New Developments in GI Malignancies

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Developments

I. New techniques and procedures
   - EUS -- NOTES
   - Robotics -- SIRT

II. New approaches to older procedures
   - Staged hepatectomy
   - Portal vein embolization

III. Evolution of philosophy
   - Expanded indications for hepatectomy
   - The intact primary
I. Technical Advancements

Endoscopic Ultrasound

- Diagnosis: good for pancreas
- T stage: esophagus, stomach, rectum
- N stage: able to biopsy
- Cancer therapy
## Gene Mediated Cytotoxic Immunotherapy for Pancreatic Adenocarcinoma

- **Phase I clinical trial**
  - Arm A: resectable
  - Arm B: locally advanced
- **Intratumoral injection of HSV-thymidine kinase vector followed by anti-herpetic prodrug in conjunction with:**
  - Arm A: surgery
  - Arm B: chemoradiation

## Gene Mediated Cytotoxic Immunotherapy for Pancreatic Adenocarcinoma

- Diagnosis confirmed by EUS
- Virus injected by EUS into tumor followed by 2 weeks of Valacyclovir
- Arm A: surgery with repeat injection of virus into resection bed
- Arm B: repeat intratumoral injection during chemoradiation
Gene Mediated Cytotoxic Immunotherapy for Pancreatic Adenocarcinoma

- 24 patients treated
- Toxicities
  - Grade 3: 5 patients (pain, azotemia)
  - Grade 4: none
- 2 patients on Arm A alive at nearly 2 years
- 6 patients on Arm B alive at 5-34 months

NOTES

- Natural Orifice Transluminal Endoscopic Surgery
- No skin incisions
- Useful for identifying occult metastases or obtaining tissue from suspicious lesions
Minimally Invasive Surgery

Preoperative Considerations

- Site of tumor
- Tumor size/invasion
- Obesity
- Previous surgery
- Must be able to find tumor/polyp
- Possibility of converting to open
Data

What difference does it make?

Laparoscopic Colectomy

- Return of bowel function 1-2 days sooner
- Less need for narcotics
- Quicker return of lung function
- Length of stay ~1 day less
- May be influenced by biased expectations
Laparoscopic Colectomy

- Return to work and quality of life
  - No statistical difference
  - Anecdotally improved
- Cost
  - Equipment costs and OR time are greater
  - May be balanced by shorter hospital stay
- Operative Time – 30-60 minutes longer

COST Trial
Clinical Outcomes of Surgical Therapy Study Group

- 872 patients with colonic adenocarcinoma
- Recurrence
  - 16% laparoscopic
  - 18% open
- Survival
  - 86% laparoscopic
  - 85% open
- Post-operative stay
  - 5 days laparoscopic
  - 6 days open

# COST Trial
Clinical Outcomes of Surgical Therapy Study Group

- 5 year data
- Disease-free 5 year survival
  - 68.4% Open
  - 69.2% Laparoscopic
- Overall survival
  - 74.6% Open
  - 76.4% Laparoscopic
- Recurrence
  - 21.8% Open
  - 19.4% Laparoscopic

Ann Surg 2007;246:655-64
Robotic Surgery
No Surgery?
Selective Internal Radiotherapy (SIRT)

- Radiolabelled particles ($^{90}$Y)
  - TheraSpheres® - MDS Nordion (HCC)
  - SIRSpheres – SIRTex (CRC)
- Injected through hepatic artery
- High dose radiation to tumor
- Low dose radiation to liver
- $\beta$ particle emission
  - 2-3mm of penetration

Microspheres
Delivery of Microspheres

Radiation Dose Deposited
II. New Approaches

2-Stage Hepatectomy

- 16 patients with bilobar disease
- Major resection at 1\textsuperscript{st} stage in 8 (no deaths)
- Chemotherapy pre- and post-operative
- 3 patients progressed (1 intra- and 2 extra-)
- Major resection at 2\textsuperscript{nd} stage in 8 (2 deaths)
- 4 liver recurrences (3\textsuperscript{rd} resection in 3)
- Median survival 31 months from 2\textsuperscript{nd} and 44 months from 1\textsuperscript{st} resections

