

Year ⁱⁿ Review

A CME monograph and speaker's slide kit summarizing the year's most important meeting presentations and journal articles

Gastrointestinal Cancers: 2009-2010

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U P D A T E



Year in Review — Gastrointestinal Cancers: 2009-2010 Continuing Medical Education (CME) Information

OVERVIEW OF ACTIVITY

Given the prevalent nature of the disease, extensive resources are allocated to colorectal cancer (CRC) research and education. Interestingly, however, although individually less frequently encountered, the collection of other, “non-CRC” gastrointestinal (GI) neoplasms accounts for more per annum cancer-related deaths than those attributed to tumors of the colon and rectum combined. Educational opportunities relevant to the clinical management of both CRC and non-CRC GI tumors are essential to general oncologist delivery of comprehensive cancer care. The introduction of novel biomarkers, genomic signatures and molecular-targeted systemic agents has led to a rapid paradigm shift in the clinical algorithms for these diseases that presents a challenge to practicing oncologists who must grapple with the presentation of ambiguous data sets and their immediate impact on treatment decisions. To bridge the gap between research and patient care, this CME activity uses the input of cancer experts and community physicians to frame a relevant discussion of recent research advances in GI cancers that can be applied to routine clinical practice. This information will help medical oncologists and hematology-oncology fellows formulate up-to-date clinical management strategies for patients.

LEARNING OBJECTIVES

- Apply the results of emerging clinical research to the best-practice management of select GI cancers originating within (CRC) and outside of (non-CRC) the colon and rectum.
- Employ biomarkers and novel genomic signatures in counseling patients with Stage II colon cancer about the long-term risk of disease recurrence.
- Communicate the benefits and risks of anti-VEGF and anti-EGFR biologic therapy to patients with metastatic CRC.
- Evaluate the role of potential radiosensitizers in the multimodality management of locally advanced rectal cancer.
- Use clinical and molecular biomarkers to select optimal local and systemic treatment strategies for patients with gastric or gastroesophageal cancer.
- Effectively integrate the evidence-based use of chemotherapy and molecular-targeted agents into the individualized management of advanced pancreatic cancer.
- Communicate the benefits and risks of existing and emerging systemic and targeted treatments for patients with advanced hepatocellular or biliary tract cancer.

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COMMERCIAL SUPPORT

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PHARMACEUTICAL AGENTS DISCUSSED IN THIS PROGRAM

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EDITOR'S NOTE

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PAPERS OF THE YEAR IN GI ONCOLOGY

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Gastrointestinal Cancers Speaker's Slide Kit Included

See the enclosed CD for PowerPoint slides of the graphics included in this monograph summarizing the year's most important meeting presentations and journal articles.



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Year in Review
Year in Review - Gastrointestinal Cancers Edition 2010

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Presentations discussed in this module:
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
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 4536.

Slides from the presentations and excerpts from a related interview with Charles D Blanke, MD (June 11, 2009)

Secondary Endpoint: Progression-Free Survival (PFS)

Time (months)	FC + T	FC	HR	95% CI
0	1.0	1.0	0.7	0.58-0.88
2	0.8	0.7	0.7	0.58-0.88
4	0.6	0.5	0.7	0.58-0.88
6	0.5	0.4	0.7	0.58-0.88
8	0.4	0.3	0.7	0.58-0.88
10	0.3	0.2	0.7	0.58-0.88
12	0.2	0.1	0.7	0.58-0.88
14	0.1	0.0	0.7	0.58-0.88
16	0.1	0.0	0.7	0.58-0.88
18	0.1	0.0	0.7	0.58-0.88
20	0.1	0.0	0.7	0.58-0.88
22	0.1	0.0	0.7	0.58-0.88
24	0.1	0.0	0.7	0.58-0.88
26	0.1	0.0	0.7	0.58-0.88
28	0.1	0.0	0.7	0.58-0.88
30	0.1	0.0	0.7	0.58-0.88
32	0.1	0.0	0.7	0.58-0.88
34	0.1	0.0	0.7	0.58-0.88

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

VISIT TODAY!

The online version of *Year in Review* — Gastrointestinal Cancers 2009-2010 includes:

- Interactive slide modules with faculty commentary reviewing the 21 “Priority 1” papers and presentations featured in the monograph
- An annotated bibliography listing all “Priority 2” papers and presentations
- References with active web links for all papers and presentations taking users to actual abstracts and full-text publications
- Downloadable PowerPoint slides for each of the Priority 1 publications
- A convenient, downloadable PDF-based version of the monograph



NEIL LOVE, MD

Papers of the year in GI oncology

This issue of our ongoing initiative to “separate the wheat from the chaff” and provide oncologists easy access to the most clinically relevant journal articles and meeting presentations focuses on a set of diseases for which progress has been distressingly gradual.

However, during this past year a number of important clinical research issues in gastrointestinal cancers were addressed and are reviewed herein with slides, graphics and clinical investigator commentary. Even in this collection of the “best of the best” a few data sets stand out.

Here are my personal picks for the most noteworthy papers/presentations of the year:

Most anticipated findings

NSABP-C-08: Bevacizumab in adjuvant therapy for colon cancer¹ — The results of this landmark study (the first ever completed evaluating bevacizumab in the adjuvant setting) were generally considered “negative” and disappointing but with an important asterisk — namely, Norm Wolmark’s question of whether longer duration is needed.

The pending report from the other major Phase III adjuvant trial, AVANT, may settle the issue once and for all, or it could just raise more questions.

Findings with the most important clinical research implications

TOGA: Trastuzumab for HER2-positive gastric cancer² — Eric Van Cutsem’s ASCO stunner last year provided strong evidence that investigators such as Dennis Slamon have been correct in stating that systemic cancer treatment needs to focus much more on targeting specific oncogenic pathways rather than individual tumor types.

Most disappointing findings

Oxaliplatin in rectal cancer³ — Two separate studies reported no benefit when this agent was combined with a fluoropyrimidine and neoadjuvant radiation therapy. The previously common use of this strategy outside a protocol setting came to an instant stop.

Most important findings from the perspective of quality of life

Memorial’s study of patients with metastatic colorectal cancer and an intact primary tumor who received up-front systemic therapy⁴ — Len Saltz and his surgical colleagues have taken a critical leadership role in addressing a number of similar issues, and this data set provided convincing evidence that when the primary tumor is not causing symptoms in patients with metastases, it’s generally better to initiate systemic therapy.

Findings most likely to move adjuvant therapy for colon cancer forward to where breast cancer was in 2002

“Oncotype DX®” for colon cancer⁵ — Once the full data set is formally published with specific rates of recurrence, there will be a lot of discussion and controversy about whether this assay is ready for “prime time.”

Most important findings in an “orphan disease”

ABC-2 trial of cisplatin/gemcitabine in biliary tract cancer⁶ — Not only was a new standard of care defined, but also and perhaps more importantly, these dedicated investigators proved that such a trial could be done.

Although these important studies will not substantially reduce the mortality of GI cancers, they do address critical issues in patient management, particularly the use of local and systemic treatments with substantial risks and costs.

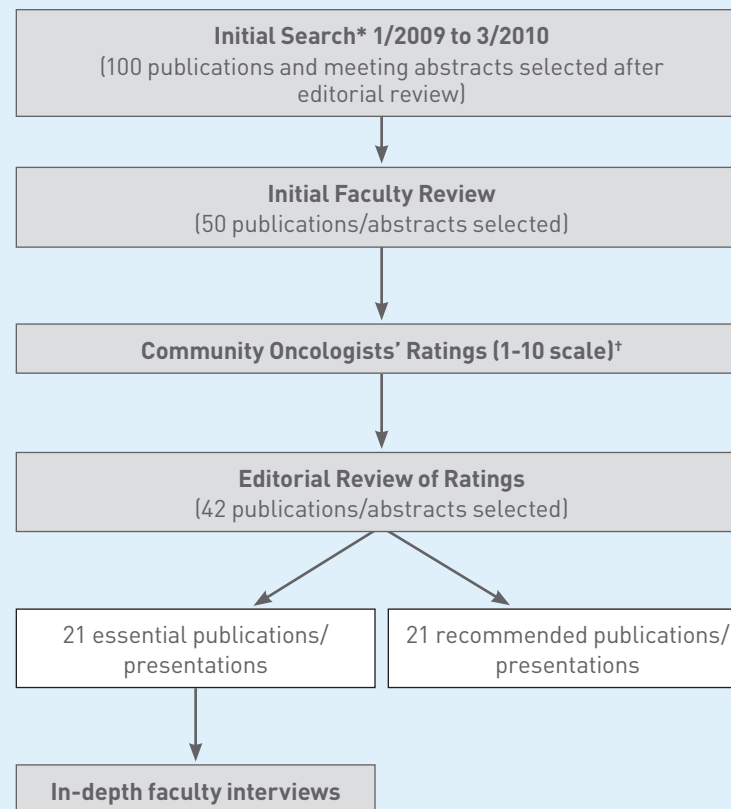
The considerable information in just this corner of oncology illustrates the challenge oncologists face in keeping up-to-date while caring for patients with dozens of cancers. In that regard, we hope this modest education program is helpful.

— Neil Love, MD
 DrNeilLove@ResearchToPractice.com
 June 18, 2010

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- ¹ Wolmark N et al. *Proc ASCO 2009;Abstract LBA4.*
- ² Van Cutsem E et al. *Proc ASCO 2009;Abstract LBA4509.*
- ³ Aschele C et al. *Proc ASCO 2009;Abstract CRA4008.*
- ⁴ Poultsides GA et al. *J Clin Oncol 2009;27(20):3379-84.*
- ⁵ Kerr D et al. *Proc ASCO 2009;Abstract 4000.*
- ⁶ Valle JW et al. *Proc ASCO 2009;Abstract 4503.*

Process for Identifying Key Recent Reports on the Management of Gastrointestinal Cancers



* PubMed. January 1, 2009 to March 11, 2010, English language, clinical trials, randomized clinical trials, practice guidelines, meta-analysis, key core clinical journals. Search of meeting abstracts from 2009 ASCO and 2010 Gastrointestinal Cancers Symposium annual meetings.
[†] Importance for medical oncologists in community-based practice, 1 = least important, 10 = very important

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COLORECTAL CANCERS

- 6 Wolmark N et al. **A phase III trial assessing bevacizumab in stage II and III carcinoma of the colon: Results of NSABP Protocol C-08.** *Proc ASCO 2009;Abstract LBA4.*
- 8 Aschele C et al. **Preoperative fluorouracil (FU)-based chemoradiation with and without weekly oxaliplatin in locally advanced rectal cancer: Pathologic response analysis of the Studio Terapia Adjuvante Retto (STAR)-01 randomized Phase III trial.** *Proc ASCO 2009;Abstract CRA4008.*
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- 14 Chibaudel B et al. **Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study.** *J Clin Oncol 2009;27(34):5727-33.*
- 16 Van Cutsem E et al. **Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer.** *N Engl J Med 2009;360(14):1408-17.*
- 18 Poultides GA et al. **Outcome of primary tumor in patients with synchronous Stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment.** *J Clin Oncol 2009;27(20):3379-84.*
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- 24 Roth AD et al. **Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: Results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial.** *J Clin Oncol 2010;28(3):466-74.*

GASTRIC/ESOPHAGOGASTRIC CANCERS

- 26 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.*

- 28 Okines AF et al. **Meta-analysis of the REAL-2 and ML17032 trials: Evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer.** *Ann Oncol 2009;20(9):1529-34.*
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PANCREATIC CANCER

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- 34 Neoptolemos J et al. **ESPAC-3(v2): A multicenter, international, open-label, randomized, controlled phase III trial of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) versus gemcitabine (GEM) in patients with resected pancreatic ductal adenocarcinoma.** *Proc ASCO 2009;Abstract LBA4505.*
- 36 Van der Gaag NA et al. **Preoperative biliary drainage for cancer of the head of the pancreas.** *N Engl J Med 2010;362(2):129-37.*
- 38 Cunningham D et al. **Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer.** *J Clin Oncol 2009;27(33):5513-8.*
- 40 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.*
- 42 Riess H et al. **A prospective, randomized trial of chemotherapy with or without the low molecular weight heparin (LMWH) enoxaparin in patients (pts) with advanced pancreatic cancer (APC): Results of the CONKO 004 trial.** *Proc ASCO 2009;Abstract LBA4506.*

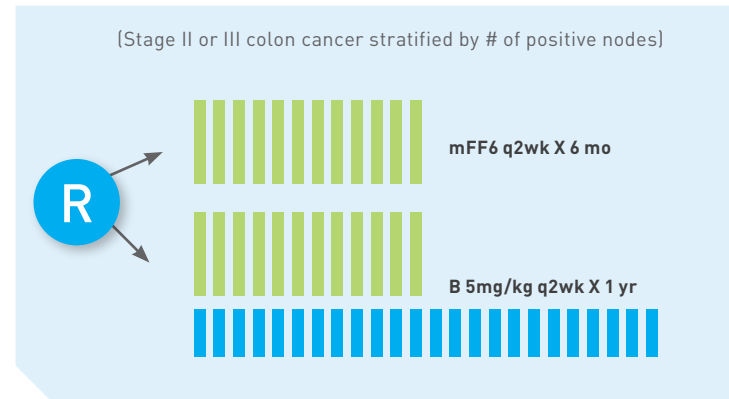
HEPATOBIILIARY TRACT NEOPLASMS

- 44 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 2009;Abstract 4503.*
- 46 Cheng AL et al. **Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial.** *Lancet Oncol 2009;10(1):25-34.*

A Phase III Trial Comparing mFOLFOX6 to mFOLFOX6 plus Bevacizumab in Stage II or III Carcinoma of the Colon: Results of NSABP Protocol C-08

Wolmark N et al.
Proc ASCO 2009;Abstract LBA4.

NSABP C-08 Trial Design



Wolmark N et al. Proc ASCO 2009;Abstract LBA4.

Introduction

- > Phase III trials have demonstrated that the addition of bevacizumab (B) to various chemotherapeutic agents (including oxaliplatin-based regimens) improves clinical outcomes for patients with advanced colorectal cancer (*NEJM* 2004;350:2335, *JCO* 2008;26:2013).
- > Phase III trials MOSAIC¹ and NSABP C-07² demonstrated that the addition of oxaliplatin to 5-fluorouracil and leucovorin-containing regimens resulted in an increase in disease-free survival for patients with Stage II and III colon cancer (¹ *NEJM* 2004;350:2343, ² *JCO* 2007;25:2198).
- > Current study objective:
 - Assess the safety and efficacy of adding B to mFOLFOX6 for the treatment of Stage II or III colon cancer.

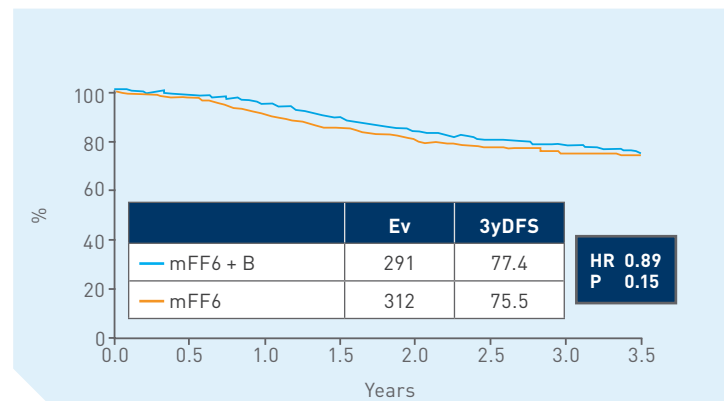
Wolmark N et al. Proc ASCO 2009;Abstract LBA4.

Methods

- > Trial accrual:
 - Patients identified from 292 NSABP centers between September 2004 and October 2006.
 - Total patients randomized: 2,710
 - Stage II disease: 25%
 - Stage III disease, 1-3 positive nodes: 45%
 - Stage III disease, ≥4 positive nodes: 30%
- > Median trial follow-up: 3 years
- > Median duration of bevacizumab: 11.5 months
- > Grade III+ toxicities significantly increased with bevacizumab included hypertension, pain, proteinuria and wound complications (*JCO* 2009;27:3385).

