Conversations with Oncology Investigators  
Bridging the Gap between Research and Patient Care

EDITOR
Neil Love, MD

INTERVIEWS
Leonard B Saltz, MD
Margaret A Tempero, MD
Peter C Enzinger, MD
Ghassan Abou-Alfa, MD

Subscribe to Podcasts or download MP3s of this program at ResearchToPractice.com/GICU110
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.

ACCREDITATION STATEMENT
Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT
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.

HOW TO USE THIS CME ACTIVITY
This CME activity contains both audio and print components. To receive credit, the participant should review the CME information, listen to the CDs, review the monograph and complete the Post-test and Educational Assessment and Credit Form located in the back of this monograph or on our website at CME.ResearchToPractice.com. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. ResearchToPractice.com/GICU110 includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated within the text of the monograph in blue, bold text.

This program is supported by educational grants from Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Genentech BioOncology, Genomic Health Inc and Sanofi-Aventis.

Last review date: April 2010; Release date: April 2010; Expiration date: April 2011
INTERVIEWS

3 Leonard B Saltz, MD
Professor of Medicine
Weill Medical College of Cornell University
Attending Physician
Colorectal Disease Management Team Leader
Memorial Sloan-Kettering Cancer Center
New York, New York

7 Margaret A Tempero, MD
Doris and Donald Fisher Distinguished Professorship in Clinical Cancer Research; Professor of Medicine, Division of Hematology and Oncology
Co-Leader, Pancreas Cancer Program
Director of Research Programs
Deputy Director, UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, California

11 Peter C Enzinger, MD
Assistant Professor of Medicine, Harvard Medical School
Clinical Director, Gastrointestinal Cancer Center
Dana-Farber Cancer Institute
Boston, Massachusetts

14 Ghassan Abou-Alfa, MD
Assistant Attending, Memorial Sloan-Kettering Cancer Center
Assistant Professor, Weill Medical College at Cornell University
New York, New York

18 POST-TEST

19 EDUCATIONAL ASSESSMENT AND CREDIT FORM

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

If you would like to discontinue your complimentary subscription to Gastrointestinal Cancer Update, please email us at Info@ResearchToPractice.com, call us at (800) 648-8654 or fax us at (305) 377-9998. Please include your full name and address, and we will remove you from the mailing list.
CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: Dr Saltz — Advisory Committee: Genomic Health Inc, Genzyme Corporation; Consulting Agreements: Bristol-Myers Squibb Company, Schering-Plough Corporation; Paid Research: Amgen Inc, AstraZeneca Pharmaceuticals LP, Genentech BioOncology, ImClone Systems Incorporated, Lilly USA LLC, Merck and Company Inc, Pfizer Inc, Roche Laboratories Inc. Dr Tempero — Consulting Agreements: Abraxis BioScience, Celgene Corporation, Sanofi-Aventis. Dr Enzinger — Advisory Committee: Bristol-Myers Squibb Company; Speakers Bureau: Sanofi-Aventis. Dr Abou-Alfa — Consulting Agreements: Bayer HealthCare Pharmaceuticals, Celson Corporation, Chugai Pharmaceutical Co Ltd, Genentech BioOncology, ImClone Systems Incorporated, Jennerex Inc, MediGene Inc, Merck and Company Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Polaris Group, Proacta Inc, Roche Laboratories Inc, Sanofi-Aventis; Paid Research: Amgen Inc, Astellas Pharma US Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Sanofi-Aventis.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Genzyme Corporation, GlaxoSmithKline, ImClone Systems Incorporated, Lilly USA LLC, Millennium Pharmaceuticals Inc, Monogram BioSciences Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Roche Laboratories Inc, Sanofi-Aventis and Spectrum Pharmaceuticals Inc.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

www.ResearchToPractice.com
Your online resource for integrated oncology education

The new www.ResearchToPractice.com remains a comprehensive online resource offering numerous interactive capabilities but now offers extended search functionality and easier access to:
• Download audio and print programs
• Sign up for audio Podcasts
• Subscribe to RTP programs
• Search specific topics of interest by specialty and tumor type
• Register for upcoming live CME events
• Watch video proceedings

VISIT TODAY!