2-Stage Hepatectomy

- 33 patients with “unresectable” CRCM
- 1st stage: clearance of left-sided disease
- Right PVE ± segment IV
- 2nd stage (5-8 weeks): major hepatectomy
- No deaths
- 2 stages completed in 28 (progression in 5)
- 3-yr survival from 2nd stage 54%, median not reached


Portal Vein Embolization

- First described in 1990
- Occlusion of blood flow to all tumor-bearing liver
- Hypertrophy of future liver remnant (FLR)
- Atrophy of embolized segments
- Recommended if FLR <20% in healthy liver (<30% if heavily pretreated)
Preoperative Volumetry

- 3-D reconstruction of CT images

Portal Vein Embolization
Portal Vein Embolization

<table>
<thead>
<tr>
<th>Image 1</th>
<th>Image 2</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Portal Vein Embolization Image 1" /></td>
<td><img src="image2.png" alt="Portal Vein Embolization Image 2" /></td>
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</tbody>
</table>

Portal Vein Embolization

<table>
<thead>
<tr>
<th>Image 3</th>
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<td><img src="image3.png" alt="Portal Vein Embolization Image 3" /></td>
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Portal Vein Embolization

Radiofrequency Ablation
**RFA**

- Limited damage to surrounding liver
- Can be done in OR or radiology
- Limited by tumor size
- User-dependent
- Higher local recurrence rates (vs. resection)
- Efficacy: open > laparoscopic > percutaneous
Role of RFA

- Adjunct to resection
- Few, small unresectable tumors
- Unfit patient

Microwave Ablation
III. Philosophic Evolution

What does “operable” mean?

• Defined in relative terms
  – Based on expertise, resources, attitude
• “High-risk surgery”
  – Knowledge of internal liver anatomy
  – Operative techniques
  – Mortality 20% (1980s) → <5% (2000s)
• “Poor outcomes”
  – Better imaging (spiral CT, MRI, PET, I/O U/S)
  – Better patient selection
  – Better chemotherapy
**Traditional Dogma**

- Definitions of inoperable disease
  - Bilobar disease
  - >4 lesions
  - Extrahepatic disease
  - Lesion >5 cm
  - Synchronous disease

**Debunking Dogma**
## Bilobar Disease

- **Tomlinson et al. 2007**
  - Actual 10+ year survivors (N=102)
  - 25% had bilateral disease resected
    - 29% for 2-5 and 5-10 year survivors (P=NS)
- **Bolton et al. 2000**
  - Simple (N=121) vs complex (N=44) resections
  - 98% of complex had bilobar disease (vs 0%)
  - Similar perioperative mortality (9% vs. 5%)
  - Similar survival (36% 5-yr, median 43 months)

## Bilobar Disease

- **Fong et al. 1999**
  - 1001 resections
  - 40% bilobar disease
  - 5-yr survival 29% vs. 38%
  - Not predictive by multivariate analysis (p=0.4)
Traditional Dogma

- Definitions of Unresectability
  - Bilobar disease
  - >4 lesions
  - Extrahepatic disease
  - Lesion >5 cm
  - Synchronous disease
Tumor Number

- Pawlik et al. 2006
  - 159 patients with ≥4 lesions
  - Median 5 lesions (4 – 14)
  - Resection ± RFA in 94%
  - Overall survival: median 62 months, 5-yr 51%
- Kornprat et al. 2007
  - 98 patients with ≥4 lesions
  - Median 5 lesions (4 – 15)
  - Overall survival: median 41 months, 5-yr 33%

Traditional Dogma

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Extrahepatic Disease

• Elias et al. 2005
  – 308 resections, 84 (27%) with EHD
  – EHD not predictive of survival
    • 5-yr survival 34% vs. 28%
• Kornprat et al. 2007
  – Multiple liver mets, 18% with EHD
  – Predictor of poor outcome
  – Median survival 32 months
### SSO/AHPBA/SSAT Consensus

“The presence of extrahepatic disease should no longer be considered an absolute contraindication to hepatic resection provided .... complete resection of both intra- and extrahepatic disease is feasible.”

