<table>
<thead>
<tr>
<th>Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support/P.I.</td>
</tr>
<tr>
<td>Bayer</td>
</tr>
<tr>
<td>Honoraria/Advisory Board</td>
</tr>
<tr>
<td>Roche, Amgen, Bayer, Lilly</td>
</tr>
</tbody>
</table>
Objectives

• 1) Demonstrate knowledge of the epidemiology of colorectal cancer

• 2) Relate the importance of staging in treatment decisions

• 3) Summarize the management of adjuvant and metastatic therapies
Definitions
The Colorectum...
Side also matters! 

Bettington, et al Histopathology, 2013
Colorectal Cancer

- **Third** most common cancer in men and women alike
- **Lifetime probability** 1 in 17
BC Incidence Rates - Colorectal Cancer

Males

Females

Age-standardized rate per 100,000 (log scale)


Prostate
Lung
Colorectal
Bladder
Stomach
Non-Hodgkin Lymphoma
Kidney
Melanoma

Breast
Lung
Colorectal
Uterus
Ovary
Non-Hodgkin Lymphoma
Pancreas
Melanoma
Survival with Colorectal Cancer

BC Men

BC Women
Colorectal Cancer (CRC)

- Sporadic (average risk) (65%–85%)
- Family history (10%–30%)
- Rare syndromes (<0.1%)
- HNPCC (5%)
- FAP (1%)
Who is at risk?

- Males=Females
- Risk increases with age
  - Average age at diagnosis is 67-70 yrs
- Industrialized nations
- Most cancers start as polyps - precancerous growths
Adenoma to Carcinoma Pathway

Normal → Adenoma → Cancer

- APC loss
- K-ras mutation
- Chrom 18 loss
- p53 loss

Normal Epithelium, Hyperproliferation, Early Adenoma, Intermediate Adenoma, Late Adenoma, Cancer

ASCO 2001 - www.asco.org
Colon Screening in BC

Colon Check Pilot Program
- Funding from Ministry of Health in July 2008
- Screening began in January 2009 in Penticton; Powell River (September 2009) and Vancouver core (April 2010)
- Approximately 20,000 screened

Provincial Colon Screening Program
- Announced in **November 2012** by Ministry of Health
- FIT covered by MSP on April 1, 2013
- Program rolled out in province wide November 15, 2014
## Colon Screening Program Overview

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Men &amp; Women age 50-74</th>
</tr>
</thead>
</table>
| **Screening Test** | Patient obtains requisition for screening from health care provider  
  – Fecal immunochemical test (FIT) for average risk  
  – Screening colonoscopy for higher than average risk  
  FIT Specimens are returned to the lab for processing and reporting |
| **Results**       | Results mailed to both patient and health care provider |
| **Reminder**      | Mailed to patient and health care provider when time to rescreen |
# Colon Screening Policy

<table>
<thead>
<tr>
<th>Risk</th>
<th>Screening Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Risk</td>
<td>Fecal immunochemical test (FIT) is recommended every two years for people who do not have a personal history of adenomas or a significant family history of colon cancer.</td>
</tr>
<tr>
<td>Higher than Average Risk</td>
<td>Colonoscopy is recommended every five years for people with at least one of the following:</td>
</tr>
<tr>
<td></td>
<td>• One first degree relative (mother, father, sister, brother, daughter or son) with colon cancer diagnosed under the age of 60; or,</td>
</tr>
<tr>
<td></td>
<td>• Two or more first degree relatives with colon cancer diagnosed at any age; or,</td>
</tr>
<tr>
<td></td>
<td>• A personal history of adenomas.</td>
</tr>
</tbody>
</table>
Early Program Statistics

– 45% of eligible patients who have had a FIT have been registered
– Over 91,000 FITs have been completed through the program
– Over 22,000 patients have been referred to colonoscopy to investigate an abnormal FIT or for primary screening in higher risk individuals.
Early Program Statistics

– Of the **1,483 patients with an abnormal FIT** results that have had their colonoscopy and have pathology results available for review:
  
  • 34% had a normal colonoscopy
  • 16% had other pathology such as hyperplastic polyps
  • 25% had low risk pre-cancerous polyps
  • 24% had high risk pre-cancerous polyps
  • 1% had cancer.
Staging
Staging – 4 stages