Wolmark N et al. Proc ASCO 2009;Abstract LBA4.

Results: 3-Year Disease-Free Survival (DFS)



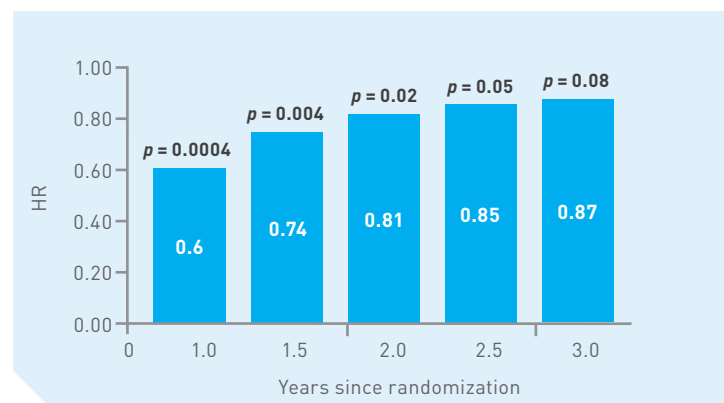
With permission from Wolmark N et al. *Proc ASCO* 2009;Abstract LBA4.

Summary and Conclusions

- > The addition of B to mFOLFOX6 did not result in a statistically significant prolongation in 3-year DFS, but there was a transient benefit in DFS during the one year that bevacizumab was utilized.
- > Grade III+ toxicities increased with the addition of B.
 - Hypertension (1.8% vs 12%)
 - Pain (6.3% vs 11.1%)
 - Proteinuria (0.8% vs 2.7%)
 - Wound complications (0.3% vs 1.7%)
- > Consideration should be given to clinical trials assessing a longer duration of bevacizumab administration.
- > AVANT trial is comparing FOLFOX4 to FOLFOX4 + B to XELOX + B in patients with Stage II and III colon cancer.

Wolmark N et al. *Proc ASCO* 2009;Abstract LBA4.

Hazard Ratio (HR) mFF6 + B versus mFF6



Wolmark N et al. *Proc ASCO* 2009;Abstract LBA4.

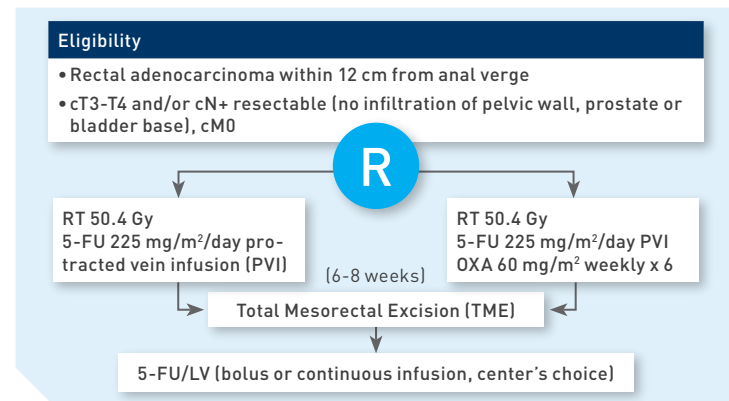
Faculty Comments

DR HOCHSTER: This was a key study and our best lead for making progress in the adjuvant treatment of colon cancer. It's disappointing that it was negative, but it wasn't completely negative. I agree with Dr Wolmark's perspective that there was a transient effect of bevacizumab, which is worth continuing to explore. We shouldn't "write off" bevacizumab in the adjuvant setting. The NSABP will likely go forward with another adjuvant study with a longer duration of bevacizumab if the AVANT trial yields similar results. Some models suggest that longer durations of bevacizumab may prevent more micrometastases from activating the angiogenic switch. If bevacizumab was a completely nontoxic, inexpensive drug that could be taken orally — like tamoxifen — people would be discussing five years of bevacizumab.

Preoperative Fluorouracil (FU)-Based Chemoradiation +/- Weekly Oxaliplatin in Locally Advanced Rectal Cancer. Pathologic Response Analysis of STAR-01

Aschele C et al.
Proc ASCO 2009; Abstract CRA4008.

STAR Phase III Study Design (N = 747)



Aschele C et al. Proc ASCO 2009; Abstract CRA4008.

Introduction

- > Locally advanced rectal cancer (LARC) is associated with a high risk of distant metastases (30-35%) and a positive circumferential resection margin (CRM) in 10-30% of “resectable” tumors.
- > Oxaliplatin (OXA) improves the efficacy of fluorouracil (FU)-based chemotherapy in the treatment of colon cancer, has radiosensitizing properties and shows promising activity when combined with preoperative radiation therapy (RT) and FU in Phase I/II studies.
- > Current study objective:
 - Evaluate the impact of adding OXA to preoperative FU-based pelvic chemoradiation in patients with LARC.

Aschele C et al. Proc ASCO 2009; Abstract CRA4008.

Adverse Events

Adverse event	5-FU/RT (n = 379)	5-FU/OXA/RT (n = 353)	p-value
Any Grade 3/4 event	8%	24%	<0.0001
Diarrhea (Grade 3/4)	4%	15%	<0.0001
Radiation dermatitis (Grade 3/4)	2%	5%	0.038
Sensory neuropathy			
Grade 2	0.5%	36%	
Grade 3	0%	1%	<0.0001
Treatment-related deaths	0.3%	0.6%	NR

Aschele C et al. Proc ASCO 2009; Abstract CRA4008.

Pathologic Outcomes*

Pathologic complete response	5-FU/RT (n = 379)	5-FU/OXA/RT (n = 368)
pT0N0* [95% CI]	16% (13-20%)	16% (13-20%)
Pathology (T)		
pT0	17%	18%
pT1-2	35%	35%
pT3-4	44%	42%
Median diameter	26 mm	24 mm
CRM-positive*	6%	4%

* No statistically significant differences between treatment arms

Aschele C et al. *Proc ASCO 2009*;Abstract CRA4008.

Summary and Conclusions

- > These data do not support the addition of OXA to preoperative 5-FU/RT to maximize tumor shrinkage in LARC.
 - No improvement in local tumor response was observed.
 - Toxicity was significantly increased.
 - OXA-based regimens may not be the optimal backbone for incorporation of new radiosensitizing agents.
- > The number of occult distant metastases at surgery lends support to the study's primary hypothesis that the addition of OXA will result in improvements in overall survival (confirmation with more mature data is required).
- > Follow-up is ongoing to assess the impact on efficacy endpoints.

Aschele C et al. *Proc ASCO 2009*;Abstract CRA4008.

Metastases at Surgery: Unplanned/Exploratory Analysis

	5-FU/RT (n = 379)	5-FU/OXA/RT (n = 368)	p-value
pM1	11 (3%)	2 (0.5%)	0.014
Liver	6	1	—
Peritoneal	4	1	—
Nodes	1	0	—

Aschele C et al. *Proc ASCO 2009*;Abstract CRA4008.

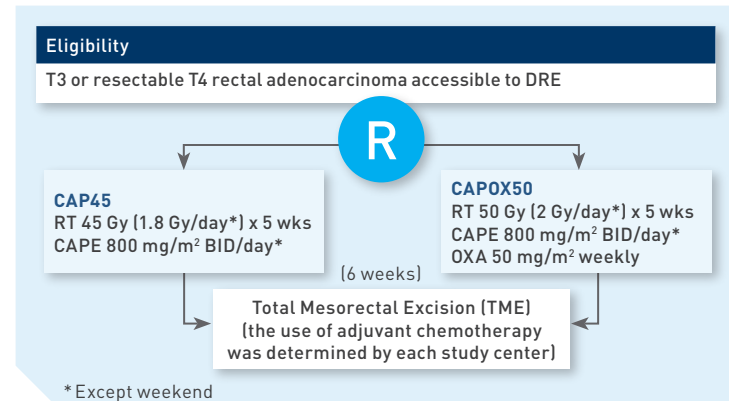
Faculty Comments

DR HOCHSTER: Unlike some of the rectal cancer clinical trials that have been done in Europe, STAR-01 at least used a conventional radiation therapy schedule and infusional 5-FU chemotherapy. The addition of weekly oxaliplatin added more toxicity, mainly neuropathy and diarrhea, but unfortunately did not have a major impact on the pathologic outcome. So these data suggest that oxaliplatin may not act as a radiosensitizer. However, the study does not inform us about the long-term benefit of oxaliplatin. Normally, we would use preoperative and postoperative therapy and look for a long-term survival benefit.

Comparison of Two Neoadjuvant Chemoradiotherapy Regimens for Locally Advanced Rectal Cancer: ACCORD 12/0405-Prodige 2

Gerard JP et al.
J Clin Oncol 2010;28(10):1638-44.

Phase III Trial of Advanced Rectal Cancer: ACCORD 12/0405-Prodige 2



Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Introduction

- > The German Rectal Cancer Study Group CAO/ARO Phase III trial established preoperative chemoradiation therapy (CRT) as the standard of care for T3/4 rectal cancer (*NEJM* 2004;351:1731).
 - Cumulative incidence of local relapse: 6% for preoperative CRT vs 13% for postoperative CRT
 - Reduced toxicity was observed.
 - No difference in overall survival was seen.
- > **Current study objective:**
 - Evaluate the impact of radiation therapy (RT) dose increase from standard 45 Gy/5 weeks to 50 Gy/5 weeks and chemotherapy intensification with the addition of oxaliplatin to capecitabine (CAPOX50) on pathologic complete response in patients with T3/4 rectal cancer.

Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Dworak-Quirke Criteria for Grading of Operative Tumor Specimen

- > Primary endpoint: Pathologic complete response (ypCR)
- > Dworak-Quirke tumor grading criteria (*Int J Colorectal Dis* 1997;12:19, *J Clin Oncol* 2005;23:8688)
 - 0 = No or very little response
 - 1 = Partial response
 - 2 = Major response with few residual cancer cells
 - 3 = Complete response with no detectable cancer cells (ypCR)

Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Pathologic Response and Circumferential Rectal Margin (CRM)

Endpoint	CAP45 (n = 282)	CAPOX50 (n = 283)	p-value
ypCR	14%	19%	0.09
ypCR or very few residual tumor cells	30%	39%	0.008
CRM	CAP45 (n = 149)	CAPOX50 (n = 143)	p-value
R1 (≤1 mm)	13%	8%	0.17
R+ (≤2 mm)	19%	10%	0.022

Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Summary and Conclusions

- > Escalation of RT dose and the addition of OXA to CAPOX50 did not significantly increase pCR or the rate of negative CRM compared to CAP45.
 - ypCR = 19% vs 14% ($p = 0.11$)
 - CRM-negative = 92% vs 87% ($p = 0.17$)
 - ypCR may not be a suitable surrogate endpoint for neoadjuvant chemoradiation trials in rectal cancer.
- > The improved efficacy outcomes (19% ypCR) may be mainly attributable to radiotherapy dose intensification.
- > Grade 3/4 toxicity was increased with CAPOX50.
- > High-dose radiotherapy (ie, 50 Gy/25 fraction) plus CAPOX merits investigation for T3-4 rectal cancers.

Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Adverse Events

Adverse event	CAP45 (n = 293)	CAPOX50 (n = 291)	p-value
All Grade 3/4 toxicity	11%	25%	<0.001
Diarrhea (Grade 3/4)	3%	13%	<0.001
Hematologic (Grade 3/4)	4%	5%	NS
Fatigue (Grade 3)	1%	5%	0.004
Hand-foot syndrome (Grade 2)	<1%	0%	NS
Peripheral neuropathy (Grade 2)	0.4%	5%	0.002

Gerard JP et al. *J Clin Oncol* 2010;28(10):1638-44.

Faculty Comments

DR HOCHSTER: This is a prospective, randomized trial of neoadjuvant capecitabine with or without oxaliplatin in combination with radiation therapy for rectal cancer. The addition of oxaliplatin may have improved the pathologic response to a certain extent, with increased toxicity, but it was not a positive study and the use of oxaliplatin in this setting should not become a standard practice until additional data are available, particularly concerning longer-term outcome. Similar to STAR-01, this study informs us about the effect of oxaliplatin on the operative specimen, but it doesn't tell us about what happens in the long run. Oxaliplatin could still improve overall survival by reducing the rate of distant metastases.

Phase III Trial of Capecitabine + Oxaliplatin (XELOX) versus Bolus 5-FU/Leucovorin (LV) in Stage III Colon Cancer: Impact of Age on Disease-Free Survival

Haller DG et al.
Gastrointestinal Cancers Symposium 2010;Abstract 284.

NO16968: A Phase III Trial of XELOX versus Bolus 5-FU/LV in Stage III Colon Cancer

Accrual: 1,886 (Closed)

Eligibility

Chemotherapy and radiotherapy-naïve
Stage III colon carcinoma
≥1 positive node
Randomized ≤8 weeks after surgery



XELOX (6 months):
Capecitabine (1,000 mg/m² bid d1-14) + Oxaliplatin (130 mg/m² d1) q3wk x 8 cycles (n = 944)

Bolus 5-FU/LV (6 months)
Mayo Clinic (n = 664) or Roswell Park (n = 278)

Primary endpoint: DFS
Secondary endpoints: RFS, OS, tolerability

Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

Introduction

- > Capecitabine is noninferior to bolus 5-FU/LV in disease-free survival (DFS) and overall survival (OS) as adjuvant therapy in Stage III colon cancer (*NEJM* 2005;352:2696).
 - Patients ≥70 years showed improved outcome with capecitabine.
- > ACCENT database concluded that newer adjuvant regimens (including oxaliplatin combinations) were not associated with significant efficacy benefits versus 5-FU/LV in patients ≥70 years, when compared with younger patients (ASCO 2009;Abstract 4010).
- > Current study objective:
 - Examine DFS across age groups in NO16968, a Phase III trial comparing XELOX versus bolus 5-FU/LV in Stage III colon cancer.

Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

NO16968 Subgroup Analysis of 3-Year DFS by Age

<65 versus ≥65 years	XELOX	5-FU/LV	HR (95% CI)
<65 years (n = 1,142)	72%	69%	0.80 [0.65,0.98]
≥65 years (n = 744)	68%	62%	0.81 [0.64,1.03]
<70 versus ≥70 years	XELOX	5-FU/LV	HR (95% CI)
<70 years (n = 1,477)	72%	69%	0.79 [0.66,0.94]
≥70 years (n = 409)	66%	60%	0.87 [0.63,1.18]

HR = hazard ratio

Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

NO16968 Subgroup Analysis of 5-Year OS by Age

<65 versus ≥65 years	XELOX	5-FU/LV	HR (95% CI)
<65 years (n = 1,142)	80%	77%	0.87 (0.67,1.13)
≥65 years (n = 744)	73%	70%	0.90 (0.68,1.19)
<70 versus ≥70 years	XELOX	5-FU/LV	HR (95% CI)
<70 years (n = 1,477)	80%	76%	0.86 (0.69,1.08)
≥70 years (n = 409)	69%	67%	0.94 (0.66,1.34)

Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

Summary and Conclusions

- > XELOX significantly improved DFS compared with bolus 5-FU/LV as adjuvant therapy for Stage III colon cancer.
- > XELOX efficacy was observed in patients ≥65 and ≥70 years.
- > Efficacy in the elderly subgroup eligible for trial was achieved despite decreased treatment duration and dose intensity.
- > These findings differ from those of the MOSAIC study and the ACCENT analysis.
 - Reasons for this apparent difference are unknown.
- > Current analysis supports consideration of XELOX for patients with Stage III colon cancer; age alone should not drive clinical decision-making.

Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

Select Grade III/IV Toxicities

Grade 3/4 adverse events	<70 years		≥70 years	
	XELOX (n = 748)	5-FU/LV (n = 711)	XELOX (n = 190)	5-FU/LV (n = 215)
Diarrhea	18%	19%	26%	25%
Nausea/Vomiting	8%	6%	11%	5%
Stomatitis	<1%	9%	1%	8%
Neutropenia (includes granulocytopenia)	9%	16%	10%	17%
Hand-foot syndrome	6%	<1%	4%	<1%
Neurosensory	11%	<1%	11%	0%

Haller DG et al. Gastrointestinal Cancers Symposium 2010;Abstract 284.

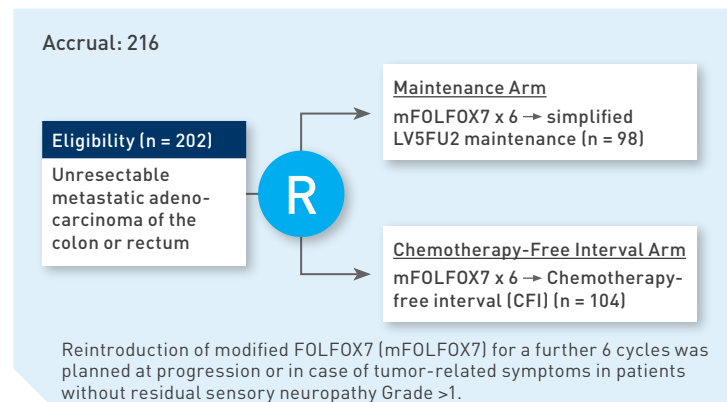
Faculty Comments

DR BENSON: This study builds upon the adjuvant data supporting oxaliplatin-containing combination regimens for patients with Stage III colon cancer. The original report demonstrated that capecitabine in combination with oxaliplatin was superior to bolus 5-FU. This presentation specifically attempted to determine whether age had an impact on disease-free survival. They concluded that CAPOX showed a similar advantage over 5-FU in patients younger than 70 and older than 70 years old. These data reinforce that age is not a determining factor in the selection of adjuvant therapy. Rather, other factors, such as patient comorbidities, are more important. The trial will require more mature follow-up until overall survival can be evaluated, but disease-free survival is an appropriate endpoint, so there can be some degree of comfort with these results.

Can Chemotherapy Be Discontinued in Unresectable Metastatic Colorectal Cancer? The GERCOR OPTIMOX2 Study

Chibaudel B et al.
J Clin Oncol 2009;27(34):5727-33.

GERCOR OPTIMOX2 Phase III Trial Design



Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

Introduction

- > The OPTIMOX1 study demonstrated that using a stop-and-go strategy with oxaliplatin reduced toxicity without compromising efficacy in patients with advanced colorectal cancer (*JCO* 2006;24:394).
 - Oxaliplatin was stopped after six cycles of FOLFOX7 and maintenance therapy was continued with a simplified LV plus bolus and infusional FU (LV5FU2) regimen.
 - Efficacy of the stop-and-go strategy was comparable to that of continuing FOLFOX4 until progression or toxicity.
- > Current study objective:
 - Compare the stop-and-go strategy evaluated in OPTIMOX1 and a novel strategy, OPTIMOX2, which involves the complete, but temporary, discontinuation of all chemotherapy.

Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

Efficacy Results (median follow-up 40.7 months)

	Maintenance (n = 98)	CFI (n = 104)	p-value
Median duration of disease control (DDC)	13.1 mo	9.2 mo	0.046
Median progression-free survival (PFS)	8.6 mo	6.6 mo	0.0017
Median overall survival (OS)	23.8 mo	19.5 mo	0.42
Median duration of maintenance therapy/CFI	4.8 mo	3.9 mo	—
Overall response rate Induction with mFOLFOX7 (n = 98, 104)	59.2%	59.6%	—

Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

FOLFOX Reintroduction

	Maintenance (n = 54)	CFI (n = 66)	p-value
Reintroduction rate in eligible patients	81.8%	84.6%	NR
Median PFS of the first FOLFOX reintroduction	4.8 mo	3.9 mo	0.08
Overall response rates after first FOLFOX reintroduction ^a	20.4%	30.3%	NR
Control of tumor (partial response plus stable disease)	59.3%	57.6%	NR

^aNinety percent of patients who had a partial response at reintroduction previously had a partial response at initial chemotherapy.

Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

Summary and Conclusions

- > Complete discontinuation of chemotherapy (OPTIMO2) had a negative impact on DDC and PFS, but not OS, compared with the maintenance therapy strategy (OPTIMO1).
 - DDC: 9.2 mos vs 13.1 mos ($p = 0.046$)
 - PFS: 6.6 mos vs 8.6 mos ($p = 0.0017$)
 - OS: 19.5 mos vs 23.8 mos ($p = 0.42$)
- > Chemotherapy discontinuation cannot be prescheduled before therapy is initiated in patients with advanced colorectal cancer, since individual responses cannot be predicted.
- > The ongoing DREAM GERCOR OPTIMO3 study (NCT00265824) is evaluating maintenance therapy with targeted drugs alone after chemotherapy with bevacizumab.

Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

Select Grade 3/4 Toxicities

Toxicity*	Maintenance Arm			CFI Arm	
	Cycles 1-6	Maint.	Reintroduction	Cycles 1-6	Reintroduction
Neutropenia	21.4%	9.8%	10.0%	11.7%	14.0%
Thrombocytopenia	8.2%	1.6%	6.7%	3.9%	2.0%
Neuropathy G3 ^a	2.9%	4.9%	6.7%	4.9%	7.8%
Hand-foot syndrome	0%	4.9%	0%	0%	0%

*Toxicity per patient, using NCI-CTC criteria (v2.0)

^aDefined by Lévi scale
Maint. = maintenance

Chibaudel B et al. *J Clin Oncol* 2009;27(34):5727-33.

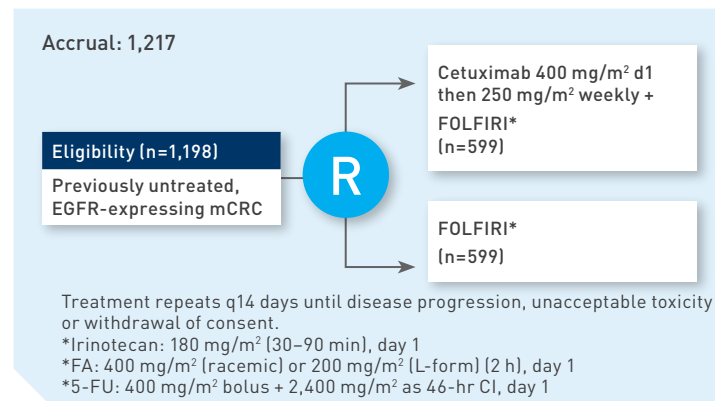
Faculty Comments

DR BENSON: This is an important French study. We recognize that continuation of chemotherapy for patients with advanced disease has a price in terms of toxicity, particularly neurotoxicity with FOLFOX. The study demonstrated that patients who continued chemotherapy had significant improvement in disease control compared to those who had a chemotherapy-free interval. In addition, progression-free survival was significantly better for those individuals who continued therapy without a drug holiday. The authors concluded that a planned, complete discontinuation of chemotherapy is not an optimal strategy for many patients. So we cannot routinely recommend a chemotherapy-free interval as a standard of care for patients with metastatic disease who are responding to therapy because it does appear to negatively affect outcome.

Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer

Van Cutsem E et al.
N Engl J Med 2009;360(14):1408-17.

Study Design



Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Introduction

- > Cetuximab is effective in combination with irinotecan or alone in irinotecan-refractory metastatic colorectal cancer (mCRC) (*NEJM* 2004;351:337, *JCO* 2006;24:4914).
- > Cetuximab is active when added to irinotecan-based (*Ann Oncol* 2006;17:450, *JCO* 2004;22:Suppl:248s) or oxaliplatin-based (*JCO* 2007;25:5225, *Eur J Cancer Suppl* 2007;5:236, *Ann Oncol* 2008;19:1442) therapy as first-line treatment.
- > No biomarkers reliably predict response to cetuximab but K-ras mutation status shows promise.
- > Current study objectives:
 - Evaluate the safety and efficacy of first-line FOLFIRI with or without cetuximab.
 - Investigate the influence of K-ras mutation status on outcome.

Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Primary and Secondary Efficacy Analyses

	Cetuximab + FOLFIRI (N = 599)	FOLFIRI (N = 599)	Hazard or Odds Ratio	p-value
Progression-Free Survival (PFS)				
Progression event	49.7%	53.8%	0.85	0.048
Median PFS	8.9 mo	8.0 mo		
Overall Survival (OS)				
Deaths	68.8%	69.4%	0.93	0.31
Median OS	19.9 mo	18.6 mo		

Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Efficacy Analysis According to K-ras Status

	Cetuximab + FOLFIRI	FOLFIRI	Hazard or Odds Ratio
Progression-Free Survival			
K-ras mutant (n = 105, 87)	7.6 mo	8.1 mo	1.07
K-ras wild-type (n = 172, 176)	9.9 mo	8.7 mo	0.68
Overall Survival			
K-ras mutant (n = 105, 87)	17.5 mo	17.7 mo	1.03
K-ras wild-type (n = 172, 176)	24.9 mo	21.0 mo	0.84

Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Summary and Conclusions

- > The addition of cetuximab to first-line FOLFIRI reduced the risk of progression of mCRC.
 - Progression event: 49.7% vs 53.8%
 - Median PFS: 8.9 vs 8.0 months
- > The benefit of cetuximab was limited to patients with K-ras wild-type tumors.
 - PFS: 9.9 vs 8.7 months, HR = 0.68
 - OS: 24.9 vs 21.0 months, HR = 0.84
- > The overall incidence of Grade 3 or 4 adverse events was significantly higher with cetuximab plus FOLFIRI than with FOLFIRI alone (79.3% vs 61.0%), including increased diarrhea (15.7% vs 10.5%) and skin reactions (19.7% vs 0.2%).

Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Most Common Grade 3/4 Adverse Events and Special Adverse Events in the Safety Population

	Cetuximab + FOLFIRI (N = 600)	FOLFIRI (N = 602)	p-value
Neutropenia	28.2%	24.6%	0.16
Leukopenia	7.2%	5.1%	0.15
Diarrhea	15.7%	10.5%	0.008
Rash	8.2%	0%	<0.001
Dermatitis acneiform	5.3%	0%	<0.001
Special Adverse Events			
Skin reactions, all	19.7%	0.2%	<0.001
Acne-like rash	16.2%	0%	<0.001

Van Cutsem E et al. *N Engl J Med* 2009;360(14):1408-17.

Faculty Comments

DR BENSON: This is an important study because it builds upon past cetuximab data showing benefits for patients who receive cetuximab with or without chemotherapy in the second- and third-line settings. This trial evaluated FOLFIRI with or without cetuximab in the first-line setting for patients with metastatic colorectal cancer. They looked at K-ras status and linked that to the clinical benefit of cetuximab. This study demonstrated an improvement in progression-free survival for the addition of cetuximab to FOLFIRI, which was limited to patients with K-ras wild-type tumors. So determination of K-ras status is important when considering the use of anti-EGFR therapy in patients with metastatic colorectal cancer.

Outcome of Primary Tumor in Synchronous Stage IV Colorectal Cancer Following Combination Chemotherapy without Surgery as Initial Treatment

Poultides GA et al.
J Clin Oncol 2009;27(20):3379-84.

Methods

- > Inclusion criteria:
 - Patients presenting to MSKCC with synchronous mCRC and intact primary between 1/2000 and 12/2006
 - Asymptomatic with regard to primary tumor
 - No prior primary tumor-directed surgery, radiation therapy, endoscopic stenting or ablation
- > Up-front, first-line therapies:
 - Bolus 5-FU/leucovorin and irinotecan
 - Infusional 5-FU/leucovorin and irinotecan
 - Infusional 5-FU/leucovorin and oxaliplatin
 - With or without bevacizumab

Poultides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Introduction

- > In the absence of symptoms, the role of surgical resection of a primary colorectal cancer and metastases is uncertain.
- > With recent advances in systemic chemotherapy and improvement in survival of metastatic colorectal cancer (mCRC), the risks and benefits of a deferred surgical strategy have not been completely evaluated.
- > Current study objective:
 - Describe the frequency of primary tumor-related complications requiring operative or nonoperative intervention in patients with synchronous mCRC who received initial treatment with modern, triple-drug, oxaliplatin- or irinotecan-based combination chemotherapy with or without bevacizumab, in the absence of prophylactic surgery.

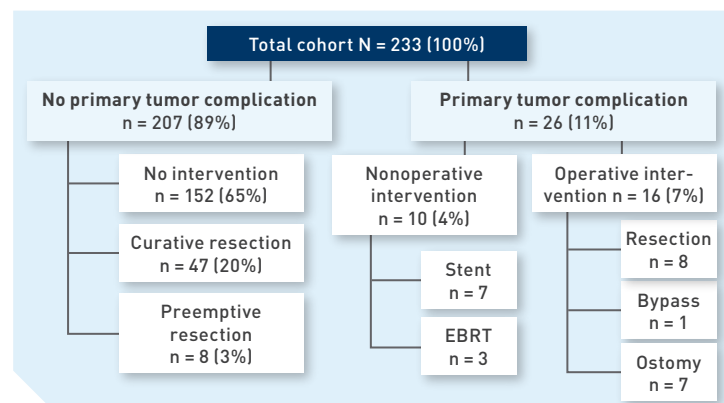
Poultides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Patient Characteristics (n = 233)

Primary Tumor Location	
Right colon	37%
Left colon	29%
Rectum	34%
Major Site(s) of Metastatic Disease at Presentation	
Liver	95%
Retroperitoneal lymph nodes	39%
Lung	30%
Metastatic Sites Involved	
1 site/2 sites/3 or more sites	40%/45%/14%

Poultides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Outcome of Unresected Primary Tumor



Poultides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Conclusions

- > Of the total cohort of 233 patients, 93% never required surgery to palliate primary tumor-related complications.
- > Postoperative mortality for those patients undergoing subsequent surgical intervention was 0.8% (data not shown).
 - Rate compares favorably with prophylactic colon resection in the metastatic setting.
 - The need for surgical intervention did not correlate with overall survival.
- > These findings support the appropriateness of nonoperative systemic management as an initial treatment option for asymptomatic patients with intact primary CRC and synchronous mCRC in the absence of overt obstruction or severe acute bleeding.

Poultides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Median Time to Intervention and Subsequent Survival

Intervention or Resection, n (%)	Time from Initiation of Chemotherapy to Intervention	Survival After Intervention
Operative, 16 (7%)	7 mo	6 mo
Non-operative, 10 (4%)	12 mo	8 mo
Curative resection*, 47 (20%)	8 mo	44 mo
Preemptive resection, 8 (3%)	9 mo	15 mo
Median survival from initiation of chemotherapy for the 152 patients who never required an intervention was 13 months.		

* Elective resection of primary metastases

Poultides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

Faculty Comments

DR BENSON: These patients with synchronous metastatic colorectal cancer and an unresected primary tumor received triple-drug therapy, with 5-FU/leucovorin in combination with oxaliplatin or irinotecan with or without bevacizumab as their initial treatment, and 93 percent of patients did not require surgical palliation of their primary tumor. Some patients underwent stent placement or surgery for primary tumor obstruction or perforation. These are practice-changing data. For many patients with colorectal cancer who present with synchronous metastatic disease, performing a prophylactic surgical resection of the primary is not routinely necessary. That is a practice-changing paradigm. Some patients require immediate surgical intervention, but for patients who are relatively asymptomatic, it is reasonable to proceed with chemotherapy as the initial intervention.

Phase IIIB Randomized Trial of Chemotherapy, Bevacizumab and Panitumumab versus Chemotherapy and Bevacizumab for Metastatic Colorectal Cancer

Hecht JR et al.
J Clin Oncol 2009;27(5):672-80.

