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Gastrointestinal Cancer™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

EDITOR

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INTERVIEWS

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LAUNCH ISSUE

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Gastrointestinal Cancer Update

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OVERVIEW OF ACTIVITY

Colorectal cancer (CRC) is among the most common cancer types diagnosed in the United States, and its clinical management is continuously evolving. Although less frequently encountered individually, the collection of other "non-CRC" gastrointestinal (GI) tumors accounts for more per annum cancer-related deaths than those attributed to tumors of the colon and rectum combined. Published results from ongoing trials lead to the emergence of new therapeutic agents and regimens, novel biomarkers influencing treatment selection and alterations to 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 discussions with leading oncology investigators. By providing access to the latest scientific developments and expert perspectives, this CME activity assists medical oncologists with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Apply the results of emerging clinical research to the best-practice management of GI cancer originating within (CRC) and outside of the colon and rectum (non-CRC).
- Formulate a therapeutic approach to locally advanced rectal cancer.
- Communicate the benefits and risks of existing and emerging anti-VEGF and anti-EGFR biologic therapy to patients with metastatic CRC.
- Appraise data on novel combination regimens for advanced pancreatic cancer.
- Utilize clinical and molecular biomarkers to select optimal systemic treatment strategies for patients with gastric or gastroesophageal cancer.
- Communicate the benefits and risks of existing and emerging systemic interventions to patients with advanced hepatocellular or biliary tract cancer.
- Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials.

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INTERVIEW

Leonard B Saltz, MD

Dr Saltz is Professor of Medicine at Weill Medical College of Cornell University as well as Attending Physician and Colorectal Disease Management Team Leader at Memorial Sloan-Kettering Cancer Center in New York, New York.

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Select Excerpts from the Interview

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DR LOVE: Would you discuss the rationale for studying chemotherapy up front, without radiation therapy for patients with locoregional rectal cancer?

DR SALTZ: One of my interests for a long time has been the question of how much treatment to administer to whom. Within that context, I wanted to explore the hypothesis that pelvic radiation therapy for rectal cancer was largely an anachronism left over from the 1970s when we had inferior chemotherapy and surgical techniques. Since that time, a tectonic shift has occurred in the understanding of the pelvic anatomy and with that came widespread acceptance of the total mesorectal excision. Also, we have since begun using combination oxaliplatin-containing chemotherapy with favorable results.

Around 2002 we initially administered FOLFOX to two young patients for whom we did not believe that radiation therapy was the best course of action, and both experienced a pathologic complete response. We now try to administer our best systemic chemotherapy from the start because patients with locoregional rectal cancer rarely die from the local disease but rather from distant metastatic disease.

DR LOVE: Would you discuss your pilot study of preoperative FOLFOX/bevacizumab without radiation therapy for locally advanced rectal cancer?

DR SALTZ: We enrolled patients with Stage II or Stage III resectable rectal cancer, and the primary endpoint was the R0 resection rate. The patients received FOLFOX with bevacizumab, based on encouraging data with FOLFOX/bevacizumab in rectal cancer (Willett 2009) and IFL/bevacizumab in metastatic colorectal cancer (Hurwitz 2006).

Six doses of FOLFOX were administered for 12 weeks preoperatively, and bevacizumab was added to the first four cycles. Approximately eight weeks lapsed between bevacizumab administration and surgery, and we observed no major surgical complications (Schrag 2010).

So far we've treated approximately 30 patients, and we've seen eight pathologic complete responses with no failures in the pelvis. The R0 resection rate to date is 100 percent (Schrag 2010; [1.1]).

DR LOVE: What are your thoughts on this approach outside of a protocol setting?

DR SALTZ: We have to be careful about getting too comfortable with an idea before it has been adequately reviewed. We have no long-term outcome data in terms of pelvic control. However, I might consider this approach for a

1.1

Neoadjuvant FOLFOX with Bevacizumab*, without Radiation Therapy, for Locally Advanced Rectal Cancer

Number of patients	Clinical regression	R0 resection	Pathologic complete response
27	100%	100%	26%

* Patients received preoperative FOLFOX x 6 cycles + bevacizumab x 4 cycles

Schrag D et al. Gastrointestinal Cancers Symposium 2010;**Abstract 434**.

carefully selected patient needing to avoid radiation therapy. But I would be careful to discuss with the patient first.

