Fighting a Smarter War On Colon Cancer:

Colon Cancer 2014

John L. Marshall, MD

Tel: (202) 444-0275
Fax: (202) 444-1229
http://lombardi.georgetown.edu/GI

The Ruesch Center for the Cure of Gastrointestinal Cancers
AT GEORGETOWN LOMBARDI COMPREHENSIVE CANCER CENTER
What do you see?

5-FU!
Our Current Model of Colon Cancer
Colon Cancer: More than One Disease

Molecular

MSI vs MSS
RAS WT vs MUT

Anatomic

Right vs Left
Rectal vs Colon

Stool Flora Types

??????
Testing Today

• KRAS (codon 12, 13)
  – Generally reserved for met CRC
  – BRAF sometimes done if KRAS WT

• MSI/MSS
  – IHC for MLH1, MSH2, MSH6 and PMS2 proteins
    • If MLH1 and PMS2 are absent, the patient likely has acquired methylation of the MLH1
    • If MSH2 and MSH6 are absent, the patient likely has LS.
    • If only MSH6 or PMS2 is absent, the patient may have LS.
    • Up to 15% are still missed, family history still critical
  – PCR for MSI-H

• Gene profiling
  – Adjuvant- Oncotype, Coloprint
  – Metastatic- Caris, Foundation, other
Overall Survival Stage II (55%) or Stage III (45%) Colon Cancer According to Treatment Status (570 pts)

A Patients with Tumors Exhibiting Microsatellite Stability or Low-Frequency Microsatellite Instability

<table>
<thead>
<tr>
<th>Years after Randomization</th>
<th>No. at Risk (No adjuvant chemotherapy)</th>
<th>No. at Risk (Adjuvant chemotherapy)</th>
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P = 0.02

B Patients with Tumors Exhibiting High-Frequency Microsatellite Instability

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<th>Years after Randomization</th>
<th>No. at Risk (No adjuvant chemotherapy)</th>
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P = 0.10

MSS

5FU helped

MSI-H

5FU hurt

Were are we in Adjuvant?

- We have relatively few positive studies
- Even in the best studies, adding oxali “fails” 95% of the time
- Oxaliplatin neuropathy does not really go away as first believed
- 6 mo vs 3 mo study ongoing
- Role of celecoxib, exercise
The Perfect Sorting Hat

Cured by Surgery

Not cured by surgery but 5FU will cure you

Not cured by surgery and chemo will not cure you

Not cured by surgery but 5FU and Oxali will cure you
ColoPrint:

Probability of Relapse

ColoPrint High Risk patients have a 1 in 5 risk of relapse within 3 yrs.

ColoPrint Low Risk patients have a 1 in 13 risk of relapse within 3 yrs.
Integrating the Quantitative Recurrence Score® Result into Your Patient’s Recurrence Risk Assessment and Treatment Plan

Resected Colon Cancer

Stage II

T-Stage Mismatch Repair (MMR) Status

- T3 & MMR-D* Low Risk
- T3 & MMR-P Standard Risk
- T4 & MMR-P High Risk

Consider Observation

Consider Chemotherapy

Stage III

III A/B

Oxaliplatin-containing Chemotherapy; 5FU/LV or Capecitabine**

III C

5FU + Oxali

5FU

No Rx

* MMR-D = mismatch repair deficient; MMR-P = mismatch repair proficient
**Patients not considered candidates for oxaliplatin
Right Target, Wrong Setting?

Epithelial-Mesenchymal Transition (EMT)

Adapted from Kalluri & Weinberg, J Clin Invest 119: 1420-8, 2009
PUTATIVE MOLECULAR PATHWAYS TO COLORECTAL CARCINOMA

Serrated pathways

Normal mucosa

BRAF CIMP-H

SSA

MLH1 loss

p16 loss

MGMT loss

SSAD

MSI (frameshift mutations e.g. TGFβIII IGFIIIR)

BRAF CIMP-H

MSI CRC

Good prognosis

Resistant to 5FU

Resistant to anti-EGFR therapy

Familial pathways

Lynch

(germline mutation of a MMR gene)

APC

Loss of remaining MMR allele, p53

TSA + HGD

TA HGD

Hundreds of TAs

FAP

(germline mutation of APC gene)