Phase IIIB Open-Label Trial of CT/Bev/Pmab versus CT/Bev in Metastatic Colorectal Cancer

Accrual: 1,240 (Closed)

Eligibility (n = 1,053)

Metastatic colorectal cancer
 No prior chemotherapy or biologic therapy for metastatic disease
 No adjuvant treatment within past 6 mo



Ox-CT or Iri-CT (investigator's choice), Bev q2wk, Pmab 6 mg/kg, q2wk (n = 528)

Ox-CT or Iri-CT (investigator's choice), Bev q2wk (n = 525)

Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

Introduction

- > Within the past decade, important advances in the treatment of metastatic colorectal cancer have included the use of biologic agents and multiagent chemotherapy.
- > When combined with chemotherapy (CT), bevacizumab (Bev) improves overall survival in first- and second-line settings (*NEJM* 2004;350:2335, *JCO* 2007;25:1539).
- > Blocking both VEGF and EGFR pathways may increase antitumor activity (*JCO* 2007;25:4557).
- > Current study objective:
 - Evaluate the efficacy and safety of Bev and oxaliplatin-based (Ox) or irinotecan-based (Iri) CT with or without panitumumab (Pmab), an antibody targeting EGFR, in previously untreated metastatic colorectal cancer.

Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

Survival (Intent-to-Treat)

Median survival	Pmab + Bev Ox-CT (n = 413)	Bev Ox-CT (n = 410)	Pmab + Bev Iri-CT (n = 115)	Bev Iri-CT (n = 115)
Progression-free survival	10 mo	11.4 mo	10.1 mo	11.7 mo
Hazard ratio (95% CI)	1.27 (1.06 to 1.52)		1.19 (0.79 to 1.79)	
Overall survival	19.4 mo	24.5 mo	20.7 mo	20.5 mo
Hazard ratio (95% CI)	1.43 (1.11 to 1.83)		1.42 (0.77 to 2.62)	

Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

Objective Response Rate by Blinded Central Review (Intent-to-Treat)

Clinical response	Pmab + Bev Ox-CT (n = 413)	Bev Ox-CT (n = 410)	Pmab + Bev Iri-CT (n = 115)	Bev Iri-CT (n = 115)
Best overall RR	46%	48%	43%	40%
Complete RR	0%	<1%	0%	0%
Partial RR	46%	47%	43%	40%
Stable disease	29%	33%	27%	37%
Progressive disease ¹	7%	4%	13%	3%

RR = response rate

¹ Central review unable to evaluate clinical disease progression or progressive disease after surgical resections

Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

Conclusions

- > The addition of Pmab to CT/Bev was associated with decreased progression-free survival.
 - Ox-CT PFS: 10 mo vs 11.4 mo
 - Iri-CT PFS: 10.1 mo vs 11.7 mo
- > A trend toward worse survival was observed with Pmab in the wild-type K-ras group of the oxaliplatin cohort.
- > The addition of Pmab to CT/Bev results in increased toxicity.
- > The addition of Pmab to Bev and Ox- or Iri-CT is not recommended for the treatment of patients with metastatic colorectal cancer in clinical practice.

Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

Select Grade 3/4 Adverse Events

Toxicity	Pmab + Bev Ox-CT (n = 407)	Bev Ox-CT (n = 397)	Pmab + Bev Iri-CT (n = 111)	Bev Iri-CT (n = 113)
Skin toxicity	36%	1%	38%	0%
Diarrhea	24%	13%	28%	9%
Nausea/vomiting	13%	7%	13%	8%
Infections	18%	10%	14%	9%
Neutropenia	24%	24%	17%	21%
Deep vein thrombosis	7%	8%	13%	6%

Hecht JR et al. *J Clin Oncol* 2009;27(5):672-80.

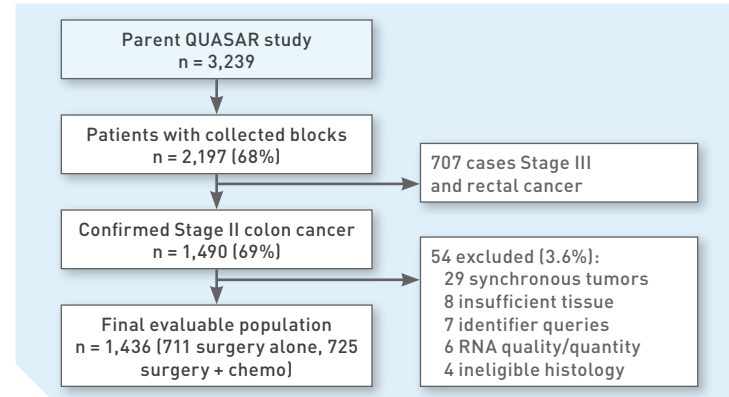
Faculty Comments

DR BENSON: This is an important study, with lessons to be learned. The rationale for dual biologic therapy in combination with chemotherapy in the first-line setting appeared reasonable, based upon previous data supporting the benefits of panitumumab and bevacizumab. These agents both partner well with chemotherapy and do not appear to have overlapping toxicities. The results were striking in that chemotherapy in combination with bevacizumab/panitumumab resulted in a worse outcome. Even patients with K-ras wild-type tumors who received panitumumab fared more poorly. This study represents a warning that we cannot assume that more is better or that we understand how these biologic agents interact together and with chemotherapy. We need more biologically driven studies to determine the best strategy to select biologic therapy combinations.

A Quantitative Multi-Gene RT-PCR Assay for Prediction of Recurrence in Stage II Colon Cancer (CC): QUASAR Validation Study

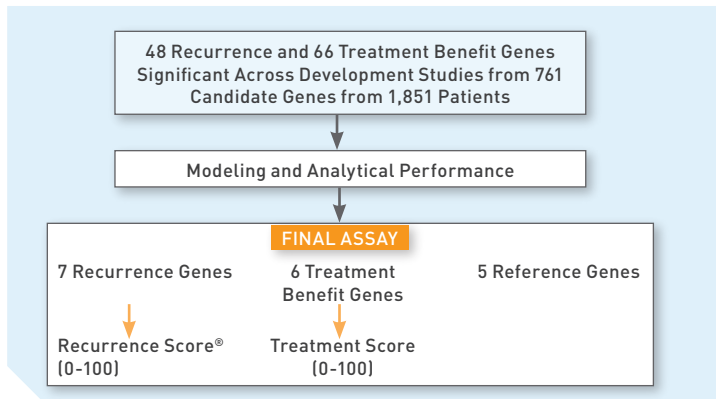
Kerr D et al.
Proc ASCO 2009;Abstract 4000.

QUASAR: Evaluable Stage II Colon Cancer (CC) Patients



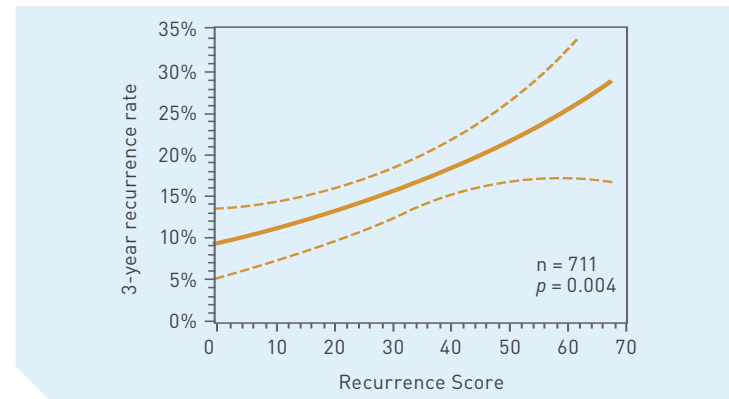
Kerr D et al. *Proc ASCO 2009*;Abstract 4000.

Final Assay for QUASAR Validation



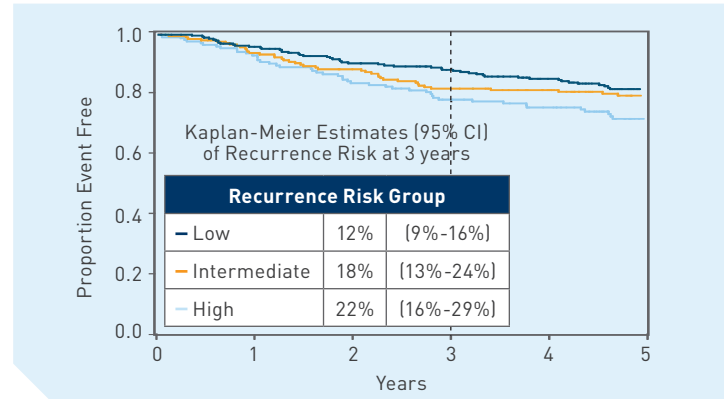
Kerr D et al. *Proc ASCO 2009*;Abstract 4000.

Continuous RS Predicts Recurrence in Stage II CC Following Surgery



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

Recurrence Risk in Prespecified Recurrence Risk Groups (n = 711)



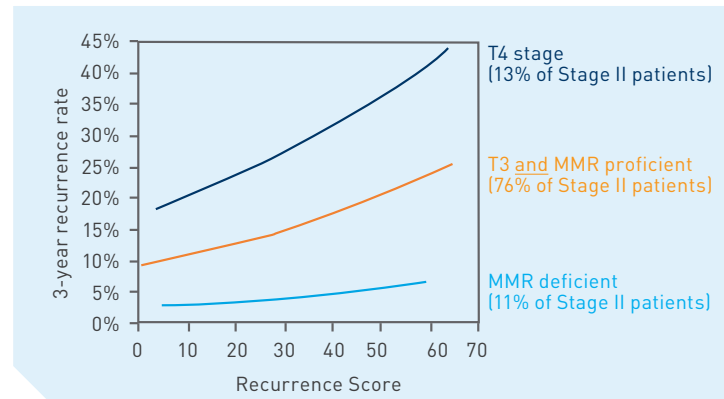
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Conclusions

- > First demonstration that a prospectively-defined gene expression assay can independently predict recurrence in Stage II CC following surgery.
 - Recurrence Score (RS) provides independent value beyond available prognostic factors.
- > RS provides individualized assessment of recurrence risk.
 - Greatest clinical utility when used in conjunction with T stage and Mismatch Repair (MMR/MSI), particularly for the majority of patients for whom those markers are uninformative (~70% of patients)
- > The continuous Treatment Score did not predict a differential benefit from 5FU/LV (data not shown).

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

RS, T Stage and MMR Deficiency: Key Independent Predictors of Recurrence in Stage II CC



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

Faculty Comments

DR HOCHSTER: The *Oncotype DX* assay may be helpful in identifying patients with higher-risk, Stage II colon cancer. Approximately 18,000 patients per year in the United States have T3, non-MSI-high colon cancer that could benefit from a molecular determination of their risk for recurrence. I'm sure that the NSABP and other groups will attempt to validate *Oncotype DX* in clinical trials, and this test could become part of our clinical practice. I tell patients that we currently estimate their risk of recurrence using nineteenth-century technology by looking at cells under a microscope, but perhaps we could do better using modern molecular biology techniques and determine who does and does not need adjuvant chemotherapy.

Prognostic Role of KRAS and BRAF in Stage II and III Resected Colon Cancer: Results of the Translational Study on PETACC-3, EORTC 40993, SAKK 60-00 Trial

Roth AD et al.
J Clin Oncol 2010;28(3):466-74.

K-ras Tumor Mutation Interactions with Other Prognostic Markers

Patient Population/Prognostic Markers	Odds Ratio (95% CI)	p-value
Stage III vs II (n = 894, 405)	1.10 (0.85-1.43)	0.45
Tumor site right vs left (n = 516, 783)	1.43 (1.11-1.84)	0.0052
Female vs male (n = 550, 749)	0.88 (0.69-1.11)	0.28
>60 yo vs ≤60 yo (n = 655, 644)	1.07 (0.84-1.36)	0.57
Grade 3/4 vs 1/2 (n = 120, 1,170)	0.46 (0.28-0.73)	0.0016
MSI high vs low/stable (n = 188, 1,047)	0.72 (0.50-1.05)	0.091

MSI = microsatellite instability

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

Introduction

- > Mutations within the K-ras proto-oncogene have predictive value but are of uncertain prognostic value in the treatment of advanced colorectal cancer.
- > The PETACC-3 trial is a large Phase III trial comparing adjuvant fluorouracil/leucovorin with or without irinotecan in Stage II/III colon cancer in which patient tissue blocks (n = 1,404) have been prospectively collected.
 - Analysis of K-ras exon 2 and B-raf exon 15 mutations has been successfully performed in 1,321 cases (409 Stage II, 912 Stage III).
- > Current study objective:
 - Examine the prognostic value of K-ras and B-raf tumor mutation status in patients with Stage II or III colon cancer enrolled in PETACC-3.

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

B-raf Tumor Mutation Interactions with Other Prognostic Markers

Patient Population/Prognostic Markers	Odds Ratio (95% CI)	p-value
Stage III vs II (n = 900, 407)	1.18 (0.72-1.98)	0.52
Tumor site right vs left (n = 517, 790)	4.03 (2.39-7.02)	3.7 x 10 ⁻⁷
Female vs male (n = 552, 755)	1.75 (1.11-2.77)	0.017
>60 yo vs ≤60 yo (n = 659, 648)	3.03 (1.86-5.06)	1.3 x 10 ⁻⁵
Grade 3/4 vs 1/2 (n = 120, 1,179)	3.72 (2.04-6.70)	1.4 x 10 ⁻⁵
MSI high vs low/stable (n = 188, 1,055)	3.59 (2.09-6.19)	3.8 x 10 ⁻⁶

MSI = microsatellite instability

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

Survival Analysis (RFS and OS) According to K-ras Status

Population/Stage	RFS		OS	
	HR	p-value	HR	p-value
Population by K-ras status				
Stages II and III (n = 1,299)	1.05	0.66	1.09	0.48
Stage II (n = 405)	1.09	0.74	1.16	0.63
Stage III (n = 894)	1.04	0.71	1.08	0.55
K-ras MSI-L/S patients only				
Stages II and III (n = 1,047)	1.14	0.24	1.15	0.29
Stage II (n = 305)	1.19	0.52	1.20	0.57
Stage III (n = 742)	1.13	0.32	1.14	0.36

RFS = recurrence-free survival; OS = overall survival; HR = hazard ratio; MSI-L/S = microsatellite instability low/stable

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

Summary and Conclusions

- > K-ras (37%) and B-raf (7.9%) tumor mutation rates were not significantly different according to tumor stage (data not shown).
- > In a multivariate analysis, K-ras mutation was associated with grade ($p = 0.0016$).
- > In a multivariate analysis, B-raf mutation was significantly associated with female sex ($p = 0.017$) and with right-sided tumors, older age, high grade and MSI-high tumors (all $p < 10^{-4}$).
- > In univariate and multivariate analysis, K-ras mutations did not have a major prognostic value regarding RFS or OS.
- > B-raf mutation was not prognostic for RFS, but was for OS, particularly in patients with MSI-low and stable tumors (HR = 2.2; $p = 0.0003$).

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

Survival Analysis (RFS and OS) According to B-raf Status

Population/Stage	RFS		OS	
	HR	p-value	HR	p-value
Population by B-raf status				
Stages II and III (n = 1,307)	1.19	0.34	1.66	0.0069
Stage II (n = 407)	0.94	0.85	1.13	0.82
Stage III (n = 900)	1.23	0.28	1.76	0.0050
B-raf MSI-L/S patients only				
Stages II and III (n = 1,055)	1.49	0.067	2.19	0.00034
Stage II (n = 307)	1.84	0.24	2.81	0.05
Stage III (n = 748)	1.40	0.16	2.07	0.0025

RFS = recurrence-free survival; OS = overall survival; HR = hazard ratio; MSI-L/S = microsatellite instability low/stable

Roth AD et al. *J Clin Oncol* 2010;28(3):466-74.