Tracks 6-8

DR LOVE: What are your thoughts on the data presented at ASCO 2009 on the Onco*type* DX colon cancer assay in patients with Stage II colon cancer (Kerr 2009; [1.2])?

DR SALTZ: I don't believe we have yet achieved in colon cancer what has been achieved in breast cancer with the Onco*type* DX assay. In colon cancer they have been able to segregate patients with Stage II disease into higher-risk and lower-risk groups, but that does not tell us who will have the risk mitigated by chemotherapy.

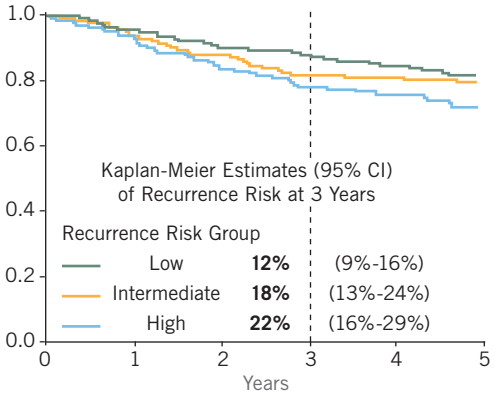
DR LOVE: In the ASCO presentation of the Onco*type* data, Dr Kerr concluded that the relative risk reduction was the same in the patients at higher risk and lower risk, so it appears that an absolute risk reduction can be derived.

DR SALTZ: I believe we are just getting started in this arena, and I hope it's where we will be heading in the future because we need to become more sophisticated. Currently, we rely upon morphology, nodal sampling, degree of differentiation and other factors to make clinical decisions. I would like to

1.2

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

Recurrence Risk Group	Range of RS	Proportion of Patients
Low	<30	43.7%
Intermediate	30-40	30.7%
High	≥41	25.6%



"This is the first study in which a prospectively-defined gene expression assay can independently predict recurrence with certainty in colon cancer. In that sense, it is a landmark study... Importantly, across the different Recurrence Score prognostic categories the proportional benefits of chemotherapy were maintained. Therefore, if a patient had a high chance of tumor recurrence, as predicted by the prognostic score, then the absolute benefits of chemotherapy would be somewhat higher than patients with a low risk of recurrence."

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

believe that we will be able to utilize molecular profiling also, but I'm not certain that we are ready and we need to be cautious.

Tracks 13-17

DR LOVE: What are your thoughts about the use of the anti-EGFR antibodies cetuximab and panitumumab in colorectal cancer?

DR SALTZ: At ASCO 2001, we reported a 17 percent response rate when cetuximab was added to irinotecan for 121 patients with refractory disease (Saltz 2001), which was validated by the BOND study that reported a response rate of 22.9 percent (Cunningham 2004). On the basis of the data from the third-line setting, we expected cetuximab to have a large effect in the up-front and adjuvant settings. However, the front-line data with these agents have been disappointing. The CRYSTAL study, which evaluated FOLFIRI with or without cetuximab, reported that patients with K-ras mutations received no benefit and those with wild-type K-ras disease had a progression-free survival benefit that was very modest (Van Cutsem 2009).

DR LOVE: How do you see the anti-EGFR antibodies being used clinically?

DR SALTZ: Randomized studies suggest that modest numbers of patients obtain a response benefit with the addition of these agents to front-line chemotherapy, and without question in the salvage setting some patients experience a real benefit — it's about 20 percent in the K-ras wild-type population with a single agent. These agents can be used later in the course of therapy. I believe cetuximab and panitumumab are essentially equivalent, but in certain geographic regions a high rate of serious hypersensitivity reactions to cetuximab appears to occur and I would use panitumumab for those patients. We obtain K-ras genotyping when patients are initially diagnosed with metastatic disease, so we know what their options will be down the road. The agents may be administered earlier if the need to shrink the tumor to increase resectability is critical, and an earlier role in K-ras wild-type disease may also be reasonable. ■

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Cunningham D et al. **Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.** *N Engl J Med* 2004;351(4):337-45.

Hurwitz HI et al. **Analysis of outcomes of patients with metastatic colorectal cancer (mCRC) treated with IFL with or without bevacizumab (BV) in a phase III clinical trial based on baseline risk.** Gastrointestinal Cancers Symposium 2006;**Abstract 249**.