### Traditional Dogma

- **Definitions of Unresectability**
  - Bilobar disease
  - $\geq 4$ lesions
  - Extrahepatic disease
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  - Synchronous disease
Traditional Dogma

- Definitions of Unresectability
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The Modern Era of Liver Surgery for CRC Metastases
### New Rules

- Complete resection a must
  - Negative liver margins
  - All extrahepatic disease
- Preservation of 2 contiguous segments
- Preservation of vascular inflow, outflow, and biliary drainage
- Preservation of adequate future liver remnant (>20% in healthy liver)

### Asymptomatic Colorectal Primary
Traditional Dogma

- Must resect primary
  - Risk of obstruction
  - Risk of bleeding
  - Nidus for more metastases

Unresected Primary CRC

- 233 patients with stage IV CRC and intact primary tumor
- All received modern chemotherapy
- 89% never required intervention
- 7% required emergency surgery
- 4% required other intervention (eg stent)

Poultsides et al. JCO 2009
Updates On Gastrointestinal Malignancies

Tanios Bekaii-Saab, MD
Medical Director, Gastro-intestinal Cancer Program
Division of Medical Oncology
Department of Pharmacology
OSUCCC – Arthur James Cancer Hospital

Gastrointestinal Malignancies

- Lung (1.4 million deaths)
- Stomach (740 000 deaths)
- Liver (700 000 deaths)
- Colorectal (610 000 deaths)
- Breast (460 000 deaths)

http://www.who.int factsheet N°297 February 2011

Courtesy of Florian Lordick, MD
Gastric and Gastro-Esophageal Cancers

Introduction: Epidemiology

- 35,000 new cases a year with 25,000 deaths
- 3 entities:
  - Squamous cell carcinoma of the esophagus
  - Adenocarcinoma of the distal esophagus, GE junction and proximal stomach
  - Adenocarcinoma of the distal stomach
- Esophageal cancer is the most rapidly growing cancer in the USA and is affecting middle aged Caucasian males mostly. Its incidence rate is 6 times, and its mortality 7 times what it was in the 1970s.
Early Stage Disease

CLASSIC study design

- Surgically (D2) resected Stage II, IIIA, or IIIB GC, 6 weeks prior to randomization
- No prior chemotherapy or radiotherapy
- n=1035

RANDOMIZATION

n=520
- 8 cycles of XELOX (6 months)
  - Capecitabine: 1,000mg/m² bid, d1–14, q3w
  - Oxaliplatin: 130mg/m², d1, q3w

n=515
- Observation: No adjuvant therapy

- Primary endpoint: 3-year DFS
- Secondary endpoints: overall survival and safety profile

1Stratified by stage and country with age, sex, and nodal status as covariates
2GASTRIC project: 3-year DFS and 5-year overall survival are strongly associated, Burzykowski et al. ASCO 2009
GASTRIC Group Meta-analysis

Figure 3. Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years

No. at risk
Any chemotherapy 1924 1699 1395 1217 1060 929 709 526 390 297 243
Surgery alone 1897 1598 1300 1092 952 782 583 402 267 172 138

6% difference at 5 years
HR = 0.82; p < 0.001

The Gastrointestinal Group. JAMA 2010; 303: 1729-1737
Postoperative adjuvant chemoradiation for gastric or GE junction adenocarcinoma using ECF before and after 5-FU/radiotherapy compared to bolus 5-FU/LV before and after 5-FU/radiotherapy:

Intergroup trial CALGB 80101

CS Fuchs, JE Tepper, D Niedzwiecki, D Hollis, HJ Mamon, RS Swanson, DG Haller, T Dragovich, SR Alberts, G Bjarnson, CG Willett, PC Enzinger, RM Goldberg, AP Venook, RJ Mayer