Loss of remaining APC allele

Hypomethylation

Normal mucosa

Conventional pathways

Normal mucosa

APC

APC

TA

Hypomethylation

TA HGD

TVA HGD

TA HGD

SMAD4, p53

CIMP-MSS CRC

Standard prognosis

Sensitive to 5FU

Sensitive to anti-EGFR therapy

CIMP-MSS CRC

Standard prognosis

Sensitive to 5FU

Sensitive to anti-EGFR therapy

KRAS, CIMP-L MSS CRC

Standard prognosis

Sensitive to 5FU

Resistant to anti-EGFR therapy

KRAS, CIMP-L MSS CRC

Standard prognosis

Sensitive to 5FU

Resistant to anti-EGFR therapy
Advances in the Treatment of Colorectal Cancer

- 2000: 5-FU
- 2005: Irinotecan
- 2008: Capecitabine
- 2012: Oxaliplatin
- 2014?: Targeted therapies
  - Cetuximab
  - Bevacizumab
  - Panitumumab
- KRAS
- Ziv-Aflibercept
- Regorafenib
CAIRO-3

Primary endpoint: PFS2
- Time from R until PD upon re-introduction of CAPOX-B

TT2PD
- Time from randomization to progression upon any treatment given after PFS1

CAIRO-3: Outcomes

PFS1

<table>
<thead>
<tr>
<th>Mos</th>
<th>Maintenance</th>
<th>Observation</th>
<th>HR, P</th>
</tr>
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<tbody>
<tr>
<td>PFS1</td>
<td>8.5</td>
<td>4.1</td>
<td>0.43, &lt; 0.0001</td>
</tr>
<tr>
<td>PFS2</td>
<td>11.7</td>
<td>8.5</td>
<td>0.67, &lt; 0.0001</td>
</tr>
<tr>
<td>TT2PD</td>
<td>13.9</td>
<td>11.1</td>
<td>0.68, &lt; 0.0001</td>
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<tr>
<td>OS</td>
<td>21.6</td>
<td>18.1</td>
<td>0.89, 0.22</td>
</tr>
</tbody>
</table>

Induction treatment of 6x cycles Bev + CAPEOX prior to randomization not included (4-5 months).

Stage 4 NED-Role for Chemo?

• Pre-op
• Post-op
• Treating Mets? - treat to progression
• Treating Adjuvant? - fixed time but only 5FU and Oxali
Rationale for Neoadjuvant Therapy

- Assess biology / chemo-responsiveness of disease
- Treat micro-metastatic disease (which chemotherapy can cure) as soon as possible
- *Potentially decrease surgical complications by making surgery more feasible*

- **Potential downsides:** hepatotoxicity; complications; complete response can hide metastatic sites; fear of “lost opportunity” if progression; etc
EORTC 40983, Peri-Operative FOLFOX for Hepatic Metastases
(For patients with initially resectable disease)

CRC w/ resectable liver metastases n = 364

FOLFOX4 6 cycles (3 m), n = 182
Surgery
FOLFOX4 6 cycles (3 m)

Surgery
No chemotherapy n = 182

Important toxicity data: only small increase in peri-operative complications with chemo, although only 63% in chemo group received it post-operatively

Nordlinger B. Lancet Oncology. 2013;14:1208-1215.
EORTC 40983: Peri-Op FOLFOX for Liver Mets

Nordlinger B. Lancet Oncology. 2013;14:1208-1215.

**Progression-Free Survival**
- mPFS, 20 m vs 12.5 mo
- Absolute difference: 8.2%
- HR = 0.81, $P = 0.068$

**Overall Survival**
- mOS, 61 m vs 54 mo
- Absolute difference: 3.4%
- HR = 0.88, $P = 0.34$
EPOC: Chemotherapy ± Cetuximab Before and After Liver Resection in KRAS WT CRC

Operable (including borderline operable) colorectal liver metastases

CT → Liver Resection → Chemotherapy

CT + Cetuximab → Liver Resection → CT + Cetuximab

• Cetuximab + CT ↑ the pre-operative RR

Progression-Free Survival

Overall Survival

TRIBE Study Design

Treatment-naïve unresectable mCRC N = 508
Stratified by center, PS 0/1-2, adjuvant CT

INDUCTION

FOLFOXIRI + Bevacizumab (up to 12 cycles)

FOLFIRI + Bevacizumab (up to 12 cycles)

MAINTENANCE

5-FU/LV + Bevacizumab

5-FU/LV + Bevacizumab

PS, performance status; CT, chemotherapy.