Saltz L et al. **Cetuximab (IMC-C225) plus irinotecan (CPT-11) is active in CPT-11-refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR).** *Proc ASCO* 2001. No abstract available

Van Cutsem E et al. **Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer.** *N Engl J Med* 2009;360(14):1408-17.

Willett CG et al. **Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: A multidisciplinary phase II study.** *J Clin Oncol* 2009;27(18):3020-6.

INTERVIEW

Margaret A Tempero, MD

Dr Tempero holds the Doris and Donald Fisher Distinguished Professorship in Clinical Cancer Research and is Professor of Medicine in the Division of Hematology and Oncology, Co-Leader of the Pancreas Cancer Program, Director of Research Programs and Deputy Director at the UCSF Helen Diller Family Comprehensive Cancer Center in San Francisco, California.

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Track 1 Desmoplasia in the regulation of pancreatic carcinogenesis and response to therapy

Track 2 Hypothesized direct antitumor effect of bevacizumab in pancreatic cancer (PC)

Track 3 Nanoparticle albumin-bound (*nab*) paclitaxel targets tumor stroma and is efficacious in PC in combination with gemcitabine

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Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss your concept of the unique biology of pancreatic cancer?

DR TEMPERO: This disease has a more perturbed microenvironment than virtually any other cancer. It is characterized by profound desmoplasia, with which sometimes the actual cancerous component is a small fraction of the tumor mass (2.1). Understanding the desmoplasia and whether it's a barrier to drug delivery is currently of high interest.

2.1

Desmoplasia of Pancreatic Cancer

"Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer and is characterized by remarkable desmoplasia. The desmoplasia is composed of extracellular matrix (ECM) proteins, myofibroblastic pancreatic stellate cells, and immune cells associated with a multitude of cytokines, growth factors, and ECM metabolizing enzymes. The mechanisms of participation of this complex matrix process in carcinogenesis are only starting to be appreciated. Recent studies showed key roles for stellate cells in the production of ECM proteins as well as cytokines and growth factors that promote the growth of the cancer cells all present in the desmoplastic parts of PDAC.

In addition, interactions of ECM proteins and desmoplastic secreted growth factors with the cancer cells of PDAC activate intracellular signals including reactive oxygen species that act to make the cancer cells resistant to dying. These findings suggest that the desmoplasia of PDAC is a key factor in regulating carcinogenesis of PDAC as well as responses to therapies. A better understanding of the biology of desmoplasia in the mechanism of PDAC will likely provide significant opportunities for better treatments for this devastating cancer."

Pandol S et al. *Clin Gastroenterol Hepatol* 2009;7(11 Suppl):44-7.

Tracks 3, 5, 14

DR LOVE: What novel therapeutic agents and regimens are being investigated for pancreatic cancer?

DR TEMPERO: Probably the most exciting combination is gemcitabine and nanoparticle albumin-bound (*nab*) paclitaxel, which is being investigated in a Phase III trial by Dan Von Hoff and colleagues. *Nab* paclitaxel is a taxane that's coated with albumin, and the albumin is trapped in the tumor tissue by the SPARC protein. An abundance of SPARC is associated with pancreatic cancer — it's not only present in the stroma but in the tumor also.

Dan demonstrated that a correlation exists between clinical response to gemcitabine and *nab* paclitaxel and SPARC, although it's not perfect (Von Hoff 2009). Some patients whose disease was not considered positive for the SPARC protein experienced a tumor response. Therefore, SPARC wouldn't be a perfect enrichment tool, but I believe it would be worth addressing in future trials.

Dan's group also reported interesting preclinical data from an animal model indicating that *nab* paclitaxel may cause stromal collapse. In this model, they demonstrated that after treatment with *nab* paclitaxel, less stroma and about three and a half times the amount of gemcitabine were found in the

tumor tissue (Maitra 2009). It may be that the effect we see in response to *nab* paclitaxel is not a direct effect but one that allows another drug to reach the tumor tissue. If that's true, it could revolutionize our thinking as to how we develop drugs in the context of pancreatic cancer in that drug development should consider the stroma.

DR LOVE: Do any other agents appear promising for the treatment of pancreatic cancer?

