SYSTEMIC TREATMENT FOR COLORECTAL CANCER

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Harvard Medical School
Disclosure
I have nothing to disclose.

Off Label/Investigational Discussion
In accordance with Annenberg Center policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
Which one of the following represents the most plausible explanation for the poorer prognosis of right sided versus left sided colon cancers?

1. colonoscopic screening is less effective for right sided lesions

2. such tumors more frequently demonstrate signet ring cell pathologic features

3. right sided tumors are often larger than left sided lesions at the time of diagnosis

4. right sided tumors have a higher frequency of poor prognostic molecular aberrancies

5. right sided lesions spread more rapidly to the liver while left sided tumors spread more frequently to the lungs
Which one of the following statements regarding early stage colon cancer is true?

1. gene expression profiles are predictive for benefits from adjuvant therapy in patients with stage II disease
2. stage II tumors are more likely to be microsatellite unstable than are stage III tumors
3. the addition of oxaliplatin to 5-FU/leucovorin (i.e. FOLFOX) improves overall survival in patients receiving adjuvant therapy for stage II disease
4. six months of bevacizumab maintenance therapy after six months of FOLFOX-bevacizumab adjuvant therapy further reduces the likelihood of recurrence in patients with stage III disease
5. FOLFIRI is superior to FOLFOX as adjuvant therapy for stage III disease when tumors are microsatellite unstable
ADVANCED DISEASE
5-Fluorouracil
(5-FU)
Irinotecan (CPT-11)
Issues

- diarrhea and leucopenia are dose-limiting
- tolerance related to genetic polymorphisms of UGT1A1, enzyme involved in metabolic glucuronidation

- 10-15% of patients are homozygous for the UGT1A1*28 genotype, which is associated with delayed drug metabolism and severe neutropenia
### Phase III Assessment of Weekly Irinotecan (CPT-11) as Initial Treatment for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th># evaluable patients</th>
<th>Overall response rate</th>
<th>Median progression-free survival (months)</th>
<th>Median overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11 + 5-FU/leucovorin weekly</td>
<td>231</td>
<td>39%</td>
<td>7.0</td>
<td>14.8</td>
</tr>
<tr>
<td>5-FU/leucovorin (bolus [“loading”])</td>
<td>226</td>
<td>21.0%</td>
<td>4.3</td>
<td>12.6</td>
</tr>
<tr>
<td>CPT-11</td>
<td>226</td>
<td>18.0%</td>
<td>4.2</td>
<td>12.0</td>
</tr>
</tbody>
</table>

*p* = 0.001  
*p* = 0.004  
*p* = 0.04

### Phase III Assessment of Irinotecan (CPT-11) with Continuous Infusional 5-Fluorouracil/Leucovorin as Initial Treatment for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th></th>
<th># evaluable patients</th>
<th>overall response rate</th>
<th>median progression-free survival (months)</th>
<th>median overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11 + 5-FU/leucovorin</td>
<td>199</td>
<td>49%</td>
<td>6.7</td>
<td>17.4</td>
</tr>
<tr>
<td>5-FU/leucovorin</td>
<td>188</td>
<td>31%</td>
<td>4.4</td>
<td>14.1</td>
</tr>
</tbody>
</table>

- \( p = <0.001 \)
- \( p = <0.001 \)
- \( p = 0.031 \)

Oxaliplatin (I-OHP)
Issues

• peripheral neuropathy
  • two forms
    • acute cold sensitive
    • chronic cumulative
  • usually but not always reversible
• not preventable (as was once thought) with the administration of magnesium and calcium
• no effective treatment once it has occurred
# PHASE III TRIAL ASSESSING OXALIPLATIN AS INITIAL TREATMENT FOR METASTATIC COLORECTAL CANCER

<table>
<thead>
<tr>
<th>Randomize</th>
<th># patients</th>
<th>objective response rate</th>
<th>median progression-free survival</th>
<th>median overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxaliplatin 85mg/m² CI 2 hours + 5-fluorouracil 400 mg/m² bolus + 600 mg/m² CI 22 hours + leucovorin 200 mg/m² CI 2 hours</td>
<td>210</td>
<td>51%</td>
<td>9.0 months</td>
<td>16.2 months</td>
</tr>
<tr>
<td>5-fluorouracil 400 mg/m² bolus + 600 mg/m² CI 22 hours + leucovorin 200 mg/m² CI 2 hours</td>
<td>210</td>
<td>22%</td>
<td>6.2 months</td>
<td>14.7 months</td>
</tr>
</tbody>
</table>

p=<0.0001  p=0.0003  p=0.12

- repeat biweekly; median follow-up time: 28 months

WHICH IS BETTER IN ADVANCED COLON CANCER?