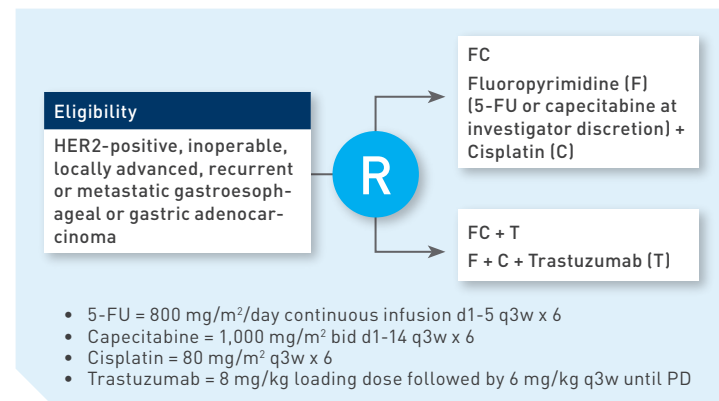
Faculty Comments

DR AJANI: This is a new field and a lot of assumptions are being made. If one interrupts the proximal area of the pathway, such as the cell-surface receptor, the pathway can still be activated downstream. We have much more to learn, and increasingly molecular biologists believe that we need to interrupt pathways as distally as possible to yield the highest therapeutic advantage. B-raf is further downstream from K-ras, but it may not be enough. So this is a good exploratory study that will be advantageous for developing further therapeutic strategies, but I believe we don't know enough yet to make sense of these results.

Efficacy Results from the ToGA Trial: A Phase III Study of Trastuzumab Added to Standard Chemotherapy in First-Line HER2-Positive Advanced Gastric Cancer

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

ToGA Trial Design (n = 584)



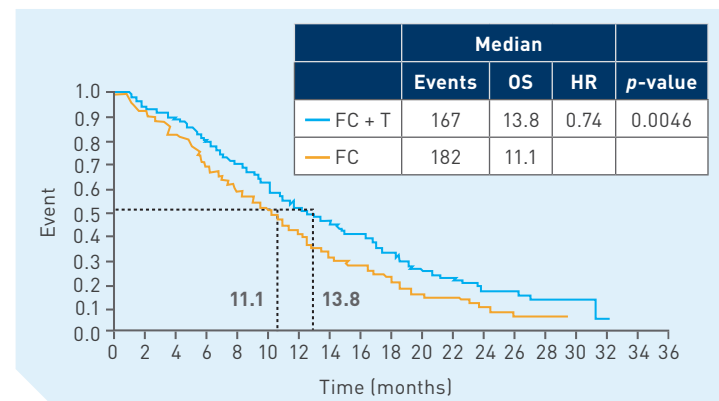
Van Cutsem E et al. *Proc ASCO 2009*;Abstract LBA4509.

Introduction

- > Chemotherapy improved survival compared to best supportive care in patients with advanced gastric cancer (GC) and combination chemotherapy was superior to monotherapy (*JCO* 2006;24:2903).
- > Roughly 22% of patients with advanced GC have HER2-positive disease (*ASCO 2009*;Abstract 4556).
- > Anti-HER2 antibody trastuzumab is active in GC cell lines in vitro and in vivo.
- > Current study objective:
 - Evaluate the addition of trastuzumab to fluoropyrimidine/cisplatin in patients with HER2-positive advanced GC.

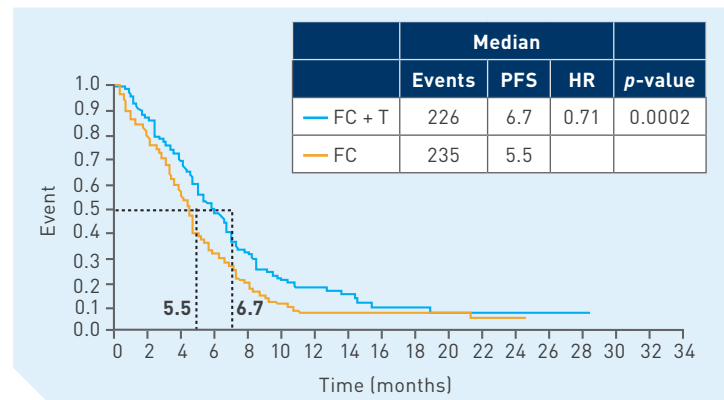
Van Cutsem E et al. *Proc ASCO 2009*;Abstract LBA4509.

Primary Endpoint: Overall Survival (OS)



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

Secondary Endpoint: Progression-Free Survival (PFS)



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

Conclusions

- > ToGA met its primary overall survival endpoint.
 - Trastuzumab reduced the risk of death by 26% when combined with fluoropyrimidine/cisplatin (HR = 0.74).
 - Trastuzumab prolongs median survival by nearly 3 mo in patients with HER2-positive advanced GC.
- > All secondary efficacy endpoints (PFS, TTP, ORR, CBR, DoR) significantly improved with the addition of trastuzumab (data not shown).
- > Addition of trastuzumab to chemotherapy was well tolerated, with no difference in the overall safety profile between treatment arms, including cardiac AEs.
- > Trastuzumab in combination with chemotherapy is a new treatment option for patients with HER2-positive advanced GC.

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

Cardiac Adverse Events (AEs)

	FC (n = 290)		FC + T (n = 294)	
	All	Grade 3/4	All	Grade 3/4
Total cardiac AEs	6%	3%	6%	1%
Cardiac failure	<1%	<1%	<1%	<1%
Asymptomatic LVEF decline <50%	1.1%		5.9%	
<50% and by ≥10%	1.1%		4.6%	
Cardiac AEs leading to death	<1%		<1%	
Cardiac AEs related to treatment	<1%		<1%	

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

Faculty Comments

DR ILSON: ToGA is a landmark study that validates an improvement in outcome with the use of a targeted therapy in combination with chemotherapy. The primary endpoint of overall survival was achieved, with nearly a three-month improvement, which was highly statistically significant. The secondary endpoints of progression-free survival and response rate were also improved, and trastuzumab did not add any toxicity or negatively affect quality of life. This study establishes a new standard of care in HER2-positive esophageal and gastric adenocarcinomas. Patients who overexpress HER2 should receive first-line chemotherapy/trastuzumab. The next step is to evaluate trastuzumab in the adjuvant setting, which is currently under development in RTOG-1010.

Meta-Analysis of REAL-2 and ML17032: Capecitabine and Infused 5-FU-Based Combination Chemotherapy for Advanced Oesophago-Gastric Cancer

Okines AF et al.
Ann Oncol 2009;20(9):1529-34.

Introduction

- > The Phase III REAL-2^a and ML17032^b trials demonstrated that capecitabine (CAPE) is noninferior to 5-fluorouracil (5-FU) for overall survival (OS) and progression-free survival (PFS), respectively, in advanced esophago-gastric cancer (^a *NEJM* 2008;358:36, ^b ASCO 2006;Abstract LBA4108).
- > Both trials demonstrated that the toxicity profile of CAPE is similar to that of 5-FU within the doublet and triplet chemotherapy regimens utilized.
- > Current study objective:
 - Conduct a meta-analysis of REAL-2 and ML17032 trials to determine whether CAPE is superior to 5-FU for survival in the treatment of advanced esophago-gastric cancer.

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

REAL-2 Trial

- > Phase III REAL-2 trial (n = 1,002; two-by-two design) compared first-line CAPE- versus 5-FU-containing triplets and oxaliplatin-versus cisplatin-containing triplets in advanced esophago-gastric cancer (*NEJM* 2008;358:36).
- > Trial was designed to demonstrate noninferiority for OS of CAPE- and oxaliplatin-containing regimens, as compared to 5-FU- and cisplatin-containing regimens, respectively.
 - The study met both of its primary endpoints.
- > The unadjusted hazard ratio (HR) for death in the CAPE group relative to the 5-FU groups was 0.86 (95% CI 0.80-0.99).
- > The unadjusted HR for death in the oxaliplatin group relative to the cisplatin group was 0.92 (95% CI 0.80-1.10).

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

ML17032 Trial

- > Phase III ML17032 trial (n = 316) compared first-line cisplatin plus capecitabine (CX) versus cisplatin plus 5-FU (CF) in advanced gastric cancer (ASCO 2006;Abstract LBA4108).
- > Designed to demonstrate noninferiority of CX as compared to CF for PFS.
- > The study met its primary endpoint.
 - PFS = 5.6 months in the CX arm vs 5 months in the CF arm (HR = 0.81, 95% CI 0.63-1.04)
- > Median OS was comparable; 10.5 months for CX arm and 9.3 months for CF arm ($p = 0.27$).
- > Superiority of capecitabine was demonstrated for response rate (41% vs 29%, $p = 0.03$).

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

Multivariate Analysis: Overall Survival*

Variable	Group	n	HR (95% CI)	p-value
Performance status	0-1	1,175	1.87 (1.55-2.26)	0.0000
	2	138		
Age	<60 years	582	0.83 (0.73-0.94)	0.0026
	≥60 years	731		
Extent of disease	Locally advanced	273	1.64 (1.40-1.91)	0.0000
	Metastatic	1,040		

* Histopathological subtype did not have a significant effect on overall survival.

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

Summary and Conclusions

- > OS was superior in the patients with advanced esophago-gastric cancer treated with capecitabine combinations compared with those treated with 5-FU combinations.
- > Poor performance status, age < 60 years and metastatic disease were independent predictors of poor survival.
- > There was no significant difference in PFS between treatment groups on multivariate analysis (data not shown).
- > Assessable patients treated with capecitabine combinations were significantly more likely to have an objective response than those treated with 5-FU combinations.
- > Capecitabine may replace 5-FU in the treatment of advanced esophageal or gastric cancer.

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

Multivariate Analysis: Unconfirmed Response Rate

Variable	Group	n	HR (95% CI)	p-value
Performance status	0-1	1,098	0.62 (0.42-0.91)	0.0140
	2	133		
Age	<60 years	549	1.32 (1.05-1.67)	0.0174
	≥60 years	682		
Gender	Female	270	1.58 (1.19-2.10)	0.0017
	Male	961		
Treatment	CAPE based	613	1.38 (1.10-1.73)	0.0057
	5-FU based	618		

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

Faculty Comments

DR ILSON: This study combines the results of two large Phase III clinical trials. The Kang study compared capecitabine/ cisplatin to infusional 5-FU/cisplatin. The REAL-2 trial looked at capecitabine versus infusional 5-FU and substituted cisplatin with oxaliplatin. Both studies individually demonstrated noninferiority of capecitabine. In the pooled analysis, there appears to be a modest survival advantage for capecitabine compared to infusional 5-FU. Capecitabine is a mixed blessing in that it allows the patient to avoid a Mediport but at the cost of increased hand-foot syndrome and patient-compliance issues. In my practice, I tend to use more infusional 5-FU but with a different schedule than the Kang or REAL-2 studies. Most practitioners are tailoring 5-FU as it's used in colorectal cancer, with a two-day infusion every two weeks.

Capecitabine/Cisplatin versus 5-Fluorouracil/Cisplatin as First-Line Therapy in Patients with Advanced Gastric Cancer: A Randomised Phase III Noninferiority Trial

Kang Y-K et al.
Ann Oncol 2009;20(4):666-73.

Phase III Open-Label Trial of CAP-CIS versus 5FU-CIS in Advanced Gastric Cancer

Accrual: 316 (Closed)

Eligibility

Patients with advanced gastric cancer (AGC)
 Karnofsky PS of ≤ 70
 No prior chemotherapy (neoadjuvant or adjuvant permitted)
 No radiotherapy to target lesions



CIS 80 mg/m², d1
 CAP 1,000 mg/m² BID, d1-14,
 q3wk (n = 160)

CIS 80 mg/m², d1
 5FU 800 mg/m², d1-5, q3wk
 (n = 156)

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.

Introduction

- > There is no globally accepted standard of care for patients with advanced gastric cancer, though combination chemotherapy is well accepted.
- > The combined use of 5-fluorouracil (5FU) and cisplatin (CIS) is the standard of care in Korea and many other countries based on superior response rates compared with the use of 5FU alone (*Cancer* 1993;71:3813).
- > Capecitabine (CAP) combined with CIS (CAP-CIS) has demonstrated favorable response rates in a Phase II study (*Ann Oncol* 2002;13:1893).
- > Current study objective:
 - Compare the efficacy and safety of CAP-CIS versus 5FU-CIS in the first-line treatment of advanced gastric cancer.

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.

Survival (Per-Protocol Population)

Median Survival	CAP-CIS n=139 (95% CI)	5FU-CIS n=137 (95% CI)	Hazard ratio (95% CI)	p-value
Progression-free survival (PFS)	5.6 mo (4.9-7.3 mo)	5.0 mo (4.2-6.3 mo)	0.81* (0.63-1.04)	<0.001
Overall survival	10.5 mo (9.3-11.2 mo)	9.3 mo (7.4-10.6 mo)	0.85 (0.64-1.13)	0.008

*The upper limit of the two-sided 95% CI for the hazard ratio did not exceed the prespecified noninferiority margin of 1.25.

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.

Clinical Response (Per-Protocol Population)

Clinical Variable	CAP-CIS n = 139 (95% CI)	5FU-CIS n = 137 (95% CI)	Hazard or odds ratio (95% CI)	p-value
Overall response	46% (38-45%)	32% (24-41%)	1.80 (1.11-2.94)	0.02
Complete response	2%	3%	—	—
Partial response	44%	29%	—	—
Median time to response*	3.7 mo	3.8 mo	1.61 (1.10-2.35)	0.015
Median duration of response*	7.6 mo	6.2 mo	0.88 (0.56-1.36)	0.554

* Intent-to-treat population

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.

Conclusions

- > CAP-CIS showed significant noninferiority for PFS, compared to 5FU-CIS, in the first-line treatment of AGC.
 - PFS: 5.6 mo vs 5.0 mo ($p < 0.001$)
 - OS: 10.5 mo vs 9.3 mo ($p = 0.008$)
 - Overall response rate: 46% vs 32% ($p = 0.02$)
- > CAP-CIS and 5FU-CIS had similar toxicity profiles and were well tolerated.
- > CAP offers the potential for a simplified dosing schedule and avoids the inconvenience and adverse effects associated with intravenous dosing.
- > These findings suggest that CAP-CIS can be used instead of 5FU-CIS as a new treatment option for patients with advanced gastric cancer.

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.

Select Grade 3/4 Adverse Events (Safety Population)

Toxicity	CAP-CIS n = 156	5FU-CIS n = 155
Neutropenia	25 (16%)	29 (19%)
Vomiting	11 (7%)	13 (8%)
Diarrhea	8 (5%)	7 (5%)
Hand-foot syndrome	6 (4%)	—
Leukopenia	4 (3%)	6 (4%)
Nausea	3 (2%)	4 (3%)
Stomatitis	3 (2%)	10 (6%)
Anorexia	3 (2%)	1 (<1%)

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.

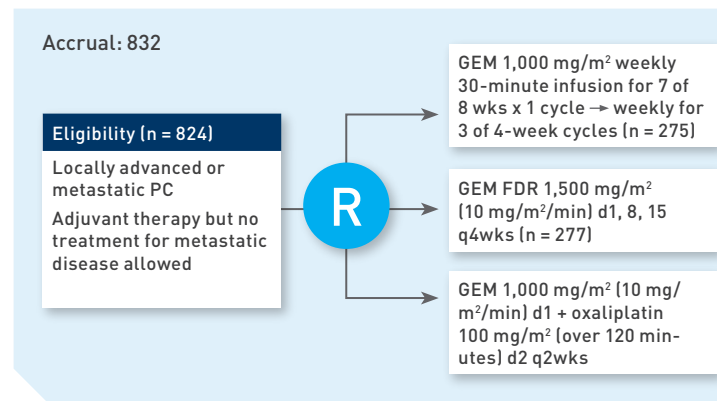
Faculty Comments

DR AJANI: The primary endpoint is progression-free survival, but it's a highly underpowered study. Nobody should do a Phase III trial with 300 patients. All of the previous generations of Phase III trials in gastroesophageal cancer were small because everyone believed we could double the survival benefit. In reality, we have achieved minor advantages. Additionally, we should be targeting endpoints that the regulatory agencies expect. This study simply suggests that capecitabine may be a substitution for 5-FU as a noninferior agent without a safety advantage. Capecitabine solely offers convenience, but I use it frequently.