2
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.

Tracks 1-19

Track 1 Role of radiation therapy in the treatment of rectal cancer during an era of improved systemic therapy and surgical techniques

Track 2 Rationale for preoperative systemic therapy without radiation therapy in patients with locoregional rectal cancer

Track 3 Chemoradiation therapy in rectal cancer for sphincter preservation

Track 4 Neoadjuvant FOLFOX/bevacizumab without radiation therapy for locally advanced rectal cancer

Track 5 Pathologic complete response in primary versus metastatic colorectal cancer (CRC)

Track 6 Utility of the Oncotype DX® colon cancer assay

Track 7 Prediction of absolute benefit from chemotherapy with the Oncotype DX colon cancer assay

Track 8 Perspective on the use of molecular profiling to individualize systemic therapy for patients with colon cancer

Track 9 Outcome of primary tumor in patients with synchronous metastatic CRC (mCRC) receiving combination chemotherapy without surgery as initial treatment

Track 10 Tumor response to neoadjuvant FOLFOX/bevacizumab for locally advanced rectal cancer

Track 11 Bevacizumab and perioperative wound-healing complications

Track 12 Use of FOLFOX with or without bevacizumab without radiation therapy for locally advanced rectal cancer

Track 13 Evidence base for the activity of EGFR antibody therapy in combination with chemotherapy for mCRC

Track 14 K-ras mutation status and response to EGFR monoclonal antibodies in mCRC

Track 15 Perspective on the efficacy and safety of the EGFR antibodies cetuximab and panitumumab

Track 16 Low incidence of hypersensitivity allergic reactions with panitumumab

Track 17 Incorporation of EGFR antibody therapy into the treatment algorithm for mCRC

Track 18 Novel investigational anti-angiogenic therapies in CRC — Cediranib and VEGF Trap

Track 19 Pending data on PLX4032 in patients with V600E B-raf-mutant mCRC

Select Excerpts from the Interview

Tracks 1-2, 4, 11

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

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Clinical regression</th>
<th>R0 resection</th>
<th>Pathologic complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>100%</td>
<td>100%</td>
<td>26%</td>
</tr>
</tbody>
</table>

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

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 Oncotype 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 Oncotype 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 Oncotype 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/Oncotype DX Results: Recurrence Risk in Prespecified Recurrence Risk Groups (n = 711)

<table>
<thead>
<tr>
<th>Recurrence Risk Group</th>
<th>Range of RS</th>
<th>Proportion of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;30</td>
<td>43.7%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30-40</td>
<td>30.7%</td>
</tr>
<tr>
<td>High</td>
<td>≥41</td>
<td>25.6%</td>
</tr>
</tbody>
</table>

“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.

SELECT PUBLICATIONS
Cunningham D et al. Cetuximab monotherapy and cetuximab plus irinotecan in irino-
Hurwitz HJ 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
case-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
Van Cutsem E et al. Cetuximab and chemotherapy as initial treatment for metastatic
Willett CG et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radia-
tion therapy, and fluorouracil in rectal cancer: A multidisciplinary phase II study. J Clin
Tracks 1-14

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

Track 4  Clinical use of nab paclitaxel in combination with gemcitabine for advanced PC

Track 5  Use of a fixed-dose versus standard-infusion rate with gemcitabine in advanced PC

Track 6  Therapeutic implications of BRCA1/2 mutations in PC

Track 7  Erlotinib in combination with gemcitabine versus gemcitabine alone in patients with advanced PC

Track 8  Identification of biologic differences in tumors resulting in death from locally advanced versus metastatic PC

Track 9  Tumor cells with mesenchymal features in PC may predict response to chemotherapy