DR TEMPERO: We're excited about a novel combination of gemcitabine and capecitabine, on which we presented data at the 2010 Gastrointestinal Cancers Symposium. We used a fixed-dose rate of gemcitabine, administered every other week, and we combined it with alternate-week capecitabine. The rationale was that if you separated the doses of capecitabine, maybe you could ameliorate some of the toxicity. We demonstrated an overall survival of 10.4 months for patients with metastatic disease, and our disease control rate was 70 percent (Espinoza 2010; [2.2]).

2.2

Phase I Study of Biweekly Fixed-Dose Rate Gemcitabine with Capecitabine for Patients with Advanced Pancreatic or Biliary Carcinomas (APC or ABC)

Clinical parameter	Efficacy cohort* (n = 37)
Partial response†	8 (21.5%)
Stable disease†	18 (48.5%)
Disease control rate	70%
	APC cohort (n = 20)
Estimated median time to disease progression	6.2 mo
Estimated overall survival	10.4 mo

* Efficacy cohort includes patients with APC and ABC; † Partial response and stable disease observed for at least four cycles (median number of cycles received = 10)

Espinoza AM et al. Gastrointestinal Cancers Symposium 2010;**Abstract 202**.

Track 7

DR LOVE: Where do you think gemcitabine and erlotinib fit in the treatment algorithm of advanced pancreatic cancer?

DR TEMPERO: Malcolm Moore — through the NCIC — carried out a Phase III placebo-controlled study (NCIC CTG PA.3) comparing gemcitabine with erlotinib to gemcitabine alone (Moore 2007; [2.3]). They demonstrated a significant improvement in survival, but it was a small improvement that perhaps is not clinically meaningful for everyone.

However, a subset of patients within the cohort probably benefited greatly from the addition of erlotinib. One of our responsibilities is to define that subset and offer erlotinib to those patients (2.4). ■

2.3

Response and Survival in the NCIC CTG PA.3 Phase III Trial of Erlotinib and Gemcitabine in Locally Advanced or Metastatic Pancreatic Adenocarcinoma

	Erlotinib/ gemcitabine (n = 285)	Gemcitabine/ placebo (n = 284)	HR	*p*-value
Response (CR + PR)	8.6%	8.0%	—	
Progression-free survival	3.75 mo	3.55 mo	0.77	0.004
Overall survival	6.24 mo	5.91 mo	0.82	0.038

Moore MJ et al. *J Clin Oncol* 2007;25(15):1960-6.

2.4

Implications of the NCIC CTG PA.3 Trial: Importance of the Identification of Patients with an Increased Likelihood of Treatment Benefit

"[We] hope that one of the messages of this [NCIC] study is that every effort should be made to prospectively collect tumor blocks and that collection of tumor material should be mandatory in trials evaluating new and more expensive treatment regimens.

This is especially the case when only a small difference in outcome is anticipated in the whole patient population. This relatively small difference in the whole patient population can become more relevant in patients whose tumors express certain molecular characteristics."

Van Cutsem E, Verslype C. *J Clin Oncol* 2007;25(15):1949-52.

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Maitra A et al. ***Nab*(R)-paclitaxel targets tumor stroma and results, combined with gemcitabine, in high efficacy against pancreatic cancer models.** AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2009;**Abstract C246**.

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.

Pandol S et al. **Desmoplasia of pancreatic ductal adenocarcinoma.** *Clin Gastroenterol Hepatol* 2009;7(11 Suppl):44-7.

Philip PA et al. **Consensus report of the National Cancer Institute clinical trials planning meeting on pancreas cancer treatment.** *J Clin Oncol* 2009;27(33):5660-9.

Van Cutsem E et al. **Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer.** *J Clin Oncol* 2009;27(13):2231-7.

Van Cutsem E, Verslype C. **Lessons learned in the management of advanced pancreatic cancer.** *J Clin Oncol* 2007;25(15):1949-52.

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

Peter C Enzinger, MD

Dr Enzinger is Assistant Professor of Medicine at Harvard Medical School and Clinical Director of the Gastrointestinal Cancer Center at Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-8

Track 1 Background of the Phase III ToGA trial evaluating chemotherapy/trastuzumab in HER2-positive advanced gastric cancer (GC)

Track 2 ToGA trial results

Track 3 Combining trastuzumab with other chemotherapy platforms in patients with HER2-positive advanced GC

Track 4 HER2 testing and interpretation in GC

Track 5 Phase III studies of capecitabine/cisplatin with bevacizumab (AVAGAST) or cetuximab (EXPAND) as first-line therapy for advanced GC

Track 6 Differential frequency of HER2 positivity in gastroesophageal junction versus lower gastric cancer

Track 7 Staging changes (*AJCC*, 7th edition) for gastroesophageal cancer

Track 8 Role of radiation therapy in the palliation of dysphagia from gastroesophageal cancer

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: What are your thoughts on the ToGA trial results evaluating chemotherapy with or without trastuzumab in patients with HER2-positive advanced gastric cancer?