CALGB 80101 – Overall Survival

Fuchs et al, ASCO 2011
Adjuvant Gastric Cancer in 2011

Europe
Perioperative CTx
(Epirubicin)-Platin-5FU

Asia
Adjuvant CTx
S-1 or Capox

N America
Adjuvant R-CTx
45 Gy + 5FU/LV

Illustrated are the differences between a D1 lymphadenectomy and a D2 lymphadenectomy for gastric cancer. (a) A D1 lymphadenectomy is accomplished by removing the perigastric lymph nodes with the resection specimen; these nodes include those along the right and left cardiac (1, 2), those along the lesser curvature (3), those along the greater curvature (4), the suprapyloric nodes (5), and the infrapyloric nodes (6). (b) A D2 lymphadenectomy involves a more radical resection specimen, which includes nodes along the left gastric artery (7), the common hepatic artery (8), the celiac artery (9), the splenic hilum (10), the splenic artery (11), the hepatoduodenal ligament (12), the posterior pancreas (13), the root of the mesentery (14), the transverse mesocolon (15), and the aorta (16).
### D2 Resection rates across studies

**Classic**
- D2 Resection 100%
- Median 42 lymph nodes examined (range 9-127)

<table>
<thead>
<tr>
<th>Study</th>
<th>D2 Resection</th>
<th>D1 Resection</th>
<th>D0 Resection</th>
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</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>UK MAGIC Cunningham et al. 2006</td>
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<tr>
<td>D2-Resection</td>
<td>41%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1-Resection</td>
<td>19%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Resections</td>
<td>40%</td>
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What have we learned about localized gastric/GE cancers?

• Surgical approach determines the optimal adjuvant treatment strategy
  – Asia: Radical resection (D2)
    • Adjuvant chemotherapy
  – U.S.: Sub-radical resection (≤ D 1)
    • Adjuvant chemoradiation
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    - Adjuvant chemoradiation
- Awaiting data on adjuvant CRT vs. chemotherapy
  - ARTIST (capecitabine/cisplatin compared with resected gastric cancer with D2 nodal dissection trial - when surgery is controlled, is adjuvant radiation necessary?)

What have we learned about localized gastric/GE cancers?

- Is a neoadjuvant approach feasible and better?
  - Neoadjuvant much more likely to receive therapy (SAKK)
  - EORTC 40954 – 3 months neoadjuvant chemo trends towards better
  - No randomized neoadjuvant CRT gastric studies reported yet
    - Attempts have been aborted secondary to low accrual
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    • Attempts have been aborted secondary to low accrual

• Data with targeted therapies, more aggressive chemotherapy
  – MAGIC 2 – ECF +/- bevacizumab

Gastro-esophageal Cancers: Advanced disease

• Marginal differences between doublets and triplets that perhaps do not justify the differences in toxicities.

• Trastuzumab should be considered as an option added to a platinum and 5FU in the presence of Her-2 overexpression
  – LOGIC Trial
    • Rand Ph III, HER 2+ gastric cancer
    • Capecitabine + oxaliplatin +/- lapatinib

• 2nd line Irinotecan has a proven benefit in advanced gastric cancer and should be offered to patients with a PS 0-2 (Park et al Abs 4004, ASCO 2011 and Thuss-Patience P. Eur J Cancer; 2011)
Gastro-esophageal Cancers: Advanced disease

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GIST
SSGXVIII: Study design

An open-label Phase III study

Random assignment 1:1

Stratification:
1) R0 resection, no tumor rupture
2) R1 resection or tumor rupture

- Imatinib for 12 months
- Follow-up
- Imatinib for 36 months
- Follow-up

SSGXIII: Key inclusion criteria

- Histologically confirmed GIST, KIT-positive
- High risk of recurrence according to the modified Consensus Criteria*:
  - Tumor diameter >10 cm or
  - Tumor mitosis count >10/50 HPF** or
  - Size >5 cm and mitosis count >5/50 HPFs or
  - Tumor rupture spontaneously or at surgery