5-FU/LEUCOVORIN COMBINED WITH:

OXALIPLATIN
OR
IRINOTECAN
# OXALIPLATIN VS IRINOTECAN CONTAINING REGIMENS AS INITIAL TREATMENT FOR METASTATIC COLORECTAL CANCER

<table>
<thead>
<tr>
<th></th>
<th># Pts</th>
<th>Response Rate</th>
<th>Median Progression-free Survival</th>
<th>Median Survival</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tournigard 2004 JCO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX</td>
<td>111</td>
<td>54%</td>
<td>8.0 mo</td>
<td>20.6 mo</td>
<td>NS</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>109</td>
<td>56%</td>
<td>8.5 mo</td>
<td>21.5 mo</td>
<td></td>
</tr>
<tr>
<td><strong>Collucci 2005 JCO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX</td>
<td>172</td>
<td>34%</td>
<td>7.0 mo</td>
<td>15.0 mo</td>
<td>NS</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>164</td>
<td>31%</td>
<td>7.0 mo</td>
<td>14.0 mo</td>
<td></td>
</tr>
</tbody>
</table>

TAS-102

- oral combination of trifluridine (thymidine-based nucleic acid analogue) and tipiracil (thymidine phosphorylase inhibitor)

- mechanism of action
  - acts primarily as an antimetabolic (i.e. incorporated into DNA)
  - fluoropyrimidines act primarily as competitive inhibitors of thymidylate synthase
Hazard ratio for death, 0.68 (95% CI, 0.58–0.81)
P<0.001

BEVACIZUMAB IN THE TREATMENT OF COLON CANCER

• Rationale
  • humanized monoclonal antibody which inhibits the vascular endothelial growth factor (VEGF)
  • possible anti-angiogenesis agent
  • promising phase II data

• Initial Phase III Trial*

- previously untreated metastatic colorectal cancer
- IFL + bevacizumab (n=403)
- IFL + placebo (n=412)

SURVIVAL

HR = 0.65, p = 0.00003
Median Survival: 15.6 vs 20.3 mos

## Bevacizumab in Combination with Oxaliplatin-Based Chemotherapy as First-Line Therapy in Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Statify</th>
<th># Pts</th>
<th>Median Progression-free Survival</th>
<th>Median Overall Survival</th>
<th>Objective Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bevacizumab</strong> + FOLFOX or XELOX</td>
<td>699</td>
<td>9.4 mos</td>
<td>21.3 mos</td>
<td>47%</td>
</tr>
<tr>
<td><strong>Placebo</strong> + FOLFOX or XELOX</td>
<td>701</td>
<td>8.0 mos</td>
<td>19.9 mos</td>
<td>49%</td>
</tr>
</tbody>
</table>

*P = 0.0023*  
*P = 0.0769*  
*P = 0.31*

OVERALL SURVIVAL

A META-ANALYSIS COMPARING CHEMOTHERAPY + BEVACIZUMAB WITH CHEMOTHERAPY ALONE IN MCRC: HR FOR PFS AND OS

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>HR (95% CI)</th>
<th>Weight, %</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giantonio</td>
<td>E3200</td>
<td>0.61 (0.51-0.73)</td>
<td>22.4</td>
<td>2007</td>
</tr>
<tr>
<td>Hurwitz</td>
<td>AVF2107</td>
<td>0.66 (0.57-0.75)</td>
<td>24.8</td>
<td>2004</td>
</tr>
<tr>
<td>Kabbinavar</td>
<td>Phase II</td>
<td>0.45 (0.28-0.72)</td>
<td>8.9</td>
<td>2003</td>
</tr>
<tr>
<td>Kabbinavar</td>
<td>AVF2192</td>
<td>0.61 (0.48-0.78)</td>
<td>18.1</td>
<td>2005</td>
</tr>
<tr>
<td>Saltz</td>
<td>NO16966</td>
<td>0.83 (0.74-0.94)</td>
<td>25.8</td>
<td>2008</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.66 (0.56-0.77)</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>HR (95% CI)</th>
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<tr>
<td>Giantonio</td>
<td>E3200</td>
<td>0.75 (0.63-0.89)</td>
<td>28.1</td>
<td>2007</td>
</tr>
<tr>
<td>Hurwitz</td>
<td>AVF2107</td>
<td>0.66 (0.54-0.80)</td>
<td>25.1</td>
<td>2004</td>
</tr>
<tr>
<td>Kabbinavar</td>
<td>AVF2192</td>
<td>0.79 (0.56-1.11)</td>
<td>13.1</td>
<td>2005</td>
</tr>
<tr>
<td>Saltz</td>
<td>NO16966</td>
<td>0.89 (0.78-1.02)</td>
<td>33.7</td>
<td>2008</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.77 (0.67-0.89)</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Cao, et. al. Int J Colorectal Dis. 2009;24:677-685
USE OF THE SEER-MEDICARE DATABASE TO ASSESS IMPACT OF ADDING BEVACIZUMAB TO FIRST-LINE CHEMOTHERAPY IN PATIENTS WITH STAGE IV COLORECTAL CANCER

• identified 2526 patients age 65 years or older who were diagnosed with stage IV colorectal cancer between 2002 and 2007 and received first-line treatment with a fluoropyrimidine combined with either oxaliplatin (1680 patients) or irinotecan (836 patients)

• of the 2526 patients, 903 also received bevacizumab

Is the continued use of bevacizumab beneficial as part of second line therapy after tumor progression?
BEV + standard first-line CT (either oxaliplatin or irinotecan-based) (n=820)

CT switch:
- oxaliplatin → irinotecan
- irinotecan → oxaliplatin

randomize 1:1

PD

standard second-line CT (oxaliplatin or irinotecan-based) until PD

BEV (2.5 mg/kg/wk) + standard second-line CT (oxaliplatin or irinotecan-based) until PD

Primary endpoint
- overall survival (OS) from randomization

Secondary endpoints included
- progression-free survival (PFS)
- best overall response rate
- safety