DR ENZINGER: I consider the ToGA study to be one of the most important recent data sets in the treatment of this disease (Van Cutsem 2009). The ToGA study included patients with HER2-positive advanced gastric cancer, including those with involvement of the gastroesophageal (GE) junction.

The investigators determined HER2 status using both IHC and FISH testing. Patients with IHC 3+ disease were included without using FISH analysis. Approximately 20 percent of the patients tested met the HER2 criteria for study inclusion, which is similar to the rates of HER2 positivity in breast cancer.

Patients were randomly assigned to standard platinum/5-FU therapy followed by either trastuzumab or placebo. The results not only showed an improvement in response rate, but more importantly they also showed an approximate two-month improvement in overall survival (3.1). On the basis of these data, we now test for HER2 in any patient who presents with gastric/GE junction adenocarcinoma. We're also testing patients with esophageal cancer because it doesn't make sense that the paradigm stops five centimeters above the GE junction. For patients with positive HER2 results, we add trastuzumab when we go with a 5-FU/platinum strategy.

DR LOVE: What about HER2 testing in gastric cancer (3.2)? My understanding is that it differs from the breast cancer setting.

DR ENZINGER: That's correct. The test is the same, but a greater heterogeneity seems to be present in gastric cancer samples. That is, depending on

3.1

ToGA: A Phase III Study of Adding Trastuzumab (T) to Standard First-Line Therapy for Patients with Advanced Gastric Cancer

	FC* (n = 290)	FC* + T (n = 294)	HR	*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 (CR + PR)	34.5%	47.3%	—	0.0017
Complete response (CR)	2.4%	5.4%	—	0.0599
Partial response (PR)	32.1%	41.8%	—	0.0145

* FC = fluoropyrimidine (5-FU or capecitabine at investigator discretion) and cisplatin

Van Cutsem E et al. *Proc ASCO* 2009;**Abstract LBA4509**.

3.2

Modified HER2 Scoring System for Gastric Cancer: The ToGA Trial

Staining characteristics	IHC score/classification
No staining or membrane staining in <10% of cells	0/negative
Faint/barely perceptible membrane staining in >10% of cells; cells are stained in part of their membrane	1+/negative only
Weak to moderate complete or basolateral membrane staining in >10% of tumor cells	2+/equivocal
Moderate to strong complete or basolateral membrane staining in >10% of tumor cells	3+/positive

"The modified HER2-scoring system showed concordance between IHC and FISH results of 87.5%. In breast cancer most IHC 0/1 samples are FISH negative but, in ToGA, the frequency of IHC 0/1 samples testing FISH positive was almost as high as IHC 2/FISH-positive samples (23% vs 26%)."

Bang Y et al. *Proc ASCO* 2009;**Abstract 4556**.

where you sample the tumor, differences are apparent in the positivity and strength of the staining.

In breast cancer, positivity is defined as IHC 3+ or FISH-positive. The definition of HER2 positivity is less certain in gastric cancer. Data from the ToGA study suggest that patients with IHC 2+ disease may derive a similar benefit to patients with higher positivity, but the number of patients included with lower positivity make it difficult to draw conclusions. I've been arguing to include patients with lower positivity in ongoing studies simply because the breast cancer paradigm may not apply to the field of esophagogastric cancer.

Track 5

DR LOVE: Would you discuss biologic agents that are under investigation for patients with gastroesophageal cancer?

DR ENZINGER: Dr Cunningham and his group, in addition to the Europeans, are evaluating the addition of molecular biologic agents on a grand scale in randomized studies. For bevacizumab, the AVAGAST study will be particularly important. AVAGAST is a double-blind, Phase III trial evaluating first-line cisplatin and capecitabine with or without bevacizumab (NCT00548548), and another Phase III study called EXPAND is evaluating cisplatin and capecitabine with or without cetuximab (NCT00678535).

DR LOVE: What do we know about bevacizumab and cetuximab in gastric cancer?