*Fletcher CD et al. Hum Pathol 2002; 33:459-65
**HPF, High Power Field of the microscope
Conclusions: Adjuvant GIST

- 3 years adjuvant imatinib is better than 1 year in high risk patients
  - Well tolerated
  - Cost benefit?
Pancreas Cancer

FOLFIRINOX vs Gemcitabine: Overall Survival

Median 11.1 mths
HR = 0.57
P < 0.0001

Number at risk
Gemcitabine 171 134 89 48 28 14 7 6 3 3 2 2 2
FOLFIRINOX 171 146 116 81 62 34 20 13 9 5 3 2 2

Corey TJ. NCI/A 2011
Conclusions: Pancreas Cancer

• Pancreas cancer has consistently been the most lethal cancer
  – Less than 5% of patients diagnosed with it actually survive it.

• Adjuvant:
  – Gemcitabine or 5FU remain the standard for treating patients with resected pancreas cancer based on best Level 1 evidence!!
  – The role of radiation remains unanswered.
### Conclusions: Pancreas Cancer

- **Advanced disease (First Line):**
  - Gemcitabine combinations remain a SOC for most patients with PS 0-1. Fluoropyrimidines?
  - Novel taxanes seem to hold promise. No role for abraxane in pancreas cancer for now, awaiting phase III studies
  - FOLFIRINOX can be considered an option for excellent PS patients with no biliary obstruction?
    - FOLFOX or FOLFIRI?
    - Neo-adjuvant?
    - Confirms the need to move to non-gemcitabine backbones

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### Pancreas Neuroendocrine Tumors (PNET’s)

- Rare malignancies
  - 1.3% of all pancreas malignancies
  - 2-4 per million
  - 1,000 yr new diagnoses US, rising incidence
- Variable natural history, median OS with metastases > 2 yrs
- FDA drug approvals
  - 1982 Streptozotocin (+/- 5FU, doxorubicin)
  - 1998 Somatostatin (symptomatic NET’s)

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RADIANT-3:
Phase III Everolimus vs Placebo

N= 410 PNET's
Well-differentiated
Low-intermediate grade
POD within 12 mths
Measurable disease
WHO performance 0-2

Randomization 1: 1
Stratification
- Prior chemotherapy Y vs N
- WHO performance status 0 vs 1-2
Option for cross-over from placebo arm on POD

Yoo, J.C., NEJM, 2011

Randomized Phase III Sunitinib vs Placebo
SUN 1111

N= 171 PNET’s
Well-differentiated
POD within 2-12 mths
Measurable disease
ECOG performance 0-1

Randomization 1: 1, balanced by country/region
No other stratification factors used

Raymond, E., NEJM, 2011
## Efficacy of Sunitinib and Everolimus: Pancreatic NET Randomized Trials

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib</th>
<th>Everolimus</th>
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<tbody>
<tr>
<td></td>
<td>(n=171)</td>
<td>(n=410)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>11.4 mos</td>
<td>11.0 mos</td>
</tr>
<tr>
<td></td>
<td>(vs. 5.5 mos in placebo arm)</td>
<td>(vs 4.6 mos in placebo arm)</td>
</tr>
<tr>
<td>Overall Response Rate (RECIST)</td>
<td>9.3%</td>
<td>5%</td>
</tr>
<tr>
<td>Partial Response or Stable Disease</td>
<td>72%</td>
<td>78%</td>
</tr>
<tr>
<td>Survival Advantage Demonstrated?</td>
<td>No*</td>
<td>No*</td>
</tr>
</tbody>
</table>

*Pts on placebo in either study received study drug following progression


## Adverse Events in Sunitinib and Everolimus Treatment Arms: Pancreatic NET Phase III Trials

<table>
<thead>
<tr>
<th><strong>SUNITINIB</strong></th>
<th><strong>EVEROLIMUS</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Event</strong></td>
<td><strong>All Grades (%)</strong></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
</tr>
<tr>
<td>Asthenia</td>
<td>34</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26</td>
</tr>
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What should the Sequence of Therapy in Symptomatic Patients with PNET be?