Stratification factors
- first-line CT (oxaliplatin-based, irinotecan-based)
- first-line PFS (≤9 months, >9 months)
- time from last BEV dose (≤42 days, >42 days)
- ECOG PS at baseline (0/1, 2)

- study conducted in 220 centres in Europe and Saudi Arabia

ML18147 STUDY DESIGN (PHASE III)

THE ROLE OF EGFr IN TUMOR GROWTH AND CANCER

- Proliferation
- Angiogenesis
- Cell survival
- Metastatic spread

EGF
EGFr activation

TGF-a

Spread of cancer cells

Tumor

Cell survival

Angiogenesis

Proliferation

Blood vessel

Blood vessel

Metastatic spread
CRYSTAL TRIAL: STUDY DESIGN

Stratification factors:
- Regions
- ECOG PS

Populations:
- Randomized patients: n = 1217
- Safety population: n = 1202
- ITT population: n = 1198


P = 0.048
## Retrospective Studies Supporting K-Ras and Lack of Anti-EGFR Response

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>No. of patients (wt:mt)</th>
<th>Objective Response n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Wild-type</td>
<td>Mutant</td>
</tr>
<tr>
<td>A Lièvre, et al.</td>
<td>Cetuximab ± CT</td>
<td>114 (78:36)</td>
<td>34 (44%)</td>
</tr>
<tr>
<td>(J Clin Oncol 2008)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S Benvenuti, et al.</td>
<td>Panitumumab or cetuximab or cetuximab + CT</td>
<td>48 (32:16)</td>
<td>10 (31%)</td>
</tr>
<tr>
<td>(Cancer Res, 2007)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W DeRoock, et al.</td>
<td>Cetuximab or cetuximab ± irinotecan</td>
<td>113 (67:46)</td>
<td>27 (41%)</td>
</tr>
<tr>
<td>(Ann Oncol 2008)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D Finocchiaro, et al.</td>
<td>Cetuximab ± CT</td>
<td>81 (49:32)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>(ASCO Proceedings, 2007)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F DeFiore, et al.</td>
<td>Cetuximab + CT</td>
<td>59 (43:16)</td>
<td>12 (28%)</td>
</tr>
<tr>
<td>(Br J Cancer, 2007)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S Kambata-Ford, et al.</td>
<td>Cetuximab</td>
<td>80 (50:30)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>(J Clin Oncol, 2007)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RG Amado, et al.</td>
<td>Panitumumab</td>
<td>208 (124:84)</td>
<td>21 (124:84)</td>
</tr>
<tr>
<td>(J Clin Oncol, 2008)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PFS in patients with KRAS codon 12/13 wild-type tumors

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI</th>
<th>Cetuximab + FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>8.4 months</td>
<td>9.9 months</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[7.4-9.2]</td>
<td>[9.0-11.3]</td>
</tr>
<tr>
<td>HR [95% CI]</td>
<td>0.696</td>
<td>[0.558-0.867]</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0012</td>
<td>(log-rank)</td>
</tr>
</tbody>
</table>

Van Cutsem et. al. Proc 2010 GI Cancer Symposium
Patients with KRAS codon 12/13 wild-type tumors

<table>
<thead>
<tr>
<th>Study</th>
<th>Evaluable patients*</th>
<th>Method</th>
<th>Other RAS mutations, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRYSTAL</td>
<td>430</td>
<td>BEAMing†</td>
<td>14.7</td>
</tr>
<tr>
<td>OPUS</td>
<td>118</td>
<td>BEAMing†</td>
<td>26.3</td>
</tr>
<tr>
<td>FIRE-3‡</td>
<td>407</td>
<td>Pyrosequencing</td>
<td>16.0</td>
</tr>
<tr>
<td>PRIME§</td>
<td>620</td>
<td>Dideoxy sequencing/WAVE</td>
<td>17.4</td>
</tr>
<tr>
<td>PEAK</td>
<td>221</td>
<td>Dideoxy sequencing/WAVE</td>
<td>23.1</td>
</tr>
</tbody>
</table>

* for other tumor RAS mutations
† 5% mutant/wild-type alleles diagnostic cutoff
‡ KRAS codons 59 and 117 not considered
§ KRAS and NRAS codon 59 not considered
**PROGRESSION-FREE SURVIVAL**

**KRAS codon 12/13 wild-type**

- No. of events: 146, 189
- Median, months: 9.9, 8.4
- 95% CI: 9.0–11.3, 7.4–9.2
- HR (95% CI): 0.70 (0.56–0.87)

**RAS wild-type**

- No. of events: 73, 99
- Median, months: 11.4, 8.4
- 95% CI: 10.0–14.6, 7.4–9.4
- HR (95% CI): 0.56 (0.41–0.76)

**HR (95% CI)**: 0.56 (0.41–0.76)

**P = 0.0012**

**HR (95% CI)**: 0.70 (0.56–0.87)

**P = 0.0002**

Can VEGF and EGFR inhibitors be combined in the treatment of metastatic colorectal cancer?
PACCE: PANITUMUMAB ADVANCED COLORECTAL CANCER EVALUATION RANDOMIZED, OPEN-LABEL, CONTROLLED PHASE 3B TRIAL

STUDY SCHEMA

Stratification factors: ECOG score, prior adjuvant tx, disease site, Ox doses/Iri regimen, number of metastatic organs