DR ENZINGER: At this time, only Phase II studies have been completed. Both agents are safe and reasonably well tolerated, but we don't know if a worthwhile survival benefit exists.

In our study, we added bevacizumab to standard chemotherapy (ie, docetaxel, cisplatin, irinotecan) and the data suggested improved efficacy with the addition of bevacizumab (Enzinger 2008) compared to historical data (Enzinger 2004). These results are promising, but we need additional data from the ongoing large, randomized studies to corroborate the Phase II study findings. ■

SELECT PUBLICATIONS

Bang Y et al. **Pathological features of advanced gastric cancer (GC): Relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial.** *Proc ASCO* 2009;**Abstract 4556**.

Enzinger P et al. **Phase II trial of docetaxel, cisplatin, irinotecan, and bevacizumab in metastatic esophagogastric cancer.** *Proc ASCO* 2008;**Abstract 4552**.

Enzinger P et al. **Phase II study of docetaxel, cisplatin, and irinotecan in advanced esophageal and gastric cancer.** *Proc ASCO* 2004;**Abstract 4040**.

Van Cutsem E et al. **Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC).** *Proc ASCO* 2009;**Abstract LBA4509**.

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 1-13

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the results of the Phase III trial reported at ASCO 2009 evaluating gemcitabine with or without cisplatin for patients with advanced or metastatic biliary tract cancer?

DR ABOU-ALFA: The ABC-02 study presented by Dr Valle and colleagues from the United Kingdom was a continuation of a previous smaller trial, the ABC-01 study, in which patients were randomly assigned to gemcitabine/cisplatin versus gemcitabine alone. On the basis of positive data, which showed an improvement in progression-free survival with the combination (Valle 2009a), the investigators expanded their study to the ABC-02 study, which included approximately 400 patients, including those from the original study.

At ASCO 2009, ABC-02 investigators reported an improvement in overall survival of two-plus months with gemcitabine/cisplatin and a similarity in toxicity between the two arms. The authors recommended gemcitabine/cisplatin as a new standard treatment for advanced biliary tract cancer (Valle 2009b; [4.1]). Some debate stirred with regard to whether this should be recognized as standard treatment. However, we now have a platform on which to base further research for biliary tumors, so I believe that this was important.

4.1

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

	Gem (n = 206)	Gem + cis (n = 204)	Hazard ratio	*p*-value
Median overall survival	8.3 months	11.7 months	0.70	0.002
Median progression-free survival	6.5 months	8.4 months	0.72	0.003
Overall response rate (CR + PR + SD)	71%	79%	—	0.256
Complete response (CR)	0.8%	0.7%	—	—
Partial response (PR)	15%	25%	—	—
Stable disease (SD)	55%	53%	—	—

"This is the largest ever study in ABC and demonstrates a clear survival advantage for GemCis without added clinically significant toxicity, setting a new international standard of care."

Valle JW et al. *Proc ASCO* 2009b;**Abstract 4503**.

Track 3

DR LOVE: What important recent developments have taken place in hepatocellular carcinoma (HCC) research?

DR ABOU-ALFA: Since sorafenib was established as standard treatment for HCC, the attempt in the metastatic setting has been to ascertain if anything could be added to sorafenib or if other combinations could be of value.

One such trial is based on positive results from a randomized Phase II study evaluating doxorubicin with sorafenib versus doxorubicin with placebo. That study showed major improvements in time to disease progression, progression-free survival and overall survival with sorafenib (Abou-Alfa 2008; [4.2]).

The Phase III study evaluating sorafenib with or without doxorubicin is important because it will evaluate whether synergy exists between an anthracycline and an anti-angiogenic agent. The science behind this approach is interesting.

In order to be effective, anthracyclines depend on a molecule called ASK1. Raf is another target for sorafenib that binds with ASK1, and the bound pair remains in the mitochondria, making the ASK1 inaccessible. The question is, will ASK1 become more available for doxorubicin to act on if we administer sorafenib and attempt to release or deactivate Raf?

I still recommend sorafenib as first-line treatment. However, with some patients who have failed on sorafenib I've seen a reemergence of activity with the addition of doxorubicin, which may be because of that combination effect on the biologic level.