Gemcitabine and Oxaliplatin versus Gemcitabine (Fixed-Dose Rate Infusion) Compared with Gemcitabine (30-Minute Infusion) in Pancreatic Carcinoma: E6201

Poplin E et al.
J Clin Oncol 2009;27(23):3778-85.

Phase III Study Design



Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Introduction

- > Gemcitabine (GEM) is the currently accepted standard treatment for pancreatic cancer (PC), since no combination regimen has demonstrated an improvement in survival compared to GEM alone.
- > Two recent studies suggested a benefit for the use of fixed-dose rate (FDR) GEM or GEM FDR plus oxaliplatin (GEMOX).
 - Phase II: Improvement in time to treatment failure for FDR GEM at 10 mg/m²/min compared to GEM 30-minute infusion (*JCO* 2003;21:3402)
 - Phase III: GEMOX resulted in higher response rate and PFS compared to GEM (*JCO* 2005;23:3509)
- > Current study objective:
 - Compare the effect of standard GEM, GEM FDR and GEMOX on overall survival in patients with locally advanced or metastatic PC.

Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Progression-Free and Overall Survival

Patient Group	Progression-Free Survival		Overall Survival	
	Median	p-value	Median	p-value
All eligible patients (n = 824)	2.9 mo	—	5.6 mo	—
GEM (n = 275)	2.6 mo	0.09	4.9 mo	0.15
GEM FDR (n = 277)	3.5 mo		6.2 mo	
GEMOX (n = 272)	2.7 mo		5.7 mo	

Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Progression-Free and Overall Survival: Univariate Analyses

Parameter	Progression-Free Survival		Overall Survival	
	Median	p-value	Median	p-value
Disease status				
Locally advanced	5.4 mo	<0.01	9.2 mo	<0.01
Metastatic	2.7 mo		5.4 mo	
Prior radiotherapy				
No	2.9 mo	0.53	5.5 mo	0.52
Yes	3.1 mo		6.9 mo	
Prior adjuvant chemotherapy				
No	3.0 mo	0.14	5.5 mo	0.10
Yes	2.9 mo		7.3 mo	

Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Summary and Conclusions

- > Neither GEM FDR nor GEMOX significantly increased OS or PFS in patients with advanced PC compared to GEM 30-minute infusion.
- > Grade 3/4 neutropenia and thrombocytopenia were highest with GEM FDR. GEMOX resulted in higher rates of nausea, vomiting and neuropathy.
- > PC has a large number of genetic alterations, likely causing dysregulation of multiple pathways. Additional data implicate the active role of PC stroma.
 - Future studies should include the coordinated use of multiple therapeutic agents or modalities that attack the most critical of these pathways.

Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Select Grade III/IV Toxicities

	GEM (n = 264)		GEM FDR (n = 275)		GEMOX (n = 263)	
	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4
Leukocytes*	15%	1%	32%	7%	11%	1%
Neutrophils*	19%	14%	29%	30%	11%	11%
Platelets*	12%	1%	29%	4%	10%	1%
Fatigue	18%	1%	18%	1%	15%	2%
Anorexia	8%	—	6%	—	7%	<1%
Sensory neuropathy*	0%	—	1%	—	25%	—

* P < 0.001 among three treatment arms

Poplin E et al. *J Clin Oncol* 2009;27(23):3778-85.

Faculty Comments

DR ILSON: This is an important, well-powered — albeit negative — study, so the conclusion that there was no difference in overall survival is meaningful and reinforces that a 30-minute infusion of gemcitabine does remain a standard of care.

DR HOCHSTER: I'm a big fan of fixed-dose rate gemcitabine. Of interest, the fixed-dose rate gemcitabine was as effective as fixed-dose rate gemcitabine in combination with oxaliplatin and was better than 30-minute infusion gemcitabine at the $p = 0.05$ level. However, because this was a three-arm study, a p -value of <0.025 was required for statistical significance. So, although Dr Poplin presented this as a negative study, I don't entirely agree with that conclusion, and I tend to accept that the fixed-dose rate is more effective than the standard 30-minute infusion.

Phase III Randomized Open-Label Comparison of Adjuvant 5-FU/FA versus GEM in Patients with Resected Pancreatic Ductal Adenocarcinoma: ESPAC-3 (v2)

Neoptolemos M et al.
Proc ASCO 2009; Abstract LBA4505.

ESPAC-3(v2): A Phase III Randomized Trial of 5-FU/FA versus GEM in Resected Pancreatic Cancer

Accrual: 1,088 (Closed)

Eligibility

Within 8 weeks post R0 or R1 resection for pancreatic ductal adenocarcinoma*



5-FU 425 mg/m² + FA 20 mg/m² x 5d q4wk, for 6 months (n = 551)

GEM IV 1,000 mg/m²/wk x 3 q4wk, for 6 months (n = 537)

*Stratified by resection margin status and country

Neoptolemos M et al. *Proc ASCO 2009*; Abstract LBA4505.

Introduction

- > ESPAC-1 trial confirmed the clinical benefit of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) therapy for patients with resected pancreatic cancer compared to patients who received no chemotherapy (*NEJM* 2004;350:1200).
 - Hazard ratio for death (HR): 0.71 ($p = 0.009$)
- > The CONKO-001 trial demonstrated that patients with resected pancreatic cancer experience improved survival when treated with adjuvant gemcitabine (GEM) compared with untreated patients (*JAMA* 2007;297:267).
- > Current study objective:
 - Compare the survival benefit of adjuvant 5-FU/FA versus GEM in patients with resected pancreatic cancer.

Neoptolemos M et al. *Proc ASCO 2009*; Abstract LBA4505.

Efficacy Results (Intent-to-Treat)

Median Survival	5-FU/FA (n = 551)	GEM (n = 537)	p-value
Progression-free survival (PFS)	14.1 mo	14.3 mo	0.44
Overall survival (OS)	23.0 mo	23.6 mo	0.39

Neoptolemos M et al. *Proc ASCO 2009*; Abstract LBA4505.

Adjusted Treatment Effect

- > Treatment effect was adjusted by the following stratification factors at randomization:
 - Country
 - Resection status
- > Analysis of stratification factors by Frailty model:
 - Country, $p = 0.61$ (random effect)
 - Resection status, $p < 0.001$ (fixed effect)
 - **Treatment, HR = 0.94 (95% CI: 0.81-1.08), $p = 0.36$**

Neoptolemos M et al. *Proc ASCO* 2009; Abstract LBA4505.

Conclusions

- > There were no differences in survival between the use of adjuvant 5-FU/FA vs GEM.
 - Median OS: 23.0 mo vs 23.6 mo, $p = 0.39$
 - Median PFS: 14.1 mo vs 14.3 mo, $p = 0.44$
- > The safety profile of GEM was better than that of 5-FU/FA.
 - Stomatitis and diarrhea were significantly greater in the 5-FU/FA group, but thrombocytopenia was significantly greater in the GEM group.
 - Treatment-related serious adverse events were significantly greater in the 5-FU/FA group.
- > These data reinforce the design of the ESPAC-4, comparing GEM versus GEM-capecitabine in a Phase III, international, randomized controlled trial of 1,080 patients with pancreatic ductal adenocarcinoma.

Neoptolemos M et al. *Proc ASCO* 2009; Abstract LBA4505.

Select Adverse Events

Grade 3/4 Toxicity	5-FU/FA (n = 551)	GEM (n = 537)
Leukopenia	6%	10%
Neutropenia	22%	22%
Thrombocytopenia*	0%	1.5%
Nausea	3.5%	2.5%
Vomiting	3%	2%
Stomatitis*	10%	0%
Tiredness	8%	6%
Diarrhea*	13%	2%

* $p < 0.005$

Neoptolemos M et al. *Proc ASCO* 2009; Abstract LBA4505.

Faculty Comments

DR ALBERTS: This was a noteworthy study in that it looked at a multicenter, international comparison of patients undergoing adjuvant therapy using 5-fluorouracil and leucovorin compared to gemcitabine alone. Given the size of the study and multicenter participation, it provided a fair comparison between the two approaches of adjuvant therapy and showed that there was no difference in the treatment across the groups that were evaluated. That is particularly important in looking at treatment options for patients for whom gemcitabine had been considered a standard for a long time. The use of 5-fluorouracil and leucovorin showed comparable outcomes, raising the possibility that future trials now can be done with 5-fluorouracil and leucovorin and not necessarily involve gemcitabine.

Preoperative Biliary Drainage for Cancer of the Head of the Pancreas

van der Gaag NA et al.
N Engl J Med 2010;362(2):129-37.

Multicenter, Randomized Trial of Preoperative Biliary Drainage

Accrual: 202 (Closed)

Eligibility

Cancer of the pancreatic head
 Obstructive jaundice
 Bilirubin level of 40 to 250 µmol per liter
 No CT evidence of distant metastasis or local vascular involvement



Preoperative biliary drainage for 4-6 weeks followed by surgery (n = 102)

Surgery alone within one week after diagnosis (n = 94)

van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Introduction

- > Preoperative biliary drainage (PBD) was introduced to improve the postoperative outcome in patients with obstructive jaundice caused by a tumor of the pancreatic head (*J Gastrointest Surg* 2009;13:814).
- > Meta-analysis^a and a systematic review^b of the efficacy of PBD have shown that the overall complication rate was higher in patients undergoing PBD compared to patients who proceeded directly to surgery (^a*Ann Surg* 2002;236:17, ^b*Cochrane Database Syst Rev* 2008;3:CD005444).
- > Current study objective:
 - Assess the rates of serious complications and death and the length of hospital stay associated with PBD.

van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Serious Complications Related to PBD within 120 Days After Randomization¹

Complication Related to PBD	Early Surgery (n = 94)	PBD (n = 102)
Any	2%	46%
Pancreatitis	0%	7%
Cholangitis ²	2%	26%
Occlusion related to stent	1%	15%
Need for exchange related to stent	2%	30%

¹The numbers refer to patients who had one or more complications.

²In two patients, cholecystitis occurred in connection with cholangitis, prompting antibiotic treatment without the need for cholecystectomy.

van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Serious Complications Related to Surgery within 120 Days After Randomization¹

Complication Related to Surgery	Early Surgery (n = 94)	PBD (n = 102)
Any	37%	47%
Pancreaticojejunostomy leakage	12%	8%
Delayed gastric emptying	10%	18%
Wound infection	7%	13%
Pneumonia	5%	9%
Need for repeated laparotomy ²	14%	12%

¹ The numbers refer to patients who had one or more complications.

² Refers to complications of preoperative biliary drainage or another surgical procedure.

van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Conclusions

- > Routine PBD in patients undergoing surgery for cancer of the pancreatic head increases the rate of complications.
- > The rates of serious complications were 39% in the early-surgery group and 74% in the PBD group.
 - Relative risk: 0.54 (95% CI 0.41-0.71, $p < 0.001$)
- > Surgery-related complications occurred in 37% in the early-surgery group and 47% in the PBD group.
 - Relative risk: 0.79 (95% CI 0.57-1.11, $p = 0.14$)
- > PBD was successful in 94% of patients, with complications in 46% of the patients (data not shown).
- > Mortality and the length of hospital stay did not differ significantly between the two groups.

van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Major Outcomes¹

Variable	Early Surgery (n = 94)	PBD (n = 102)	Relative Risk ²
Overall complications (protocol specified)	39%	74%	0.54
Death (protocol-specified complication)	4%	9%	0.48
Median hospital stay (protocol-specified treatment)	13 days	15 days	Not reported

¹ The numbers refer to patients who had one or more complications.

² Relative risk values are for early surgery versus PBD.

van der Gaag NA et al. *N Engl J Med* 2010;362(2):129-37.

Faculty Comments

DR ALBERTS: The importance of this particular trial is in addressing what has often been regarded as the standard of care but hasn't necessarily been questioned. To date, many have accepted that it's appropriate, and probably better, to place a stent prior to surgery to reduce the bilirubin and help the patient go through surgery without additional complications. In this particular trial, however, the routine use of biliary drainage prior to surgery increased the rate of complications. It's a level of complications that should make people aware that placing a drain prior to surgery is not necessarily in the patient's best interest and may cause harm. So it's a practice-changing study.

Phase III Randomized Comparison of Gemcitabine versus Gemcitabine plus Capecitabine in Patients with Advanced Pancreatic Cancer

Cunningham D et al.
J Clin Oncol 2009;27(33):5513-8.

Phase III Randomized Trial of GEM versus GEM Plus CAP in Advanced Pancreatic Cancer

Accrual: 533 (Closed)

Eligibility

Previously untreated ductal adenocarcinoma or undifferentiated carcinoma of the pancreas (histologically or cytologically proven)



GEM IV 1,000 mg/m²/wk x 7
 1 week rest
 GEM IV 1,000 mg/m²/wk x 3
 q4wk (n = 266)

GEM IV 1,000 mg/m²/wk x
 3 q4wk
 CAP PO 1,660 mg/m²/d x
 21 days q4wk (n = 267)

Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Introduction

- > Gemcitabine (GEM) is considered the standard of care for untreated patients with advanced pancreatic cancer.
 - GEM has consistently resulted in a median survival of 5-7 months and a 1-yr survival rate of 20%.
- > Phase I trial of capecitabine (CAP) combined with GEM established a dose schedule that allows for administration of standard-dose GEM with a modified dosing schedule of CAP.
 - Modified CAP dosing schedule (1,660 mg/m²/d x 21 days) allows for similar dose intensity to the standard dose and schedule of CAP given alone (*JCO* 2002;20:582).
- > Current study objective:
 - Assess if the addition of CAP to GEM would improve survival over GEM alone in patients with advanced pancreatic cancer.

Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Efficacy Results (Intent-to-Treat)

Clinical variable	GEM (n = 266)	GEM-CAP (n = 267)	p-value
Overall response rate (ORR)	12.4%	19.1%	0.03
Complete response	0.4%	3.0%	
Partial response	12.0%	16.1%	
Stable disease	29.3%	29.6%	—
Progressive disease	19.5%	15.7%	—
Median survival	GEM (n = 266)	GEM+CAP (n = 267)	p-value
Progression-free survival (PFS)	3.8 mo	5.3 mo	0.004
Overall survival (OS)	6.2 mo	7.1 mo	0.08

Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Meta-Analysis of Published Randomized Controlled Trials (Including Current Trial)

Study or subcategory	GEM, n	GEM-CAP, n	Hazard ratio* [95% CI]
Overall survival			
Cunningham 2009	266	267	0.86 [0.72 to 1.02]
Herrmann 2007	159	160	0.87 [0.69 to 1.10]
Schelthauer 2003	42	41	0.82 [0.50 to 1.34]
Subtotal (95% CI)	467	468	0.86 [0.75 to 0.98]

*Hazard ratio of <1 favors GEM-CAP

Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Summary and Conclusions

- > Addition of CAP to GEM significantly improved response rates and PFS in patients with advanced pancreatic carcinoma.
 - ORR: 19.1% vs 12.4%
 - Median PFS: 5.3 mo vs 3.8 mo
- > A trend toward improved OS was seen with the addition of CAP to GEM.
- > Increased clinical benefit was achieved without significant toxicity or detrimental effect on quality of life (data not shown).
- > Based on these study results and those of the meta-analysis, GEM-CAP should be considered among the standard first-line options for the treatment of advanced pancreatic cancer.

Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Grade 3/4 Adverse Events

Toxicity*	GEM (n = 247)	GEM-CAP (n = 251)
Neutropenia	22%	35%
Lethargy	21%	21%
Nausea/vomiting	12%	13%
Thrombocytopenia	6%	11%
Anemia	6%	4%
Diarrhea	4%	5%
Hand-foot syndrome	0%	4%

*Toxicities observed in patients receiving at least one cycle of treatment

Cunningham D et al. *J Clin Oncol* 2009;27(33):5513-8.