- **Stage I** – Cancer has grown thru the mucosa up to the muscular layer
- **Stage II** – Cancer has spread into muscularis propria but not into lymph nodes
- **Stage III** – Cancer has spread into lymph nodes but not to other parts of the body
- **Stage IV** – Cancer has metastasized to distant organs
5-Year Relative Survival By AJCC Stage

- Stage I: (T1–2N0) 93%
- Stage IIA: (T3N0) 85%
- Stage IIB: (T4N0) 72%
- Stage IIIA: (T1–2N1) 83%
- Stage IIIB: (T3–4N1) 64%
- Stage IIIC: (TanyN2) 44%
- Stage IV: (M1) 8%

O’Connell et al., 2004.
Primary tumor (T)

- Tis: Carcinoma in situ
- T1: Tumor invades submucosa
- T2: Tumor invades muscularis propria
- T3: Tumor invades through muscularis propria or subserosa
- T4: Tumor directly invades other organs or structures

Regional lymph nodes (N)

- N0: No regional lymph node metastases
- N1a: 1 N+
- N1b: 2-3 N+
- N2a: 4-6 N+
- N2b: ≥7 N+

Distant metastases (M)

- M0: No distant metastases
- M1: Distant metastases

AJCC v7 Effective Jan 2010

AJCC = American Joint Committee on Cancer.
National Comprehensive Cancer Network (NCCN), 2008; Greene et al., 2002.
AJCC v7

Stage II

5yr rel OS (%)

Stage III

Gunderson et al, JCO 2009
Adjuvant Treatment for Colon Cancer
CRC
Demographics and Presentation

12.2% stage I
18.6% stage IV
24.5% stage II
32.6% stage III
The Evolution of Adjuvant Therapy

1990  5-FU/Levamisole 12 months > observation.
1994  5-FU/LV 12 months > than observation
1998  5-FU/LV > than 5-FU/Levamisole.
1998  6 months = 12 months.
2003  FOLFOX > 5FU/LV
2004  Capecitabine = 5FU/LV.
2005  No role for Irinotecan confirmed.
2009  CAPOX better that 5FU/LV
2010  Role of biological agents negative
       Avastin /Cetuximab
Intergroup 0035

Stage III Colon
n = 930

5-FU + Levamisole

Levamisole

No Adjuvant Rx

52 weeks

Intergroup 0035

OS

16% absolute reduction

BCCA Adjuvant Chemotherapy

• **Stage III: N1+**
  - FOLFOX / CAPOX
  - Capecitabine: Elderly or Unfit

• **Stage II**
  - High Risk T4: FOLFOX
  - Low Risk: Capecitabine
    - If treatment deemed necessary / Rule out MSI
MOSAIC: Study Design

n=2246

Completely resected colon cancer

• Stage II, 40%; Stage III, 60%

FOLFOX4
(LV5FU2 + oxaliplatin 85 mg/m²)

(n=1123)

LV5FU2

(n=1123)
MOSAIC 6-yr DFS: ASCO 2007

Events

- FOLFOX4: 304/1123 (27.1%)
- LV5FU2: 360/1123 (32.1%)

HR [95% CI]: 0.80 [0.68–0.93]

p = 0.003

5.9%
Disease-free Survival: Stage II and Stage III Patients

<table>
<thead>
<tr>
<th></th>
<th>HR [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>0.84 [0.62–1.14]</td>
<td>0.258</td>
</tr>
<tr>
<td>Stage III</td>
<td>0.78 [0.65–0.93]</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Months

Probability

FOLFOX4 stage II
LV5FU2 stage II
FOLFOX4 stage III
LV5FU2 stage III

p=0.258
p=0.005

3.8%
7.5%
XELOXA Trial

CAPOX (6 months)
- capecitabine 1000mg/m² bid d1–14
- oxaliplatin 130mg/m² d1

HR = 0.80 (95% CI: 0.69–0.93)
p = 0.0045
BCCA Adjuvant Chemotherapy

- **Stage III: N1+**
  - FOLFOX/ CAPOX
  - Capecitabine: Elderly or Unfit

- **Stage II**
  - High Risk T4: FOLFOX
  - Low Risk: Capecitabine if treatment deemed necessary (R/O MSI)
X-ACT: Unfit

Primary endpoint met and trend to superior DFS (ITT)