4.2

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

	S + D (n = 47)	P + D (n = 49)	Hazard ratio	*p*-value
Median time to disease progression	8.6 months	4.8 months	0.60	0.076
Median overall survival	13.8 months	6.5 months	0.51	0.0129
Median progression-free survival	6.9 months	2.8 months	NR	NR

NR = not reported

Abou-Alfa GK et al. Presentation. Gastrointestinal Cancers Symposium 2008;**Abstract 128**.

Track 5

DR LOVE: What data are available on the combination of bevacizumab and erlotinib in patients with advanced HCC?

DR ABOU-ALFA: A limited Phase II study published by Dr Melanie Thomas reported that the median survival with this combination is approximately 16 months. The study also reported that progression-free survival will reach close to the median survival reported with sorafenib, which is in the nine- to 10-month range (Thomas 2009; [4.3]).

I believe that bevacizumab/erlotinib is a valuable combination, and it is currently being evaluated in a randomized Phase II study versus sorafenib.

4.3

Efficacy of Bevacizumab/Erlotinib for Patients with Advanced Hepatocellular Carcinoma

	n = 40
Progression-free survival (at week 16)	63%*
Median progression-free survival	9.0 months
Median overall survival	15.7 months
Partial response	25%
Stable disease	38%

* Primary endpoint, $p = 0.022$ versus the null-hypothesized value of 45%

Thomas MB et al. *J Clin Oncol* 2009;27(6):843-50.

Tracks 6-7

DR LOVE: What key recent advances have been reported on the use of sorafenib in the treatment of advanced HCC?

DR ABOU-ALFA: In a recent subgroup analysis of the SHARP trial, patients with hepatitis C demonstrated an improvement in survival — 14 months compared to 10.7 months for the general population in that study (Bolondi 2008).

This raises the issue of whether etiology has an effect on benefit from sorafenib, which might be important from an academic standpoint. Are we dealing with HCC as one disease, or is it four diseases in one, based on the different etiologies?

DR LOVE: What about the combination of sorafenib with chemoembolization?

DR ABOU-ALFA: With regard to locally advanced disease, there is a lot of interest in combining TACE with anti-angiogenic agents, and most of the studies have evaluated sorafenib.

One such study is an ECOG trial evaluating the use of sorafenib with TACE versus TACE with a placebo control (ECOG-E1208). Another international study with a similar design is called the SPACE study (NCT00855218). Some important biological factors underlie this approach. Preclinical experiments have shown that after embolization of a tumor, other tumors can appear. This occurs because of the angiogenic drive caused by killing that first tumor — tumors are impelled to survive.

In theory it will be valuable to have an anti-angiogenic drug to help cut that surge of VEGF and angiogenesis that occurs after such treatment. ■

SELECT PUBLICATIONS

Abou-Alfa GK et al. **Final results from a phase II, randomized, double-blind study of sorafenib plus doxorubicin versus placebo plus doxorubicin in patients with advanced hepatocellular carcinoma.** Presentation. Gastrointestinal Cancers Symposium 2008;**Abstract 128**.

Bolondi L et al. **Clinical benefit of sorafenib in hepatitis C patients with hepatocellular carcinoma (HCC): Subgroup analysis of the SHARP trial.** Gastrointestinal Cancers Symposium 2008;**Abstract 129**.

Kelley RK, Venook AP. **Sorafenib in hepatocellular carcinoma: Separating the hype from the hope.** *J Clin Oncol* 2008;26(36):5845-8.

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 JW et al. **Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: A multicentre randomised phase II study — The UK ABC-01 study.** *Br J Cancer* 2009a;101(4):621-7.