TRIBE Study Outcomes (ITT)

PFS (Primary Endpoint)

<table>
<thead>
<tr>
<th></th>
<th>FOLFOXIRI + bevacizumab</th>
<th>FOLFIRI + bevacizumab</th>
<th>Stratified HR (95% CI), P</th>
</tr>
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<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>53%</td>
<td>65%</td>
<td>P = 0.006</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>9.7 mo</td>
<td>12.1 mo</td>
<td>0.75 (0.62-0.90), 0.006</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>25.8 mo</td>
<td>31 mo</td>
<td>0.79 (0.63-1.00), 0.054</td>
</tr>
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Median follow-up: 32.3 months

Targeting EGFR

Finding drivers in the rear view mirror
EGFR Biomarkers

- **KRAS MT**: ~ 40%
- **RAS WT**: ~ 50%
- **New RAS MT**: ~ 10%
- **Rare KRAS Mutations**
- **NRAS Mutations**

MT, mutation
PRIME: Panitumumab + FOLFOX vs FOLFOX

Panitumumab 6.0 mg/kg Q2W
FOLFOX4 Q2W

Until Disease Progression or Intolerability

PRIME: Overall Survival

Primary Analysis

![Primary Analysis Chart]

Updated Analysis

![Updated Analysis Chart]

Hazard ratio, 0.78 (95% CI, 0.62 - 0.99)

P = 0.043

Panitumumab-FOLFOX4 vs FOLFOX4 alone

Events no. / total no. (%)

Panitumumab-FOLFOX4: 128/259 (49)
FOLFOX4 alone: 148/253 (58)

Median Mo (95% CI)

Panitumumab-FOLFOX4: 26.0 (21.7 - 30.4)
FOLFOX4 alone: 20.2 (17.7 - 23.1)

Panitumumab-FOLFOX4 vs FOLFOX4 alone

Events no. / total no. (%)

Panitumumab-FOLFOX4: 204/259 (79)
FOLFOX4 alone: 218/253 (86)

Median Mo (95% CI)

Panitumumab-FOLFOX4: 25.8 (21.7 - 29.7)
FOLFOX4 alone: 20.2 (17.6 - 23.6)

No. at Risk

Panitumumab-FOLFOX4
FOLFOX4 alone

Primary Analysis

Updated Analysis

Key inclusion criteria
- Patients ≥ 18 years with histologically confirmed diagnosis of mCRC
- ECOG PS 0-2
- Prior adjuvant chemotherapy allowed if completed > 6 months before inclusion

Amendment in October 2008 to include only KRAS wild-type patients

Primary endpoint: Response Rate
FIRE-3: Overall Survival in All RAS WT
(No detectable mutations in KRAS 61/146, NRAS exon 2, or NRAS exon 3)


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<thead>
<tr>
<th>Events n/N (%)</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI + Cetuximab</td>
<td>91/171 (53.2%)</td>
<td>33.1</td>
</tr>
<tr>
<td>FOLFIRI + Bevacizumab</td>
<td>110/171 (64.3%)</td>
<td>25.6</td>
</tr>
</tbody>
</table>

HR 0.70 (95% CI: 0.53-0.92)
Log rank test P = 0.011

Δ = 7.5 Months

Numbers at risk:
- FOLFIRI + Cetuximab: 171
- FOLFIRI + Bevacizumab: 171

<table>
<thead>
<tr>
<th>RAS wild-type population (N = 342)</th>
<th>FOLFIRI + Cetuximab</th>
<th>FOLFIRI + Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>10.4 months 95% CI</td>
<td>10.2 months 95% CI</td>
</tr>
<tr>
<td>ORR</td>
<td>65.5% 57.9 - 72.6</td>
<td>59.6% 51.9 - 67.1</td>
</tr>
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</table>

Ratio: HR 0.93 (0.74 - 1.17) P = 0.54
OR: 1.28 (0.83 - 1.99) P = 0.32
CALGB / SWOG 80405: Bevacizumab vs Cetuximab in First-Line KRAS ex 2 WT mCRC

- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, TTF, DOR, and safety

NCT identifier: NCT00265850.

CALGB/SWOG 80405: OS (All RAS Wildtype Patients)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Bev</td>
<td>256 (178)</td>
<td>31.2 (26.9-34.3)</td>
<td>0.9 (0.7-1.1)</td>
<td>.40</td>
</tr>
<tr>
<td>Chemo + Cetux</td>
<td>270 (177)</td>
<td>32.0 (27.6-38.5)</td>
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