use of chemotherapy with biologic agents, such as anti-HER2 and anti-VEGF agents, into the treatment of gastroesophageal cancer when appropriate. . . . . 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

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

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

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

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

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Axel Grothey, MD	4 3 2 1	4 3 2 1
Jaffer A Ajani, MD	4 3 2 1	4 3 2 1
Malcolm J Moore, MD	4 3 2 1	4 3 2 1
Al B Benson III, 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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Name: ..... Specialty: .....

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Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

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

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Gastrointestinal Cancer™

UPDATE

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