Valle JW et al. **Gemcitabine with or without cisplatin in patients (pts) with advanced or metastatic biliary tract cancer (ABC): Results of a multicenter, randomized phase III trial (the UK ABC-02 trial).** *Proc ASCO* 2009b;**Abstract 4503**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the neoadjuvant trial evaluating FOLFOX with bevacizumab without radiation therapy as initial therapy for locally advanced rectal cancer, the proportion of patients in whom an R0 resection was accomplished was _____.**
   a. 40 percent
   b. 60 percent
   c. 100 percent
2. **Patients with Stage II colon cancer and a high-risk Recurrence Score® have approximately a _____ risk of relapse based on the Onco*type* DX colon cancer assay.**
   a. 12 percent
   b. 22 percent
   c. 50 percent
3. **A Phase I study of biweekly fixed-dose rate gemcitabine with capecitabine for patients with advanced pancreatic or biliary carcinomas demonstrated a disease control rate (response rate plus stable disease for at least four cycles) of _____.**
   a. 20 percent
   b. 40 percent
   c. 70 percent
4. **The NCIC CTG PA.3 trial was a Phase III study that compared _____ with gemcitabine to gemcitabine alone for patients with advanced pancreatic cancer.**
   a. Capecitabine
   b. Erlotinib
   c. *Nab* paclitaxel
   d. Cisplatin
5. **In the Phase III ToGA trial for patients with HER2-positive advanced gastric cancer, the addition of trastuzumab to first-line chemotherapy was associated with an improvement in overall survival of approximately _____.**
   a. Two months
   b. Four months
   c. Eight months
6. **During the ToGA trial, approximately _____ of patients tested positive for HER2 according to the modified HER2 scoring system for gastric cancer.**
   a. 10 percent
   b. 20 percent
   c. 40 percent
7. **The AVAGAST trial is a double-blind, Phase III trial that is evaluating the use of _____ for patients with advanced gastric cancer.**
   a. Bevacizumab
   b. Cetuximab
   c. Trastuzumab
   d. None of the above
8. **In the Phase III trial evaluating gemcitabine with or without cisplatin for patients with advanced or metastatic biliary tract cancer, what was the improvement in median overall survival with the combination?**
   a. No improvement
   b. 3.5 months
   c. 8.0 months
9. **A Phase II trial evaluating sorafenib with doxorubicin versus placebo with doxorubicin for patients with advanced hepatocellular carcinoma reported an improvement in _____ with the combination.**
   a. Median time to disease progression
   b. Median overall survival
   c. Median progression-free survival
   d. All of the above
10. **A Phase II trial evaluating the combination of bevacizumab and erlotinib for patients with advanced hepatocellular carcinoma reported that the primary study endpoint of progression-free survival at week 16 was _____.**
    a. 23 percent
    b. 63 percent
    c. 93 percent

Post-test answer key: 1c, 2b, 3c, 4b, 5a, 6b, 7a, 8b, 9d, 10b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Gastrointestinal Cancer Update — Issue 1, 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
Neoadjuvant FOLFOX/bevacizumab without radiation therapy for locally advanced rectal cancer	4 3 2 1	4 3 2 1
Outcome of the primary tumor in patients with synchronous metastatic colorectal cancer (mCRC) receiving combination chemotherapy without surgery as initial treatment	4 3 2 1	4 3 2 1
Activity of EGFR antibody therapy in combination with chemotherapy for mCRC	4 3 2 1	4 3 2 1
Erlotinib in combination with gemcitabine versus gemcitabine alone for patients with advanced pancreatic cancer (PC)	4 3 2 1	4 3 2 1
ToGA: Results of a Phase III study of first-line chemotherapy/ trastuzumab in HER2-positive advanced gastric cancer	4 3 2 1	4 3 2 1
CALGB-80802: A Phase III study of sorafenib with or without doxorubicin in advanced hepatocellular carcinoma (HCC)	4 3 2 1	4 3 2 1
ECOG-E1208: A Phase III study of chemoembolization with or without sorafenib in unresectable 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:.....

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:

- Apply the results of emerging clinical research to the best-practice management of GI cancer originating within (CRC) and outside of the colon and rectum (non-CRC)..... 4 3 2 1 N/M N/A
- Formulate a therapeutic approach to locally advanced rectal cancer..... 4 3 2 1 N/M N/A
- Communicate the benefits and risks of existing and emerging anti-VEGF and anti-EGFR biologic therapy to patients with metastatic CRC..... 4 3 2 1 N/M N/A
- Appraise data on novel combination regimens for advanced pancreatic cancer..... 4 3 2 1 N/M N/A
- Utilize clinical and molecular biomarkers to select optimal systemic treatment strategies for patients with gastric or gastroesophageal cancer..... 4 3 2 1 N/M N/A
- Communicate the benefits and risks of existing and emerging systemic interventions to patients with advanced hepatocellular or biliary tract cancer.... 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)

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
Leonard B Saltz, MD	4 3 2 1	4 3 2 1
Margaret A Tempero, MD	4 3 2 1	4 3 2 1
Peter C Enzinger, MD	4 3 2 1	4 3 2 1
Ghassan Abou-Alfa, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

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UPDATE

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