CAPECITABINE
1250mg/m² BID, d1–14, q21d
BCCA Adjuvant Chemotherapy

• Stage III: N1+
  • FOLFOX
  • CAPOX (XELOX): Funding October 1 2011
  • Capecitabine: Elderly or Unfit

• Stage II
  • High Risk T4: FOLFOX
  • Low Risk: Capecitabine if treatment deemed necessary (R/O MSI)
MOSAIC: DFS High-risk Stage II

Disease-free survival (months)

- FOLFOX4 n=286
- LV5FU2 n=290

Probability

HR: 0.74; (CI): 0.52–1.06

ASCO criteria
- T4 tumour with adherence to or invasion of local organs
- Bowel obstruction at presentation
- Perforation at tumour site
- Poorly differentiated tumour histology
- Peritumoural lymphovascular involvement
- Questionable surgical margin
- <12 nodes examined

7.2%
Microsatellite Instability - Colon cancer

- Tumors: Poorly differentiated, Signet-ring-cell, Lymphocytic infiltration, near diploid
- Right sided, Female, Early stage, Better prognosis
- Malignant cells resistant to 5-FU¹,²

¹Carethers, 1999; ²Arnold 2003
Overall Survival stage II MSI
Treatment 5FU

Untreated: 93%
Treated: 75%

HR: 3.15 (1.07-9.29)
p=0.03

N = 55
N = 47

5 yr OS
What happened to the biologics?

- **EGFR Monoclonal Antibodies**
  - Panitumumab, Cetuximab
- **VEGF Monoclonal Antibodies**
  - Bevacizumab
- **ALL NEGATIVE !!!**
Future in Adjuvant?

New drugs?
IDEA
International Duration Evaluation in Adjuvant

• Worldwide effort to address Duration

• 6 vs 3 months

Group-specific question

e.g.
+/- BEV
+/- Celecoxib
+/- Agents X/Y/Z

FOLFOX or XELOX
Adjuvant Treatment for Rectal Cancer
Radiation and Surgery

- Surgery vs Radiation and Surgery
  - 5 Y OS 62 vs 63%
  - Pre-op 46% reduced LRR
  - Post-op 37% reduced LRR

Total Mesorectal Excision established as the superior surgery

1970s | 1980s | 1990s | 2000s

2001: Radiation reduces Loco Regional Relapse (LRR) even when TME is done.

CCCG Lancet 2001; Kapitejn NEJM 2001
Radiation

- **Preoperative preferred: Short or Long Course**

- **Short:** The tumour **doesn’t need** to be smaller
  - 5 days treatment followed within a week by surgery. Chemotherapy after if necessary

- **Long:** The tumour **needs** to be made smaller before surgery:
  - 5 radiation treatments/week for 5 weeks with capecitabine followed 4-6 weeks later by surgery
  - Chemotherapy after if necessary
Rectal Cancer: Short Course XRT

- Radiation
  - 1 week

- Surgery

- Chemo
  - N: Pathology
  - N1 FOLFOX 6 months
  - N0 Cape 6 months

6-8 weeks
Rectal Cancer: Long Course

- Chemo-radiation
  - 5 weeks

- Surgery

6-8 weeks

- Chemo
  - N: Imaging
  - N1 FOLFOX 4 months
  - N0 Cape 4 months
Surveillance

- CEA every 3 months for 3 yrs and then every 6 months for another 2 yrs = 5 years
- Imaging chest abdomen and pelvis yearly for 5 years
- Why?..
- Liver/ lung lesions may be cured with surgery
Regional Treatment Strategies

5 year survival 30-35% following resection of oligo-hepatic metastases
Metastatic Colorectal Carcinoma
Lines of Therapy Today BCCA

- **First Line**
  - FOLFIRI + Bevacizumab
  - Capecitabine PS 2

- **Second Line**
  - FOLFOX

- **Third Line**
  - Ras WT: Panitumumab or Cetuximab
FLUORINATED PYRIMIDINES, A NEW CLASS OF TUMOUR-INHIBITORY COMPOUNDS

By Prof. Charles Heidelberger, Dr. N. K. Chaudhuri, Dr. Peter Danneberg, Mrs. Dorothy Moore and Mrs. Lois Griesbach
McArdle Memorial Laboratory, The Medical School, University of Wisconsin, Madison, Wisconsin

And

Dr. Robert Duschinsky, Dr. R. J. Schnitzer, E. Pleven and J. Scheiner
Hoffmann-LaRoche, Inc., Nutley, New Jersey