Tumor assessments: Q12W until disease progression or intolerability
PROGRESSION-FREE SURVIVAL

Ox-CT Cohort

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of events</th>
<th>(%)</th>
<th>Median (95% CI), mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmab+bev/Ox-CT</td>
<td>246</td>
<td>(60)</td>
<td>10.0 (8.9 to 11.0)</td>
</tr>
<tr>
<td>Bev/Ox-CT</td>
<td>221</td>
<td>(54)</td>
<td>11.4 (10.5 to 11.9)</td>
</tr>
</tbody>
</table>

HR = 1.27 (95% CI: 1.06 to 1.52)

PROGRESSION-FREE SURVIVAL

Iri-CT Cohort

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of events (%)</th>
<th>Median (95% CI), mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmab+bev/Iri-CT</td>
<td>54 (47)</td>
<td>10.1 (8.2 to 13.7)</td>
</tr>
<tr>
<td>Bev/Iri-CT</td>
<td>44 (38)</td>
<td>11.7 (9.0 to 13.2)</td>
</tr>
</tbody>
</table>

HR = 1.19 (95% CI: 0.79 to 1.79)

STUDY DESIGN CAIRO2

Randomization

Arm A

Capecitabine
Oxaliplatin
Bevacizumab

Arm B

Capecitabine
Oxaliplatin
Bevacizumab
Cetuximab
OVERALL SURVIVAL

IN PATIENTS WITH UNTREATED K-RAS WILD-TYPE METASTATIC COLORECTAL CANCER:

Is chemotherapy with a VEGF inhibitor better, equivalent, or inferior to chemotherapy with an EGFR inhibitor?
Overall survival among patients with KRAS wild-type colorectal cancer (primary cohort)

Adjusted HR (95% CI), 0.88 (0.77-1.01); P = .08
80405: Overall Survival by Sidedness

<table>
<thead>
<tr>
<th>Side</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>732 (550)</td>
<td>33.3 (31.4-35.7)</td>
<td>1.55 (1.32-1.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right</td>
<td>293 (242)</td>
<td>19.4 (16.7-23.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
“SIDENESS” IN COLORECTAL CANCER MATTERS

• the observation that patients having right colon cancers have a poorer prognosis than those having left colon cancers is not new
  • ECOG protocol 2290 (O’Dwyer, et. al.; J Clin Oncol 2001;19:2413)
  • SEER data (from 1990’s) (Megiud, et. al.; Ann Surg Oncol 2008;15:2388)

• subsequently, multiple further reports have confirmed this prognostic relationship and even suggested a predictive implication (patients with right sided k-ras wild type tumors benefit less from cetuximab therapy than similar patients with left sided tumors) (Heinemann, et. al. Proc ASCO 2014; abstract #3600)
80405: OS by Sidedness (Cetuximab)

<table>
<thead>
<tr>
<th>Side</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>376 (270)</td>
<td>36.0 (32.6-40.3)</td>
<td>1.87 (1.48-2.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right</td>
<td>143 (121)</td>
<td>16.7 (13.1-19.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Embryology: The origin of the colon

- Rathke’s pouch
- Lung bud
- Liver
- Gallbladder
- Ventral pancreatic bud
- Yolk sac (vitelline duct)
- Cecal bud
- Allantois
- Cloaca

Diagram showing the development of the colon, with labels for the right and left colon.
Metastatic Colorectal Cancer: Patient Selection

KRAS, Any RAS mutations

BRAF mut

Consensus transcriptional subtypes

Hypermethylation

Clinical outlier: Women, peritoneal

6 FEET OF BIOLOGICALLY COMPLEX TUBING
Right-sided tumors are associated with inferior OS

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>58</td>
</tr>
<tr>
<td>Male sex</td>
<td>61%</td>
</tr>
<tr>
<td>White race</td>
<td>80%</td>
</tr>
<tr>
<td>Right-sided</td>
<td>32%</td>
</tr>
<tr>
<td>MSI-High</td>
<td>7%</td>
</tr>
<tr>
<td>CIMP High</td>
<td>26%</td>
</tr>
<tr>
<td>BRAF Mutant</td>
<td>18%</td>
</tr>
<tr>
<td>NRAS Mutant</td>
<td>13%</td>
</tr>
<tr>
<td>PIK3CA Mutant</td>
<td>16%</td>
</tr>
</tbody>
</table>

![Kaplan-Meier curve](chart.png)

HR 1.45 (1.04-2.01)  
p=0.028

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left-sided</td>
<td></td>
</tr>
<tr>
<td>135</td>
<td>101</td>
</tr>
<tr>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Right-sided</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>37</td>
</tr>
<tr>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Age, MSI, *BRAF*, and Methylation (CIMP) are associated with right-sided primaries