Faculty Comments

DR ILSON: This is a problematic, Phase III study in advanced pancreatic cancer, comparing gemcitabine to gemcitabine in combination with capecitabine in advanced pancreatic cancer, that failed to meet its overall survival endpoint. The hazard ratio of 0.86 was not statistically significant for overall survival, although there was a trend toward a better response and progression-free survival with the combination. At the end of the day, it's a negative trial, but the authors did not accept that conclusion and performed a meta-analysis with other studies. Of note, the hazard ratio remained the same for overall survival, but it was significant for the combination with a larger pool of patients. This suggests that the gemcitabine/capecitabine may offer a benefit to some patients. In my practice, I reserve the combination for patients with a better performance status.

Phase III Trial of Bevacizumab in Combination with Gemcitabine and Erlotinib in Patients with Metastatic Pancreatic Cancer

Van Cutsem E et al.
J Clin Oncol 2009;27(13):2231-7.

Phase III Randomized Placebo-Controlled Trial of ERL, GEM, and BEV in Advanced Pancreatic Cancer

Accrual: 607 (Closed)

Eligibility

Metastatic adenocarcinoma of the pancreas
 Karnofsky PS \geq 60%
 No prior adjuvant radiotherapy
 No prior adjuvant chemotherapy within 6 months



GEM 1000 mg/m² d1 x 7, q8wk followed by d1 x 3, q4wk
 ERL 100 mg daily
 BEV 5 mg/kg, d1,15, 29, 43 x 1 followed by d1,15 (n = 306)

GEM 1000 mg/m² d1 x 7, q8wk followed by d1 x 3, q4wk
 ERL 100 mg daily
 Placebo (PBO) 5 mg/kg, d1,15, 29, 43 x 1 followed by d1,15 (n = 301)

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Introduction

- > In patients with advanced pancreatic cancer, the combination of erlotinib (ERL) plus gemcitabine (GEM) significantly improved survival (*JCO* 2007;25:1960).
- > Phase II trials have shown promising results for bevacizumab (BEV) combinations in patients with advanced pancreatic cancer (*Proc ASCO* 2006;Abstract 4040, *Proc ASCO* 2007;Abstract 4553, Gastrointestinal Cancers Symposium 2008;Abstract 198).
 - Response rates from 11 to 24%
 - Overall survival from 8.1 to 9.8 months
 - Progression-free survival from 3.6 to 5.8 months
- > Current study objective:
 - Assess the efficacy and safety of GEM-ERL-BEV therapy in patients with advanced pancreatic cancer.

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Median Survival (Intent-to-Treat)

	GEM-ERL-BEV n = 306	GEM-ERL-PBO n = 301	p-value
Overall survival			
All patients	7.1 mo	6.0 mo	0.2087
Tumors in tail of pancreas	9.0 mo	5.5 mo	0.0025
CRP >1.4 mg/L	4.8 mo	3.6 mo	0.0009
Baseline LDH >ULN	4.7 mo	3.6 mo	0.0013
Progression-free survival	4.6 mo	3.6 mo	0.0002

CRP = C-reactive protein

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Best Overall Response (Intent-to-Treat)

	GEM-ERL-BEV n = 306	GEM-ERL-PBO n = 301	p-value
Overall response	13.5%	8.6%	0.0574
Complete response	0.7%	—	—
Partial response	12.8%	8.6%	—
Stable disease	49.2%	45.2%	—
Progressive disease	19.9%	24.3%	—

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Conclusions

- > Combination of GEM-ERL-BEV did not significantly improve overall survival, although progression-free survival was significantly increased.
 - Overall survival: 7.1 mo vs 6.0 mo ($p = 0.2087$)
 - Progression-free survival: 4.6 mo vs 3.6 mo ($p = 0.0002$)
- > There were no unexpected side effects associated with the treatments, and the incidence of Grade 3-5 toxicities was similar between the two study arms.
- > It is possible that subgroups of patients with more aggressive disease (ie, elevated CRP or LDH) might benefit more from the GEM-ERL-BEV combination — further trials are needed to explore this possibility.

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Grade III/V Adverse Events

Adverse Event	GEM-ERL-BEV (n = 296)	GEM-ERL-PBO (n = 287)
Neutropenia	21%	17%
Thrombocytopenia	8%	6%
Rash	8%	3%
Anemia	7%	9%
Vomiting	5%	3%
Fatigue	5%	7%
Diarrhea	4%	6%*

* One patient experienced a Grade V adverse event.

Van Cutsem E et al. *J Clin Oncol* 2009;27(13):2231-7.

Faculty Comments

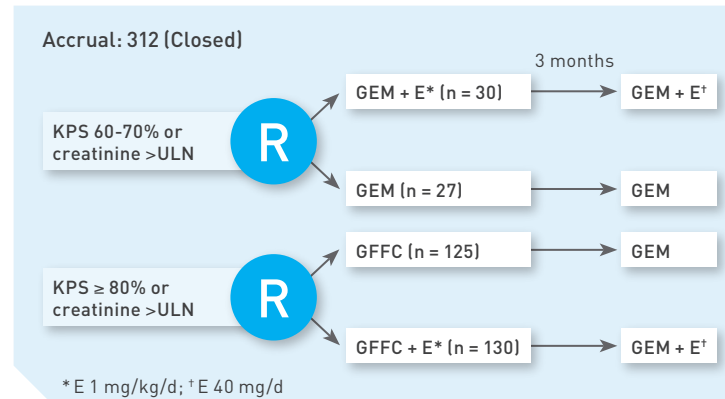
DR ILSON: I did not have positive expectations for this study because the preceding CALGB trial of gemcitabine with or without bevacizumab was a negative study. The addition of bevacizumab to gemcitabine in advanced pancreatic cancer did not improve any endpoint. In this study, the addition of bevacizumab did not result in an improvement in overall survival, although there was a trend for a progression-free survival benefit. This study validates that bevacizumab does not add benefit to gemcitabine-based chemotherapy in the treatment of metastatic pancreatic cancer.

DR ALBERTS: The addition of bevacizumab to gemcitabine and erlotinib did not add any additional benefit, so there is no reason to move this forward either as a standard of care or into a future clinical trial.

A Prospective, Randomized Trial of Chemotherapy with or without the Low Molecular Weight Heparin Enoxaparin in Advanced Pancreatic Cancer: CONKO 004

Riess H et al.
Proc ASCO 2009;LBA4506.

Open-Label Trial of Chemotherapy ± LMWH in Advanced Pancreatic Cancer



Riess H et al. Proc ASCO 2009;LBA4506.

Introduction

- > There is a high incidence of venous thromboembolic events (VTE) in patients with advanced pancreatic cancer (*Eur J Cancer* 2006;42:410).
- > Gemcitabine (GEM) is considered the standard of therapy for pancreatic cancer and combinations of GEM/cisplatin or GEM/5-fluorouracil/folinic acid show favorable outcomes (*BMC Cancer* 2008;8:82).
- > Low molecular weight heparin (LMWH) is an effective anticoagulant used to prevent VTE (*Chest* 2008;133:381S).
- > Current study objective:
 - Assess the efficacy and safety of LMWH enoxaparin (E) with GEM or GEM/5-fluorouracil/folinic acid/cisplatin (GFFC) in patients with advanced pancreatic cancer.

Riess H et al. Proc ASCO 2009;LBA4506.

Venous Thromboembolic Events (Intent-to-Treat)

Events	Observation n = 152	Enoxaparin n = 160
Pulmonary embolism	2	0
Deep vein thrombosis (DVT)		
Proximal leg	9	2
Distal leg	2	0
Upper extremity	3	0
Total events	16	2
Total patients (VTE rate)	15 (9.9%)	2 (1.3%)

Riess H et al. Proc ASCO 2009;LBA4506.

VTE — Risk Reduction (Intent-to-Treat)

Treatment	Absolute risk reduction	Relative risk reduction	p-value
All enoxaparin-containing	8.6%	87%	<0.01
GEM + enoxaparin	12.4%	79%	0.3
GFFC + enoxaparin	6.6%	90%	0.025

Riess H et al. *Proc ASCO* 2009;LBA4506.

Conclusions

- > The addition of enoxaparin to chemotherapy was associated with a reduced number of patients with VTEs.
 - 15 patients (9.9%) in the observation group vs 2 (1.3%) in the enoxaparin group
- > In the GFFC group, there was a 90% relative risk reduction ($p = 0.025$) in VTE among those treated with enoxaparin compared with those assigned to observation only.
- > There were no significant differences between the observation arm and the enoxaparin arm regarding major bleeding events.
 - At 30 weeks, the rate of bleeding events was 9.9% vs 6.3% ($p = 0.6$).

Riess H et al. *Proc ASCO* 2009;LBA4506.

VTE and Major Bleeding Rates (Median Follow-Up 30.4 Weeks)

Events	Observation n = 152	Enoxaparin n = 160	p-value
VTE	15.5%	5.0%	<0.05
Bleeding	9.9%*	6.3%	0.6

*Three lethal bleedings — two tumor-associated lethal GI-bleeding in GFFC-treated patients and one lethal esophageal hemorrhage in a GEM-treated patient

Riess H et al. *Proc ASCO* 2009;LBA4506.

Faculty Comments

DR ILSON: In pancreatic cancer the risk of developing thrombophlebitis can be as high as 10 to 20 percent, and there has always been a debate about whether patients would benefit from prophylactic anticoagulation. This study did show a reduction in the rate of deep vein thrombosis (DVT) from 9 to 10 percent to 3 to 4 percent with enoxaparin, and only one pulmonary embolism was observed on the study. Treatment with enoxaparin did not appear to affect overall survival or quality of life. Essentially we would treat 90 patients who would receive no benefit to prevent a DVT in 6 to 7 percent of patients, so I believe it's difficult to argue that this study should change standard practice. I don't believe we should be subjecting patients to daily injections when they have a limited life span to prevent a nonlife-threatening complication and not improve quality of life or survival.

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

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

ABC-02: A Phase III Multicenter Study (N = 410*)

Eligibility

Histologically/cytologically verified locally advanced or metastatic cholangiocarcinoma, gallbladder or ampullary cancer
 Life expectancy > 3 mo
 Total bilirubin ≤ 1.5 x ULN,
 Liver enzymes ≤ 5 x ULN



Gem 1,000 mg/m² d1, 8, 15
 q28 days for 24 weeks
 (6 cycles) (n = 206)

Gem 1,000 mg/m² + Cis 25
 mg/m² d1, 8 q21 days for
 24 weeks (8 cycles) (n = 204)

* Includes 86 patients from ABC-01

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

Introduction

- > Biliary tract cancers (BTC: cholangiocarcinoma, gall bladder cancer, ampullary cancer) are rare, lethal cancers with rising incidence for which no standard of care exists.
- > Phase II trial ABC-01 demonstrated that cisplatin (Cis) and gemcitabine (Gem) was superior to Gem alone (*Br J Cancer* 2009;101:621).
 - 6-mo progression-free survival (PFS): 57.1% vs 47.7%
- > Current study objective:
 - Prospectively evaluate the activity and safety of Gem and Cis vs Gem in patients with locally advanced or metastatic BTC.

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

Disease Progression and Survival (Intent-to-Treat)

Clinical Variable	Number of Patients			
Tumor progression ¹	362 (278 deaths)			
Survival	Gem (n = 206)	Cis + Gem (n = 204)	HR (95% CI)	p-value
Median overall survival (OS)	8.1 mo	11.7 mo	0.64 (0.52-0.80)	<0.001
Median PFS	5.0 mo	8.0 mo	0.63 (0.51-0.77)	<0.001

HR = hazard ratio

¹The final analysis was event driven and performed 8 months after the last patient was enrolled.

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

Gem and Cis vs Gem Hazard Ratio (Intent-to-Treat)

Subgroup	Number of Patients	HR* (95% CI)
ABC trial group		
01	86	0.65 (0.42-1.01)
02	324	0.64 (0.50-0.83)
Extent of disease		
Locally advanced	104	0.47 (0.29-0.74)
Metastatic	306	0.74 (0.57-0.95)
Previous therapy		
No	100	0.65 (0.41-1.01)
Yes	310	0.64 (0.49-0.82)
All patients	410	0.64 (0.52-0.80)

* Hazard ratio of <1 favors Gem and Cis

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

Summary and Conclusions

- > Gem and Cis significantly improves OS and PFS compared to Gem alone.
 - Median OS: 11.7 mo vs 8.1 mo
 - Reduced risk of death by 36% (HR = 0.64, $p < 0.001$)
 - Median PFS: 8 mo vs 5 mo
 - Reduced risk of disease progression by 37% (HR = 0.63, $p < 0.001$)
- > Adverse events were similar in the two treatment arms.
 - Liver function was significantly worse in patients receiving Gem compared to Gem and Cis. Authors feel this probably reflects better control of disease in the combined therapy group.
- > Cis + Gem is an appropriate option for the treatment of patients with advanced biliary cancer.

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

Select Grade 3/4 Adverse Events

Adverse Event	Gem (n = 199)	Cis + Gem (n = 198)	p-value
Any Grade 3/4 event	68.8%	70.7%	0.69
Fatigue	16.6%	18.7%	0.58
Leukopenia	9.5%	15.7%	0.07
Neutropenia	16.6%	25.3%	0.03
Thrombocytopenia	6.5%	8.6%	0.44
Infection	19.1%	18.2%	0.82
Any abnormal liver function	27.1%	16.7%	0.01

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

Faculty Comments

DR AJANI: This is a good study in an uncommon tumor, for which few, if any, Phase III studies are done, and it demonstrates that adding cisplatin to gemcitabine improves survival. It is game changing in that patients with advanced extrahepatic biliary cancers should receive gemcitabine/cisplatin or, perhaps, gemcitabine/oxaliplatin.

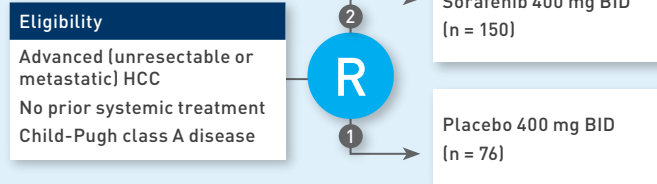
DR ALBERTS: This was a landmark study. Until this study was performed, there had never been a completed Phase III trial in biliary tract cancers. This study not only has changed how we treat patients, but also shows that in a rare disease, such as biliary tract cancers, with a concerted effort it is possible to conduct a randomized Phase III trial and have meaningful outcomes that do change the standard of care.

Efficacy and Safety of Sorafenib in Asian-Pacific Patients with Advanced Hepatocellular Carcinoma: A Double-Blind, Placebo-Controlled Phase III Trial

Cheng A-L et al.
Lancet Oncol 2009;10(1):25-34.

Phase III, Placebo-Controlled Trial of Sorafenib for Advanced HCC in Asian-Pacific Patients

Protocol ID: NCT00492752



Patients stratified by the presence of macroscopic vascular lesion and/or extrahepatic spread, ECOG performance score (PS) and geographical region (China, Taiwan or South Korea)

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Introduction

- > The Asia-Pacific region is a high-risk population for the development of hepatocellular carcinoma (HCC).
 - Greater than 75% of HCC cases worldwide occur in the Asia-Pacific region (*Int J Cancer* 2001;94:290).
 - Hepatitis virus B infection is a significant risk factor for HCC in this region (*Lancet* 2003;362:1907).
- > Phase III, placebo-controlled SHARP trial demonstrated sorafenib is efficacious in patients from North America and Europe with advanced HCC (*NEJM* 2008;359:378).
 - Median overall survival: 10.7 mo vs 7.9 mo ($p < 0.001$)
- > Current study objective:
 - Assess the safety and efficacy of sorafenib in patients from the Asia-Pacific region with advanced HCC.