In view of the profound biological effects often obtained when fluorine is substituted for hydrogen in several classes of compounds and because of the effectiveness, albeit limited, of various nucleic acid analogues in the treatment of human and animal cancer, it was felt that a fluorine-substituted purine or pyrimidine might display tumour-inhibitory activity. Attention was focused on the pyrimidines because of suggestions that uracil may be utilized and from the demonstration by Welch and his colleagues of tumour-inhibitory activity of 6-azauracil. Accordingly, we have synthesized a number of hitherto unknown 5-fluoropyrimidines and their 2-thio derivatives. 5-Fluorouracil (I Ro 2-9757) and 5-fluoro-oxotic acid (II Ro 2-9945) exert considerable anti-tumour activity against transplanted tumours in rats and mice, whereas 5-fluorocytosine (III Ro 2-9915)
First Line

FOLFOX or FOLFIRI?
FOLFOX 6 vs FOLFIRI

226 Patients Randomized (Tournigand et al)

Arm A

FOLFIRI

CPT-11 180 mg/m² IV + simplified LV5FU

until progression

FOLFOX6

until progression

Arm B

FOLFOX6

L-OHP 100 mg/m² IV + simplified LV5FU

until progression

until progression

R

FOLFIRI

until progression
FOLFIRI with FOLFOX6 sequencing trial in advanced CRC: survival

Conclusion: no survival advantage to starting with one regimen over starting with the other

FOLFIRI = 5-FU/LV plus irinotecan
FOLFOX = 5-FU/LV plus oxaliplatin

<table>
<thead>
<tr>
<th>N pts</th>
<th>FOLFOX (1&lt;sup&gt;st&lt;/sup&gt; line) 111</th>
<th>→</th>
<th>FOLFIRI (2&lt;sup&gt;nd&lt;/sup&gt; line) 69</th>
<th>→</th>
<th>FOLFIRI (1&lt;sup&gt;st&lt;/sup&gt; line) 109</th>
<th>→</th>
<th>FOLFOX (2&lt;sup&gt;nd&lt;/sup&gt; line) 81</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>54%</td>
<td></td>
<td>4%</td>
<td></td>
<td>56%</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>Liver resection</td>
<td>21%</td>
<td></td>
<td>9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS (mos)</td>
<td>8.1</td>
<td></td>
<td>2.5</td>
<td></td>
<td>8.5</td>
<td></td>
<td>4.2</td>
</tr>
<tr>
<td>OS (mos)</td>
<td>20.6</td>
<td></td>
<td></td>
<td></td>
<td>21.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2nd line: 62%

2nd line: 74%

Tournigand et al., JCO 2004
Why add the bevacizumab?
VEGF Overexpression and Abnormal Blood Vessels

A. Vasculature from wild type mice

B. Vasculature from mice overexpressing VEGF

IFL and Avastin: OS

HR = 0.66 (95% CI: 0.54–0.81)

p < 0.001

ITT population Hurwitz et al. NEJM 2004
HR = 0.83 [97.5% CI 0.72–0.95] (ITT)

p = 0.0023

Saltz et al., JCO 2008
How long do you treat for in first line?

Drug Holidays or Treatment to Progression?
OPTIMOX 2

6 FOLFOX   FOLFOX

5FU/LV

6 FOLFOX   FOLFOX

Maindrault-Goebel et al, ASCO 2006
Lesson from OPTIMOX2:
Complete chemo free intervals may not be ideal

OPTIMOX 2: OS

Maintenance

- 26 months
- $P = 0.0549$

CFI

- 19 months

OS 7 months

Maindrault-Goebel et al, ASCO 2007
Second Line?

What ever you didn’t use first line
Concept of “All-3-Drugs”
11 Phase III Trials, 5768 Patients

First-Line Therapy
- Infusional 5-FU/LV + irinotecan
- Infusional 5-FU/LV + oxaliplatin
- Bolus 5-FU/LV + irinotecan
- Irinotecan + oxaliplatin
- Bolus 5-FU/LV LV5FU2
- FOLFOXIRI CAIRO