<table>
<thead>
<tr>
<th></th>
<th>Right-Sided n=63 (32%)</th>
<th>Left-Sided n=135 (68%)</th>
<th>Odds Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age</strong></td>
<td>62 (30-81)</td>
<td>56 (24-76)</td>
<td>1.05 (1.02-1.08)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>37/63 (58.7%)</td>
<td>84/135 (62.2%)</td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td><strong>White race</strong></td>
<td>55/63 (87.3%)</td>
<td>103/135 (76.3%)</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td><strong>MSI-High</strong></td>
<td>5/31 (16.1%)</td>
<td>2/71 (2.8%)</td>
<td>6.63 (1.21-36.3)</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>PIK3CA mutant</strong></td>
<td>7/51 (13.7%)</td>
<td>19/112 (17.0%)</td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td><strong>BRAF mutant</strong></td>
<td>22/61 (36.1%)</td>
<td>12/116 (10.3%)</td>
<td>5.45 (2.47-12.0)</td>
<td>0.00003</td>
</tr>
<tr>
<td><strong>NRAS mutant</strong></td>
<td>7/50 (14.0%)</td>
<td>14/107 (13.1%)</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td><strong>CIMP High</strong></td>
<td>24/63 (38.1%)</td>
<td>28/135 (20.7%)</td>
<td>2.35 (1.22-4.54)</td>
<td>0.015</td>
</tr>
</tbody>
</table>
Side is not significant on multivariate analysis of anti-EGFR PFS

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right-sided</td>
<td>1.32 (0.81-2.16)</td>
<td>0.27</td>
</tr>
<tr>
<td>\textit{BRAF} mutant</td>
<td>1.96 (1.04-3.70)</td>
<td>0.04</td>
</tr>
<tr>
<td>\textit{NRAS} mutant</td>
<td>1.97 (1.16-3.33)</td>
<td>0.01</td>
</tr>
<tr>
<td>CIMP High</td>
<td>1.80 (1.02-3.17)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Also adjusted for age, antibody monotherapy vs. combination therapy, and number of prior regimens
ADVANCES IN THE SYSTEMIC THERAPY FOR COLORECTAL CANCER

5-FU = 5-fluorouracil; CT = chemotherapy
Venook, et. al. J Clin Oncol 2014;32(suppl); LBA#3
PD-1 BLOCKADE FOR MISMATCH REPAIR (MMR)-DEFICIENT COLORECTAL CANCER (CRC)

• rationale
  • MMR deficient tumors demonstrate lymphocytic infiltration and express immune checkpoint ligands
  • anecdotal “exceptional” responses have been observed when a PD-1 inhibitor has been given to patients with MMR deficient CRC

• phase II study in metastatic CRC (Le, et. al. N Engl J Med 2015;372:2509)
  • 11 patients with MMR deficient and 21 patients with MMR proficient CRC were treated with pembrolizumab
• update (ASCO 2016) – 28 patients with MMR deficiency and 25 patients with MMR proficiency
B-RAF MUTATED METASTATIC COLORECTAL CANCER

• present in about 10% of patients
• occurs more often in right sided tumors
• seemingly the same V600E mutation as in melanoma
• associated with a poorer prognosis and a shorter duration of response to chemotherapy
B-RAF MUTATED METASTATIC COLORECTAL CANCER

B-RAF MUTATED METASTATIC COLORECTAL CANCER

- In contrast to clinical experience in melanoma, the V600E B-RAF inhibitor vemurafenib is ineffective as a single agent in B-RAF mutated metastatic colorectal cancer.
- Laboratory models suggested synergy between vemurafenib and cetuximab in B-RAF mutated metastatic colorectal cancer, leading to a SWOG randomized phase II trial.
  - Primary objective – progression-free survival.
### RANDOMIZED PHASE II TRIAL OF IRINOTECAN AND CETUXIMAB +/- VEMURAFENIB IN B-RAF MUTANT METASTATIC COLORECTAL CANCER

<table>
<thead>
<tr>
<th>Eligibility</th>
<th># pts</th>
<th>Rate Disease Control</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• B-RAF V600E mutation</td>
<td>50</td>
<td>22%</td>
<td>2.0 months</td>
</tr>
<tr>
<td>• RAS wild type</td>
<td>49</td>
<td>67%</td>
<td>4.4 months</td>
</tr>
<tr>
<td>• 1-2 prior regimens of chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Stratify**

- prior irinotecan

Kopetz S, et. al. Proc 2017 ASCO GI (abstract #520)
**PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Median</th>
<th>95% Conf Int</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + Irinotecan</td>
<td>50</td>
<td>46</td>
<td>2.0</td>
<td>(1.8 – 2.1)</td>
</tr>
<tr>
<td>Vemurafenib + Cetuximab + Irinotecan</td>
<td>49</td>
<td>36</td>
<td>4.4</td>
<td>(3.6 – 5.7)</td>
</tr>
</tbody>
</table>

HR = 0.42 (95% CI 0.26 – 0.66)
P = 0.0002

Kopetz S, et. al. Proc 2017 ASCO GI (abstract #520)
ADJUVANT THERAPY
INTERGROUP STUDY 0035
SURGICAL ADJUVANT THERAPY FOR COLON CANCER

Stage B$_{2,3}$
- Randomize
- surgery alone
- levamisole + 5-FU

Stage C
- Randomize
- surgery alone
- levamisole alone
- levamisole + 5-FU
## SUBSET ANALYSIS FOR B2 INTERGROUP STUDY

<table>
<thead>
<tr>
<th>Covariate</th>
<th>% Survival at 7 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observation</td>
<td>5-FU/levamisole</td>
</tr>
<tr>
<td>Adhesion to adjacent organs</td>
<td>70</td>
<td>82</td>
</tr>
<tr>
<td>Invasion to adjacent organs</td>
<td>64</td>
<td>86</td>
</tr>
<tr>
<td>Obstruction</td>
<td>58</td>
<td>70</td>
</tr>
<tr>
<td>Perforation</td>
<td>51</td>
<td>67</td>
</tr>
</tbody>
</table>