Track 10  Human equilibrative nucleoside transporter 1 (hENT1) levels predict response to gemcitabine in PC

Track 11  Second-line therapy with oxaliplatin/folinic acid/fluorouracil (OFF) for advanced PC

Track 12  Adjuvant chemotherapy with or without radiation therapy in PC

Track 13  Potential role of cancer stem cells in drug resistance and metastasis in PC

Track 14  Phase I study, with expanded cohort, of biweekly fixed-dose rate gemcitabine combined with capecitabine in advanced pancreatic and biliary cancer

Select Excerpts from the Interview

Tracks 1-2

**DR LOVE:** Would you discuss your concept of the unique biology of pancreatic cancer?
DR TEMPEIRO: 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 desmoplasic parts of PDAC.

In addition, interactions of ECM proteins and desmoplasic 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.”


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

DR TEMPEIRO: 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)

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

* 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)


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

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


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.”


SELECT PUBLICATIONS


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.


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
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**

<table>
<thead>
<tr>
<th></th>
<th>FC* (n = 290)</th>
<th>FC* + T (n = 294)</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>11.1 mo</td>
<td>13.8 mo</td>
<td>0.74</td>
<td>0.0046</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>5.5 mo</td>
<td>6.7 mo</td>
<td>0.71</td>
<td>0.0002</td>
</tr>
<tr>
<td>Overall response rate (CR + PR)</td>
<td>34.5%</td>
<td>47.3%</td>
<td>—</td>
<td>0.0017</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>2.4%</td>
<td>5.4%</td>
<td>—</td>
<td>0.0599</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>32.1%</td>
<td>41.8%</td>
<td>—</td>
<td>0.0145</td>
</tr>
</tbody>
</table>

* 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**

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

“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%).”

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 capectabine 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


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.

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

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

“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

<table>
<thead>
<tr>
<th></th>
<th>S + D (n = 47)</th>
<th>P + D (n = 49)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to disease progression</td>
<td>8.6 months</td>
<td>4.8 months</td>
<td>0.60</td>
<td>0.076</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>13.8 months</td>
<td>6.5 months</td>
<td>0.51</td>
<td>0.0129</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>6.9 months</td>
<td>2.8 months</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NR = not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


4.3 Efficacy of Bevacizumab/Erlotinib for Patients with Advanced Hepatocellular Carcinoma

- 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%

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


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 OncoType 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?

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

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:

<table>
<thead>
<tr>
<th>LO</th>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = LO not met</th>
<th>N/A = Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>As a result of this activity, I will be able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 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).</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Formulate a therapeutic approach to locally advanced rectal cancer.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Communicate the benefits and risks of existing and emerging anti-VEGF and anti-EGFR biologic therapy to patients with metastatic CRC.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Appraise data on novel combination regimens for advanced pancreatic cancer.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Utilize clinical and molecular biomarkers to select optimal systemic treatment strategies for patients with gastric or gastroesophageal cancer.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Communicate the benefits and risks of existing and emerging systemic interventions to patients with advanced hepatocellular or biliary tract cancer.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Counsel appropriately selected patients with GI cancer about participation in ongoing clinical trials.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leonard B Saltz, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Margaret A Tempero, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Peter C Enzinger, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Ghassan Abou-Alfa, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Editor</td>
<td>Knowledge of subject matter</td>
<td>Effectiveness as an educator</td>
</tr>
<tr>
<td>Neil Love, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

Please recommend additional faculty for future activities:

Other comments about the faculty and editor for this activity:

REQUEST FOR CREDIT — Please print clearly

Name: ............................................................... Specialty: ..............................
Professional Designation:
☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other ...........................
Street Address: .......................................................... Box/Suite: ............................
City, State, Zip: ..........................................................
Telephone: ............................................................. Fax: ...........................................
Email: .................................................................

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: .................................

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at CME.ResearchToPractice.com.