• Initiating targeted therapy is reasonable in most patients with symptoms, clinically significant tumor burden, or PD on chemotherapy

• Streptozocin or TMZ-based therapy considered where tumor response is required or patients had PD on targeted therapy
**What should the Sequence of Therapy in Symptomatic Patients with PNET be?**

- Initiating targeted therapy is reasonable in most patients with symptoms, clinically significant tumor burden, or PD on chemotherapy.

- Streptozocin or TMZ-based therapy considered where tumor response is required or patients had PD on targeted therapy.

- Future studies will consider options such as new targets and combination studies.

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**Ampullary Cancer**
(Peri-)Ampullary ESPAC-3: Trial Design

Patients with adenocarcinoma of the ampulla of Vater undergoing 'curative' resection
Target N= 300

RANDOMISE

OBSERVATION
Target N= 100

5FU/ FA
5-FU 425mg/m² & FA 20mg/m² for 5 days every 28 days for 6 cycles
Target N= 100

GEMCITABINE
1000mg/m² once a week for 3 of 4 weeks for 6 cycles
Target N= 100

Ampullary: 300 patients (200 chemotherapy and 100 observation) would provide 80% power to detect a 15% 5y survival difference, p<0.05
Other periampillary to add to power

LCTU
Liverpool Cancer Trials Unit
Neoptelemos et al Abs 4006 , ASCO 2011

Ampullary overall survival:
5FU/FA vs Gemcitabine vs Observation

% Survival

Median S1(1) = 55.0 months (95% CI: 26.7, 84.0)
Median S1(1) = 47.1 months (95% CI: 41.3, ∞)
Median S1(1) = 43.0 months (95% CI: 27.6, ∞)

LCTU
Liverpool Cancer Trials Unit
Neoptelemos et al Abs 4006 , ASCO 2011
Hepatocellular Cancer (HCC)

Introduction: HCC

- 5th most common cancer worldwide
- 3rd leading cause of mortality worldwide
- Sharp rise in the USA and the rest of the world because of a hepatitis C epidemic.
- Sorafenib in Child's Pugh A patients is SOC in advanced disease
**Preliminary overall survival by Child-Pugh status\(^a\) at study entry**

![Graph showing survival distribution function over time since start of treatment for Child-Pugh A, B, and C groups.](image)

\(^a\) 3/87 patients not evaluable.

\(\text{CI, confidence interval}\)

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**SUN1170 HCC – Study Design**

**Enrollment Criteria**
- Advanced histologically confirmed HCC
- No prior systemic chemotherapy
- ECOG PS 0–1
- Child-Pugh group A

**Stratification**
- Region (Asia vs. Ex-Asia)
- Prior TACE (53 vs. >3 courses)
- Tumor invasion (presence vs. absence of vascular invasions and/or extrhepatic spread)

**Randomization**
- N=1,200

**Endpoints**
- Primary: OS
- Secondary:
  - PFS
  - TTP
  - Safety

**Statistics**
- Superiority
- Non-inferiority design
- Hypothesis: increase in median OS from 10.7 to 13.3 months
- Non-inferiority boundary of median OS (9.5, 11.5 months)
- 1-sided log-rank test: α=0.025, 90% power

BID: twice daily; CDD: continuous daily dosing; ECOG PS: Eastern Cooperative Oncology Group performance status; PFS: progression-free survival; TACE: transarterial chemoembolization.
Conclusions: HCC

- Sorafenib remains the SOC for treating patients with advanced HCC for patients with Child's Pugh A
  - Sorafenib can be used with relative safety in the C-P B HCC population. Optimal dose remains to TBD.
  - No data in CP-C
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• Sorafenib appears superior to sunitinib for HCC
  – The superiority of sorafenib over sunitinib in HCV infected patients raises interesting questions about non-VEGFR-related activities of sorafenib
• A better tolerated VEGFR agent would be welcome
  – Sunitinib does not fill this role
  – Others may, including bevacizumab
  – Studies of brivanib and linifanib vs. sorafenib continue
Colorectal Cancer