ADJUVANT THERAPY FOR HIGH RISK STAGE II COLON CANCER

• this provocative retrospective analysis has never been validated through a prospective, stratified clinical trial
### TNM STAGING SYSTEM FOR COLORECTAL CANCER

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Classification</th>
<th>Five-year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>$T_{1-2}, N_0, M_0$</td>
<td>&gt;90</td>
</tr>
<tr>
<td>II</td>
<td>$T_{3-4}, N_0, M_0$</td>
<td>83</td>
</tr>
<tr>
<td>III</td>
<td>$T_{(any)}, N_{1-2}, M_0$</td>
<td>60</td>
</tr>
<tr>
<td>IV</td>
<td>$T_{(any)}, N_{(any)}, M_1$</td>
<td>8</td>
</tr>
</tbody>
</table>

*American Joint Committee on Cancer. Cancer Staging Manual. 5th edition*
PROBABILITY OF SURVIVAL FOR 648 $T_3N_0M_0$ PATIENTS PARTICIPATING IN INTERGROUP 0089

PROGNOSTIC IMPACT OF MICROSATELLITE INSTABILITY

ALL PATIENTS WITH COLORECTAL CANCER

VALUE OF TUMOR GENE EXPRESSION PROFILES IN STAGE II COLON CANCER

• provides unique PROGNOSTIC information independent of other factors

BUT

• has NOT yet been shown to offer any PREDICTIVE information so as to guide treatment decisions

Yothers, et. al. J Clin Oncol 2013;31:4512-4519
STAGE II COLON CANCER

• Is Adjuvant Chemotherapy Beneficial?
QUASAR TRIAL

Summary

- multi-institutional international study in which 3239 patients who had undergone the resection of a colorectal cancer were randomized to receive six months of adjuvant chemotherapy (1622 patients) or observation (1617 patients)
- after a median follow-up time of 5.5 years, the authors report an absolute survival benefit of 3.0% for the group receiving chemotherapy (81.9% versus 78.9% [p=0.05])

*Lancet* 2007;370:2020-2029
QUASAR TRIAL

Issues

• population included patients with rectal cancers as well as stage I and III disease

• apparently not stratified by stage or anatomic location

• pathology reviewed in only 20% of patients; median number of lymph nodes examined per specimen only 6

• some patients received: RT; portal vein 5-FU infusional therapy; levamisole
ADJUVANT CHEMOTHERAPY VERSUS OBSERVATION IN PATIENTS WITH STAGE II COLON CANCER

<table>
<thead>
<tr>
<th>Treatment</th>
<th># pts</th>
<th>Probability freedom from recurrence</th>
<th>Probability overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU/leucovorin (about 6 months)</td>
<td>1073</td>
<td>84.7%</td>
<td>83.9%</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Observation</td>
<td>1073</td>
<td>81.9%</td>
<td>81.5%</td>
</tr>
</tbody>
</table>

Median f/u – 5.5 years

Lancet 2007;37:2020
STAGE II COLON CANCER

• is adjuvant chemotherapy beneficial?

• recent recommendations – “standard risk” patients

  • NCCN – “adjuvant chemotherapy is **not** recommended (JNCCN 2003;1 (suppl 3):S-9)
  • ASCO “the routine use of adjuvant chemotherapy...is **not** recommended” (JCO 2004;22:3408)

VALUE OF ADJUVANT CHEMOTHERAPY IN ELDERLY PATIENTS WITH COLON CANCER

• an analysis of 42,032 Medicare beneficiaries with stages II or III colon cancer who did or did not receive adjuvant chemotherapy

STAGE III PATIENTS

STANDARD RISK STAGE II PATIENTS

HIGH RISK STAGE II PATIENTS

ASSESSMENT OF MICROSATELLITE INSTABILITY (MSI) AS A PREDICTIVE BIOMARKER FOR 5-FU BASED ADJUVANT CHEMOTHERAPY IN COLON CANCER

**Design**

- DNA was extracted for microsatellite analysis from tumor tissue from 1027/1952 patients with stages II or III colon cancer who had participated in one of five randomized comparisons of 5-FU vs observation
- MSI-H was found in 16.6% (165/1027) of all specimens
  - stage II 19.2% (102/530)
  - stage III 12.7% (63/497)

STAGE II

A

MSI-H

p = 0.09

B

MSI-H

p = 0.98

C

MMS

p = 0.38

D

MMS

p = 0.001

Sargent, et. al., J Clin Oncol 2010; 28: 3219-3226
ASSESSMENT OF MICROSATellite INSTABILITY (MSI) AS A PREDICTIVE BIOMARKER FOR 5-FU BASED ADJUVANT CHEMOTHERAPY IN COLON CANCER

Interpretation

• the value of adding irinotecan or oxaliplatin in the treatment of MSI-H patients – particularly with stage III disease – is presently unknown

• testing for MSI status (either by molecular or immunohistochemical means) should be considered in all patients with stage II and – most likely - stage III disease