2007
Ras Wild Type: EGFR Inhibitors
EGFR (Epidermal Growth Factor Receptor)

Cell Membrane

EGFR

TK TK

TK TK

P P

STATs

PI3 kinase

Akt P

PTEN P

KRas

MAPK/ERK

Apoptosis

Proliferation

Angiogenesis

Invasion & metastasis

Panitumumab

Cetuximab
408 Phase III Study  **KRAS WT**
Panitumumab Monotherapy in Chemorefractory Patients With mCRC

**PFS**
HR 0.45; (95% CI: 0.34–0.59); p < 0.0001

**OS**
HR 0.99; (95% CI: 0.75–1.29)

**THIRD LINE**
NCIC CO.17 Phase III Study
Cetuximab Monotherapy in Chemorefractory mCRC

**PFS**
HR 0.40; (95% CI: 0.30–0.54); p < 0.001

**OS**
HR 0.55; (95% CI: 0.41–0.74); p < 0.001

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Events n/N (%)</th>
<th>Median (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab</td>
<td>383/499 (76.8)</td>
<td>10.4 (9.4, 11.6)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>392/500 (78.4)</td>
<td>10.0 (9.3, 11.0)</td>
</tr>
</tbody>
</table>

Retention rate: 1.06, 95% CI: (0.82, 1.29)
mCRC: Approximately 60% KS WT vs 40% KRAS MT

KRAS exon 2 wild-type subset
Other RAS Mutations

KRAS

EXON 1

12 13

EXON 2

61

EXON 3

146

NRAS

EXON 1

12 13

EXON 2

59 61

EXON 3

117 146

EXON 4
BEST BIOLOGIC FIRST LINE?

- FIRE 3
- 80408

VEGF MoA

EGFR MoA
FIRE 3

Previously untreated patients with mCRC WT KRAS N= 592

FOLFIRI and bevacizumab N=295

FOLFIRI, and cetuximab N=297

PRIMARY OBJECTIVE : RR by RECIST
FIRE 3

Progression-free survival

Events
n/N (%)  Median  95% CI
FOLFIRI + Cetuximab 250/297 (84.2%) 10.0  8.8 – 10.8
FOLFIRI + Bevacizumab 242/295 (82.0%) 10.3  9.8 – 11.3

HR 1.06 (95% CI 0.88 – 1.26)
Log-rank p = 0.547

Overall survival

Events
n/N (%)  Median  95% CI
FOLFIRI + Cetuximab 158/297 (53.2%) 28.7  24.0 – 36.6
FOLFIRI + Bevacizumab 185/295 (62.7%) 25.0  22.7 – 27.6

HR 0.77 (95% CI: 0.62 – 0.96)
Log-rank p = 0.017

RR ITT: 62% Cetuximab vs 58% Bevacizumab
P = .183
CALGB/SWOG 80405: FINAL DESIGN

mCRC
1st-line
KRAS wild type (codons 12,13)
STRATA:
FOLFOX/FOLFIRI
Prior adjuvant
Prior XRT

FOLFIRI
or
FOLFOX
MD choice

Chemo + Cetuximab

Chemo + Bevacizumab

N = 1140
1° Endpoint: Overall Survival
CALGB/SWOG 80405: Progression-Free Survival
(Investigator Determined)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>PFS (m) Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Bev</td>
<td>559 (498)</td>
<td>10.8</td>
<td>9.7-11.4</td>
</tr>
<tr>
<td>Chemo + Cetux</td>
<td>578 (499)</td>
<td>10.4</td>
<td>9.6-11.3</td>
</tr>
</tbody>
</table>

P=0.55  
HR 1.04 (0.91 -1.17)
Anything New?

• New drugs: Regorafenib
Regorafenib

- **Regorafenib inhibits multiple cell-signaling kinases:**
  - Angiogenic
    - VEGFR1–3, TIE2
  - Stromal
    - PDGFR-β, FGFR
  - Oncogenic
    - KIT, PDGFR, RET

Wilhelm SM et al. *Int J Cancer* 2011
CORRECT

mCRC after standard therapy

Randomization

Regorafenib + BSC
160 mg orally once daily
3 weeks on, 1 week off

Placebo + BSC
3 weeks on, 1 week off

2:1

Primary Endpoint: OS
Overall survival

Survival distribution function

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>6.4 mos</td>
<td>5.0 mos</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0052</td>
<td></td>
</tr>
</tbody>
</table>

Days from randomization

Placebo N=255
Regorafenib N=505

Hazard ratio: 0.77
p-value: 0.0052

6 weeks
### Response

<table>
<thead>
<tr>
<th>Best response, %</th>
<th>Regorafenib (N=505)</th>
<th>Placebo (N=255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Stable disease</td>
<td>43.8</td>
<td>14.9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>49.5</td>
<td>80.0</td>
</tr>
</tbody>
</table>

**Disease control rate, %**

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib (44.8%)</th>
<th>Placebo (15.3%)</th>
</tr>
</thead>
</table>

*DCR = PR + SD; p<0.000001
Anything New?