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Baseline Patient Characteristics

Patient Characteristic	Sorafenib (n = 150)	Placebo (n = 76)
ECOG PS		
0	25.3%	27.6%
1	69.3%	67.1%
2	5.3%	5.3%
Extrahepatic spread		
No	31.3%	31.6%
Yes	68.7%	68.4%
Hepatitis virus status		
HBV infection	70.7%	77.6%
HCV infection	10.7%	3.9%

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Efficacy Results (Intent-to-Treat)

	Sorafenib (n = 150)	Placebo (n = 76)	HR (p-value)
Median overall survival (OS)	6.5 mo	4.2 mo	0.68 (0.014)
Median time-to-progression (TTP)	2.8 mo	1.4 mo	0.57 (0.0005)
Complete response (CR)	0%	0%	—
Partial response (PR)	3.3%	1.3%	—
Stable disease (SD)	54.0%	27.6%	—
Disease control rate (DCR)*	35.3%	15.8%	—

* Defined as proportion of patients with CR, PR or SD maintained for ≥4 weeks; HR = hazard ratio

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Summary and Conclusions

- > Sorafenib is effective for the treatment of advanced HCC in patients from the Asia Pacific region.
 - OS, TTP and DCR were significantly prolonged with sorafenib.
 - Multivariate analyses suggested that sorafenib provided benefit to all subpopulations analyzed (data not shown).
- > Overall efficacy results of sorafenib were comparable with those reported in the SHARP trial.
 - Survival HR: 0.68 vs 0.69 in SHARP trial
- > Sorafenib was well-tolerated with predominately Grade 1/2 adverse events reported.

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Select Adverse Events (Safety Population)

Drug-Related Adverse Event*	Sorafenib (n = 149)		Placebo (n = 75)	
	All	Grade 3/4	All	Grade 3/4
Hand-foot skin reaction	45.0%	10.7%	2.7%	0%
Diarrhea	25.5%	6.0%	5.3%	0%
Alopecia	24.8%	—	1.3%	—
Fatigue	20.1%	3.4%	8.0%	1.3%
Rash/desquamation	20.1%	0.7%	6.7%	0%
Hypertension	18.8%	2.0%	1.3%	0%

* Observed in ≥10% of patients in any study group

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Faculty Comments

DR AJANI: Although the magnitude of benefit is less than observed in the SHARP trial, this is the second randomized study to demonstrate the benefit of sorafenib in patients with hepatocellular carcinoma. In contrast to SHARP, this study was with an Asian patient population who had much more advanced disease. I believe there is a difference in the biology of hepatocellular carcinoma, based on the antecedent liver disease. Differences exist in terms of the type of hepatitis, alcohol-related issues and obesity, which play out in the aggressiveness of the disease. This study confirms not only that sorafenib is a solid drug in hepatocellular carcinoma, but also that it works across the spectrum of the disease, whether there is a different biology or different carcinogenic drivers.

PRIORITY 2 PUBLICATIONS/PRESENTATIONS (RECOMMENDED)

COLORECTAL CANCER

- 1 Jackson McCleary NA et al. **Impact of older age on the efficacy of newer adjuvant therapies in >12,500 patients (pts) with stage II/III colon cancer: Findings from the ACCENT Database.** *Proc ASCO* 2009;Abstract 4010.
Patients with Stage II/III colon cancer who were older than 70 (n = 2,170) did not benefit from combination and/or oral adjuvant fluoropyrimidine therapy in terms of overall survival (OS), disease-free survival (DFS) or time to recurrence compared to patients younger than 70 (n = 10,499).
- 2 Ychou M et al. **A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer.** *Ann Oncol* 2009;20(12):1964-70.
In a Phase III trial (N = 306), adjuvant FOLFIRI in patients with completely resectable liver-limited metastases from colorectal cancer did not result in DFS improvements compared to 5-FU/leucovorin.
- 3 Kim GP et al. **Phase III noninferiority trial comparing irinotecan with oxaliplatin, fluorouracil, and leucovorin in patients with advanced colorectal carcinoma previously treated with fluorouracil: N9841.** *J Clin Oncol* 2009;27(17):2848-54.
In a Phase III trial (N = 491) for patients with metastatic colorectal cancer (mCRC) who experienced treatment failure on front-line 5-FU therapy, OS was not significantly different with second-line irinotecan than with FOLFOX4, although FOLFOX4 produced a higher response rate and longer time to disease progression.
- 4 Sargent DJ et al. **Pooled safety and efficacy analysis examining the effect of performance status on outcomes in nine first-line treatment trials using individual data from patients with metastatic colorectal cancer.** *J Clin Oncol* 2009;27(12):1948-55.
Pooled analysis (N = 6,286) from nine clinical trials of first-line therapy for mCRC revealed that patients with performance status (PS) 2 derived similar clinical benefit to patients with PS 0 or 1 but with increased risk of toxicities and 12 percent 60-day mortality.
- 5 Tol J et al. **Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer.** *N Engl J Med* 2009;360(6):563-72.
In a Phase III trial (N = 755) for patients with untreated mCRC, the addition of cetuximab to capecitabine, oxaliplatin and bevacizumab resulted in significantly shorter progression-free survival (PFS) and inferior quality of life. K-ras mutation was a predictor of worse outcome in the cetuximab group.
- 6 Bokemeyer C et al. **Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer.** *J Clin Oncol* 2009;27(5):663-71.
In a randomized, multicenter Phase II trial (N = 168), the addition of cetuximab to first-line FOLFOX4 resulted in a significant increase in overall response rate and a lower risk of disease progression among patients with K-ras wild-type mCRC.
- 7 Kopetz S et al. **Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy.** *J Clin Oncol* 2009;27(22):3677-83.
In a retrospective review of patients with newly diagnosed mCRC at two academic centers between 1990 and 2006 (N = 2,470), profound improvements in outcome were associated with hepatic resection in selected patients and advances in medical therapy.

- 8 Peeters M et al. **Randomized phase III study of panitumumab (pmab) with FOLFIRI versus FOLFIRI alone as second-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC): Patient-reported outcomes (PRO).** Gastrointestinal Cancers Symposium 2010;Abstract 282.
In a Phase III trial (N = 1,186), the addition of panitumumab to second-line FOLFIRI improved PFS among patients with K-ras wild-type mCRC.
- 9 Siena S et al. **Randomized phase III study of panitumumab (pmab) with FOLFOX4 compared to FOLFOX4 alone as first-line treatment (tx) for metastatic colorectal cancer (mCRC): PRIME trial.** Gastrointestinal Cancers Symposium 2010;Abstract 283.
In a Phase III trial (N = 1,183), the addition of panitumumab to first-line FOLFOX4 improved PFS among patients with K-ras wild-type mCRC, but the PFS with panitumumab was inferior to that with FOLFOX4 alone among patients with K-ras mutations.
- 10 Tejpar S et al. **Microsatellite instability (MSI) in stage II and III colon cancer treated with 5FU-LV or 5FU-LV and irinotecan (PETACC 3-EORTC 40993-SAKK 60/00 trial).** Proc ASCO 2009;Abstract 4001.
Microsatellite instability is a strong prognostic factor for recurrence-free survival and OS among patients with Stage II or III colon cancer.
- 11 Laurent-Puig P et al. **Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer.** J Clin Oncol 2009;27(35):5924-30.
In a retrospective analysis (N = 173), B-raf status, EGFR amplification and cytoplasmic expression of PTEN were associated with outcome among patients with K-ras wild-type mCRC treated with cetuximab-based therapy.
- 12 Loupakis F et al. **PTEN expression and KRAS mutations on primary tumors and metastases in the prediction of benefit from cetuximab plus irinotecan for patients with metastatic colorectal cancer.** J Clin Oncol 2009;27(16):2622-9.
A retrospective evaluation (N = 102) demonstrated that PTEN loss in metastases may be predictive of resistance to cetuximab/irinotecan. The combination of PTEN immunohistochemistry (IHC) and K-ras mutation analyses may identify a subgroup of patients with mCRC who have a higher chance of benefiting from EGFR inhibition.
- 13 Van Cutsem E et al. **Cetuximab plus FOLFIRI in the treatment of metastatic colorectal cancer (mCRC): The influence of KRAS and BRAF biomarkers on outcome: Updated data from the CRYSTAL trial.** Gastrointestinal Cancers Symposium 2010;Abstract 281.
Patients with K-ras wild-type mCRC had superior overall response rates, PFS and OS with the addition of cetuximab to first-line FOLFIRI in the Phase III CRYSTAL trial.

GASTRIC AND ESOPHAGOGASTRIC CANCER

- 14 Stahl M et al. **Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction.** J Clin Oncol 2009;27(6):851-6.
Although closed early because of slow accrual, this Phase III study (N = 126) suggested a strong trend for a survival advantage with preoperative chemoradiation therapy compared to chemotherapy for patients with locally advanced adenocarcinoma of the esophagogastric junction.
- 15 Boku N et al; Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group. **Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: A randomized phase 3 study.** Lancet Oncol 2009;10(11):1063-9.
In a Phase III study (N = 704), oral S-1 was noninferior to intravenous fluorouracil and irinotecan/cisplatin was not superior to fluorouracil for Asian patients with unresectable or recurrent gastric cancer.

- 16** Starling N et al. **Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: A report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group.** *J Clin Oncol* 2009;27(23):3786-93.

In a prospective, exploratory analysis of thromboembolic events (TEs) in a randomized, controlled trial (N = 964) of four triplet chemotherapy regimens for patients with advanced gastroesophageal cancer, TEs were more frequent with platinum-containing regimens and OS was worse among patients who experienced TEs during treatment.

PANCREATIC CANCER

- 17** Le Scodan R et al. **Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: Feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review.** *Ann Oncol* 2009;20(8):1387-96.

A Phase II study (N = 41) demonstrated that preoperative concurrent chemoradiation therapy in patients with resectable pancreatic cancer (PC) is feasible, does not prevent successful surgery and results in major histopathological response in 50 percent of patients and a high R0 resection rate.

- 18** Kulke MH et al. **Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic pancreatic cancer: CALGB 89904.** *J Clin Oncol* 2009;27(33):5506-12.

In a randomized, multi-institutional Phase II study (N = 259), gemcitabine/cisplatin, fixed-dose rate gemcitabine, gemcitabine/docetaxel and gemcitabine/irinotecan resulted in similar overall response rates and OS among patients with metastatic PC.

- 19** Colucci G et al. **Randomized Phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: The GIP-1 Study.** *J Clin Oncol* 2010;28(10):1645-51.

In a Phase III study (N = 400), the addition of weekly cisplatin to gemcitabine failed to demonstrate any improvement as first-line therapy for advanced PC.

HEPATOCELLULAR CARCINOMA

- 20** Pacella CM et al. **Long-term outcome of cirrhotic patients with early hepatocellular carcinoma treated with ultrasound-guided percutaneous laser ablation: A retrospective analysis.** *J Clin Oncol* 2009;27(16):2615-21.

Retrospective evaluation of treatment and survival parameters of cirrhotic patients with nonsurgical early hepatocellular carcinoma (HCC) (N = 432) who underwent percutaneous laser ablation (PLA) confirms that complete ablation results in improved survival and that ideal candidates for PLA are younger with normal serum albumin levels and tumor sizes less than two centimeters.

- 21** Chan SL et al. **New utility of an old marker: Serial alpha-fetoprotein measurement in predicting radiologic response and survival of patients with hepatocellular carcinoma undergoing systemic chemotherapy.** *J Clin Oncol* 2009;27(3):446-52.

Alpha-fetoprotein (AFP) responders had a better survival than nonresponders, and AFP response was strongly correlated with radiologic response in patients with HCC treated with chemotherapy on a Phase III study.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The ESPAC-3 (v2) trial compared the use of adjuvant gemcitabine to that of _____ for patients with resected pancreatic cancer.
 - a. Observation
 - b. Capecitabine
 - c. 5-Fluorouracil/folinic acid
 - d. None of the above
2. In the Phase III trial NO16968, XELOX improved disease-free survival for patients older than 65 but not for patients older than 70 when compared to bolus 5-FU/LV.
 - a. True
 - b. False
3. In the NSABP-C-08 trial, the three-year disease-free survival for patients with Stage II or III colon cancer who received bevacizumab in addition to mFOLFOX was _____ compared to that of patients who received mFOLFOX alone.
 - a. Significantly improved
 - b. Significantly decreased
 - c. Similar
4. A Phase III study by Valle and colleagues that evaluated the addition of cisplatin to gemcitabine in patients with biliary tract cancer found significant improvements in _____.
 - a. Progression-free survival
 - b. Overall survival
 - c. Both a and b
5. A Phase III study of Asian-Pacific patients with advanced hepatocellular carcinoma found that the use of sorafenib was associated with a median overall survival of _____ months.
 - a. 6.5
 - b. Three
 - c. 9.3
 - d. 15
6. In the ToGA trial for patients with HER2-positive advanced gastric cancer, the addition of trastuzumab to standard chemotherapy reduced the risk of death by _____.
 - a. 15 percent
 - b. 26 percent
 - c. 40 percent
 - d. 55 percent
7. In the QUASAR validation study, independent predictors of recurrence for patients with Stage II colon cancer include _____.
 - a. Recurrence Score
 - b. T stage
 - c. Mismatch repair (MMR) deficiency
 - d. All of the above
8. A study by Poultsides and colleagues has shown that primary combination chemotherapy with or without bevacizumab in the absence of initial surgery was appropriate for patients with an intact primary tumor and synchronous metastatic colorectal cancer.
 - a. True
 - b. False
9. A Phase III study for patients with advanced pancreatic cancer has shown that the addition of capecitabine to gemcitabine improved the median PFS by ___ months.
 - a. 1.5
 - b. Four
 - c. 7.2
 - d. None of the above
10. According to a trial by Van Cutsem and colleagues, the benefits associated with the addition of cetuximab to initial chemotherapy in patients with metastatic colorectal cancer are restricted to patients with K-ras wild-type tumors.
 - a. True
 - b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

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. **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
Oxaliplatin combined with fluoropyrimidine-based chemoradiation therapy for the management of locally advanced rectal cancer	4 3 2 1	4 3 2 1
Efficacy of adjuvant mFOLFOX6 combined with bevacizumab for early colon cancer	4 3 2 1	4 3 2 1
Efficacy and tolerability of fixed-dose rate gemcitabine with or without oxaliplatin versus standard gemcitabine for advanced pancreatic cancer	4 3 2 1	4 3 2 1
Efficacy of trastuzumab for the treatment of HER2-positive advanced gastric cancer	4 3 2 1	4 3 2 1
Efficacy and safety of cisplatin combined with gemcitabine for the treatment of advanced biliary tract cancer	4 3 2 1	4 3 2 1
Combination chemotherapy with or without bevacizumab versus surgery as initial treatment for synchronous metastatic colorectal cancer	4 3 2 1	4 3 2 1
Efficacy and safety of sorafenib for the treatment of advanced hepatocellular 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:

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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 select GI cancers originating within (CRC) and outside of (non-CRC) the colon and rectum..... 4 3 2 1 N/M N/A
- Employ biomarkers and novel genomic signatures in counseling patients with Stage II colon cancer about the long-term risk of disease recurrence. 4 3 2 1 N/M N/A
- Communicate the benefits and risks of anti-VEGF and anti-EGFR biologic therapy to patients with metastatic CRC..... 4 3 2 1 N/M N/A
- Evaluate the role of potential radiosensitizers in the multimodality management of locally advanced rectal cancer. 4 3 2 1 N/M N/A
- Use clinical and molecular biomarkers to select optimal local and systemic treatment strategies for patients with gastric or gastroesophageal cancer. 4 3 2 1 N/M N/A
- Effectively integrate the evidence-based use of chemotherapy and molecular-targeted agents into the individualized management of advanced pancreatic cancer. 4 3 2 1 N/M N/A
- Communicate the benefits and risks of existing and emerging systemic and targeted treatments for patients with advanced hepatocellular or biliary tract cancer. 4 3 2 1 N/M N/A

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

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Gastrointestinal Cancers: 2009-2010

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Gastrointestinal Cancer™

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