ASSESSMENT OF TUMOR TISSUE FOR MISMATCH REPAIR/MICROSATELLITE STATUS

• techniques
  • mismatch repair
    • immunohistochemical staining of tumor cell nuclei for MLH1, MSH2, MSH6, and PMS2 proteins
    • methylation of the MLH1 promoter is the most common cause of sporadic MLH1 protein loss in colorectal adenocarcinoma
  • inexpensive; available in standard hospital pathology departments
• microsatellite instability
  • polymerase chain reaction assay on DNA extracted from tumor tissue
  • requires a molecular pathology laboratory
## COLON CANCER

### PROBABILITY OF MICROSATELLITE INSTABILITY BY SURGICAL STAGE

<table>
<thead>
<tr>
<th>Source</th>
<th>ACCENT* # pts</th>
<th>% MSI</th>
<th>NSABP\° # pts</th>
<th>% MSI</th>
<th>PETACC/SAKK+ # pts</th>
<th>% MSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients</td>
<td>1027</td>
<td>16.6%</td>
<td>1589</td>
<td>13.0%</td>
<td>1217</td>
<td>15.1%</td>
</tr>
<tr>
<td>stage II</td>
<td>530</td>
<td>19.2%</td>
<td>420</td>
<td>18.1%</td>
<td>398</td>
<td>21.4%</td>
</tr>
<tr>
<td>stage III</td>
<td>497</td>
<td>12.7%</td>
<td>1169</td>
<td>9.8%</td>
<td>829</td>
<td>11.9%</td>
</tr>
</tbody>
</table>

\* Sargent DJ, et. al. J Clin Oncol 2010;28:3219-3226
\+ Roth AD, et. al. J Clin Oncol 2010;28:466-474
STAGE II COLON CANCER

Personal Preference

• low risk (microsatellite unstable) – no adjuvant therapy

• standard risk – no adjuvant therapy

• high-risk – consider 5-FU/leucovorin therapy
ADJUVANT TRIALS IN COLON CANCER EXAMINING THE ROLE OF IRINOTECAN AND OXALIPLATIN

<table>
<thead>
<tr>
<th></th>
<th>Study</th>
<th>Stage</th>
<th>Treatment</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irinotecan</strong></td>
<td>CALGB 89803</td>
<td>Stage III</td>
<td>Weekly IFL vs weekly FU/leucovorin</td>
<td>1264 pts</td>
</tr>
<tr>
<td></td>
<td>PETACC-3</td>
<td>Stage III</td>
<td>Infusional IFL vs infusional FU/leucovorin</td>
<td>2084 pts</td>
</tr>
<tr>
<td></td>
<td>ACCORD-02</td>
<td>Stage III (high risk)</td>
<td>Infusional IFL vs infusional FU/leucovorin</td>
<td>400 pts</td>
</tr>
<tr>
<td><strong>Oxaliplatin</strong></td>
<td>MOSAIC</td>
<td>Stages II and III</td>
<td>FOLFOX vs infusional FU/leucovorin</td>
<td>2246 pts</td>
</tr>
<tr>
<td></td>
<td>NSABP C-07</td>
<td>Stages II and III</td>
<td>FLOX vs weekly FU/leucovorin</td>
<td>2492 pts</td>
</tr>
</tbody>
</table>
“MOSAIC” TRIAL

Stratify

- $T_2$ vs $T_3$ vs $T_4$
- $N_0$ vs $N_1$ vs $N_2$
- bowel obstruction or perforation
- center

FOLFOX

5-FU/leucovorin

### MOSAIC STUDY
OVERALL SURVIVAL DATA AFTER
A MEDIAN FOLLOW-UP OF 9.5 YEARS

<table>
<thead>
<tr>
<th>Probability of Overall Survival after 10 years</th>
<th>FOLFOX</th>
<th>5-FU/leucovorin</th>
<th>difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients</td>
<td>71.7%</td>
<td>p=.043</td>
<td>67.1%</td>
</tr>
<tr>
<td>stage II - all</td>
<td>78.4%</td>
<td>p=.980</td>
<td>79.5%</td>
</tr>
<tr>
<td>stage III- all</td>
<td>67.1%</td>
<td>p=.016</td>
<td>59.0%</td>
</tr>
<tr>
<td>- N₁</td>
<td>71.4%</td>
<td>p=.248</td>
<td>65.4%</td>
</tr>
<tr>
<td>- N₂</td>
<td>59.5%</td>
<td>p=.013</td>
<td>46.6%</td>
</tr>
</tbody>
</table>

NSABP C-07

Stage II + III

Strat: # Pos. N

Randomize

FULV

FLOX
NSABP C-07 – OVERALL SURVIVAL
STAGE III PATIENTS

Oxaliplatin-stage interaction $P = .38$

<table>
<thead>
<tr>
<th>Group</th>
<th>Pts</th>
<th>Deaths</th>
<th>HR (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FULV</td>
<td>860</td>
<td>305</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLOX</td>
<td>854</td>
<td>263</td>
<td>0.85 (0.72 to 1.00)</td>
<td>.052</td>
</tr>
</tbody>
</table>

EFFECT ON OVERALL SURVIVAL OF ADDING OXALIPLATIN TO FU/LEUCOVORIN AS ADJUVANT TREATMENT OF COLON CANCER (DATA FROM MOSAIC AND C-07 STUDIES)

- stage II – no added benefit for standard risk or high risk patients
- stage III – 3-13% improvement in survival dependent on risk factors
- stages II and III for patients > 70 years of age – no benefit