- MSI Tumors: IO works!!
## Histology of MSI Cancers

<table>
<thead>
<tr>
<th>Feature</th>
<th>MSI</th>
<th>MSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prox. Spleen</td>
<td>94%</td>
<td>34%</td>
</tr>
<tr>
<td>Large Size (&gt;6 cm)</td>
<td>59%</td>
<td>29%</td>
</tr>
<tr>
<td>Poorly Diff.</td>
<td>53%</td>
<td>7%</td>
</tr>
<tr>
<td>Extracell. Mucin (pred.)</td>
<td>35%</td>
<td>7%</td>
</tr>
<tr>
<td>Lymph Infiltrates (int.)</td>
<td>47%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Pembrolizumab

Anything New?

• Left vs Right
Yes, Side does matter

Bettington, et al Histopathology, 2013
Yes, Side does matter

Bettington, et al *Histopathology*, 2013
OS by sidedness: CALGB 80405 and FIRE-3

<table>
<thead>
<tr>
<th></th>
<th>Right 1° Median OS (mos)</th>
<th>Left 1° Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>80405</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS wt N=1025</td>
<td>Cet (N=293) 16.7</td>
<td>Bev (N=732) 36.0</td>
</tr>
<tr>
<td></td>
<td>Bev (N=24.2)</td>
<td></td>
</tr>
<tr>
<td><strong>FIRE-3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All RAS wt N=394</td>
<td>Cet (N=88) 18.3</td>
<td>Bev (N=306) 38.3</td>
</tr>
<tr>
<td></td>
<td>Bev (N=23.0)</td>
<td></td>
</tr>
</tbody>
</table>

RIGHT SIDE: BEV DID BETTER
OS by sidedness: CALGB 80405 and FIRE-3

<table>
<thead>
<tr>
<th></th>
<th>Right 1° Median OS (mos)</th>
<th>Left 1° Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 293</td>
<td>N = 732</td>
</tr>
<tr>
<td>80405</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS wt N=1025</td>
<td>Cet 16.7</td>
<td>36.0</td>
</tr>
<tr>
<td></td>
<td>Bev 24.2</td>
<td>31.4</td>
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<tr>
<td>FIRE-3</td>
<td></td>
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</tr>
<tr>
<td>All RAS wt N=394</td>
<td>Cet 18.3</td>
<td>38.3</td>
</tr>
<tr>
<td></td>
<td>Bev 23.0</td>
<td>28.0</td>
</tr>
</tbody>
</table>

**LEFT SIDE: CETUX DID BETTER**
BEST BIOLOGIC FIRST LINE?

COMING SOON

VEGF MoA

RIGHT

EGFR MoA

LEFT (RAS WT)
Conclusion
BCCA Adjuvant Chemotherapy

- **Stage III: N1+**
  - FOLFOX/ CAPOX
  - Capecitabine: Elderly or Unfit

- **Stage II**
  - High Risk T4: FOLFOX
  - Low Risk: Capecitabine if treatment deemed necessary (R/O MSI)
BCCA Metastatic Colorectal Carcinoma

• First Line
  • FOLFIRI + Bevacizumab
  • Capecitabine PS 2

• Second Line
  • FOLFOX or FOLFIRI

• Third Line
  • Ras WT: Panitumumab or Cetuximab
BCCA Metastatic Colorectal Carcinoma

• **Regorafenib**: Not approved

• **MSI Tumors**: Find a trial

• **Anti- EGFR vs VEGF**
  - **RAS M+**: Anti –EGFR does not work
  - **Pretty soon**:
    - **Left RAS WT**: Anti- EGFR
    - **Right**: Anti- VEGF
Colorectal Cancer: 20 Years Later
meta-analysis 1992
80405 results

Fig 2. Overall survival. J Clin Oncol, 1992

Presented By Alan Venook at 2014 ASCO Annual Meeting
Thank you

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