Advances in the Treatment of Stage IV CRC

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</thead>
<tbody>
<tr>
<td>5-FU</td>
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<tr>
<td>Irinotecan</td>
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<tr>
<td>Capecitabine</td>
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<tr>
<td>Oxaliplatin</td>
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<tr>
<td>Cetuximab</td>
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<tr>
<td>Bevacizumab</td>
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<tr>
<td>Panitumumab</td>
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<tr>
<td>Targeted Therapies</td>
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</tbody>
</table>

Median OS

5-FU = 5-fluorouracil; OS = overall survival.
McRee & Goldberg, 2011.
Large Molecule VEGF Inhibitors

PIGF
VEGF-B

VEGF-A

Bevacizumab

VEGF-C, VEGF-D

Functions

PIGF = placental growth factor.

Large Molecule VEGF Inhibitors

PIGF
VEGF-B

Ramucirumab

Aflibercept
(VEGF Trap)

VEGF-A

Bevacizumab

VEGF-C, VEGF-D

Functions

PIGF = placental growth factor.
EFC10262: VELOUR Phase III Trial
Second-Line FOLFIRI +/- VEGF-TRAP (aflibercept)

- mCRC after failure of an oxaliplatin-based regimen

Stratification factors:
- Prior bevacizumab (Y/N)
- ECOG PS (0 vs. 1 vs. 2)

- Aflibercept 4 mg/kg IV + FOLFIRI q2wks
- Placebo + FOLFIRI q2wks

ECOG = Eastern Cooperative Oncology Group.
### Safety – Most Frequent AEs, With ≥ 5% Difference in Incidence Between Treatment Arms, Excluding Anti-VEGF Class Events

<table>
<thead>
<tr>
<th>Safety Population, % of patients</th>
<th>Placebo, N = 605</th>
<th>Aflibercept N = 611</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT, SOC, HLT*</td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>56.5</td>
<td>7.8</td>
</tr>
<tr>
<td>Neutropenia**</td>
<td>56.3</td>
<td>29.5</td>
</tr>
<tr>
<td>Complicated neutropenia</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Asthenic conditions (HLT)</td>
<td>50.2</td>
<td>10.6</td>
</tr>
<tr>
<td>Stomatitis &amp; ulceration (HLT)</td>
<td>34.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Thrombocytopenia**</td>
<td>33.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Infections (SOC)</td>
<td>32.7</td>
<td>6.9</td>
</tr>
<tr>
<td>Decrease appetite</td>
<td>23.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>14.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Palmar plantar erythrodysaesthesia</td>
<td>4.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Skin hyperpigmentation</td>
<td>2.8</td>
<td>0</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3.0</td>
<td>1.3</td>
</tr>
</tbody>
</table>

* PT = preferred term; SOC = system organ class; HLT = high level term.

** From lab. Van Cutsem, 2011.
**OS: ITT Population**

![Graph showing Kaplan-Meier survival curve with annotations](image)

Cut-off date = February 7, 2011; Median follow-up = 22.28 mos

Van Cutsem et al, 2011.

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**Optimized Medical Therapy of Advanced CRC**

1. **Identify the goal of therapy**
   - RR only matters for
     - Conversion therapy of liver metastases or
     - If patient is symptomatic from his tumor burden
   - For most patients gain of time and maintaining QOL is more important

2. **Treat to progression – and perhaps beyond?**
   - Be mindful about toxicities, stop oxaliplatin before neurotoxicity develops
   - Some select patients can have CFI

CFI = chemotherapy-free intervals.
NCCN, 2011.
3. Expose patients to all potentially active agents
   - These agents are the oncologist's tools to keep patients alive
   - Use fluoropyrimidine-based combinations as default backbone, reserve sequential single agent therapy for select patients

4. Reutilize chemotherapeutic agents (in different combinations?) in the course of the therapy
   - Continuum of care vs. distinct lines of therapy

NCCN, 2011.