Mayer, RJ. J Clin Oncol 2012;30;3325-3327
ADJUVANT THERAPIES EXAMINED IN STAGE III DISEASE THAT DO NOT WORK

• irinotecan
  • 3 negative trials
• bevacizumab
  • NSABP C08
  • AVANT (? worse outcome with bevacizumab)
• cetuximab
  • NCCTG N0147
ADJUVANT THERAPY FOR COLON CANCER

Present Treatment Recommendations:

• mature data support the use of postoperative oxaliplatin/fluoropyrimidine (i.e. FOLFOX or CAPOX) in patients with stage III disease – particularly those with four or more involved lymph nodes

• adjuvant therapy including oxaliplatin for patients with stage III disease appears to be somewhat less effective in individuals older than 70 years of age, when compared with younger individuals

• prospective data have **NOT** demonstrated any adjuvant benefit for patients with stage II disease. Whether such treatment would improve the prognosis of individuals with such ominous factors as aneuploidy, molecular aberrancies, T4 lesions, or perforation remains to be determined
ARE THREE MONTHS OF ADJUVANT CHEMOTHERAPY EQUIVALENT TO SIX MONTHS OF THE SAME CHEMOTHERAPY IN PATIENTS WITH STAGE III DISEASE?

• addressed by the IDEA (International Duration evaluation of Adjuvant Chemotherapy) collaboration
  • pooled data analysis of six independent clinical trials involving 12,834 patients from 12 countries
• objective – to evaluate the non-inferiority of three months compared to six months of adjuvant oxaliplatin-based treatment with a goal of reducing neurotoxicity without diminishing anti-tumor efficacy

Shi, et. al. J Clin Oncol 2017;35:5s (suppl LBA1)
STUDY SCHEMA

Total planned accrual $\geq 10,500$

FOLFOX: 5FU/LV + Oxaliplatin

CAPOX: Capecitabine + Oxaliplatin
**PRIMARY DFS ANALYSIS (MITT)**

- **Duration 3-yr DFS**
  - 3m: 74.6%  
  - 6m: 75.5%

- **DFS HR** = 1.07  
  - 95% CI, 1.00 to 1.15

- **3-yr DFS diff.** = -0.9%,  
  - 95% CI, (-2.4 to 0.6%)
Primary DFS Analysis (MITT), Cont.

Statistical Conclusions

- 3m TRT better
- Not proven
- 6m TRT better

Hazard Ratio

DFS HR = 1.07
95% CI, 1.00 to 1.15

Non- Inferiority Margin

TRT: treatment
DFS COMPARISON BY RISK GROUPS

**T<sub>1-3</sub> N<sub>1</sub> (58.7%)**
- 3m: 83.1%
- 6m: 83.3%

3-yr DFS diff. = -0.2%
95% CI, (-1.9 to 1.5%)

**T<sub>4</sub> or N<sub>2</sub> (41.3%)**
- 3m: 62.7%
- 6m: 64.4%

3-yr DFS diff. = -1.7%
95% CI, (-4.3 to 0.9%)

Interaction p-value = 0.11
**DFS COMPARISON BY RISK GROUPS, CONT.**

**T$_{1-3}$ N$_1$ (58.7%)**

- 3m TRT better
- 6m TRT better
- DFS HR = 1.01
- 95% CI, 0.90 to 1.12
- Non-Inferiority

**T$_4$ or N$_2$ (41.3%)**

- 3m TRT better
- 6m TRT better
- DFS HR = 1.12
- 95% CI, 1.03 to 1.23
- Inferiority

**Interaction p-value = 0.11**

**HR**
- 1.0
- 1.12

**NI Margin**

TRT: treatment
DFS COMPARISON BY RISK GROUP AND REGIMEN

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Regimen</th>
<th>3m TRT better</th>
<th>6m TRT better</th>
<th>DFS HR; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-3 N1</td>
<td>FOLFOX</td>
<td>Not proven</td>
<td></td>
<td>1.10; 0.96 to 1.26</td>
</tr>
<tr>
<td></td>
<td>CAPOX</td>
<td>Non-Inferior</td>
<td></td>
<td>0.85; 0.71 to 1.01</td>
</tr>
</tbody>
</table>

TRT: treatment
SUMMARY

• 3m (vs. 6m) treatment: higher treatment compliance
• 3m (vs. 6m) treatment: substantially lower (G2+) neurotoxicity
  – FOLFOX: 17% (3m) vs. 48% (6m)
  – CAPOX: 15% (3m) vs. 45% (6m)

• the DFS non-inferiority of 3m oxaliplatin-based adjuvant therapy was not established in overall stage III colon cancer

• however, results comparing DFS between 3m and 6m treatment depend on risk group and regimen
INTERPRETATION OF THE IDEA
COLLABORATION DATA

• there is consensus that high risk stage III patients (T_4 and/or N_2) should continue to receive six months of oxaliplatin-based adjuvant therapy

• for lower risk stage III patients (T_{1-3}, N_1)
  • subset analyses suggest non-inferiority for CAPOX but not FOLFOX; should such patients receive three months of CAPOX?
  • could one consider three months of FOLFOX followed by three months of FU/leucovorin?
  • with the addition of oxaliplatin to FU/leucovorin in the MOSAIC trial not resulting in a statistically significant survival benefit in such patients, would six months of FU/leucovorin be sufficient?