## Disclosure

<table>
<thead>
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<th>Category</th>
<th>Company</th>
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<tr>
<td>Research Support/P.I.</td>
<td>Roche, Amgen</td>
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<td>Honoraria</td>
<td>Roche, Amgen</td>
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<td>Advisory Board</td>
<td>Sanofi, Roche</td>
</tr>
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</table>
Objectives

Highlight current treatment in the adjuvant setting

Review state of the art treatment in the metastatic setting

Discuss new treatments in the future in colorectal carcinoma
Definitions
The Colorectum

• The colon + rectum = the large intestine

• Colon makes up the first 5 to 6 feet of the large intestine
  • Above the peritoneum

• Rectum makes up the last 6 inches (12-15cm) ending at the anus
  • Below the peritoneum
The Colorectum...

- Ascending colon
- Transverse colon
- Descending colon
- Sigmoid colon
- Rectum
- Appendix

Peritoneal Reflection
The Statistics
Colorectal Cancer

- Third most common cancer in men and women alike
- Lifetime probability 1 in 17
- In BC 2,400 new cases are diagnosed/year
- BC has the one of the best survival outcomes compared to other provinces
BC Incidence Rates - Colorectal Cancer

Males

Females
Survival with Colorectal Cancer

BC Men

- Lung
- Prostate
- Colorectal
- Stomach
- Pancreas
- Bladder
- Non-Hodgkin Lymphoma
- Esophagus

BC Women

- Lung
- Breast
- Colorectal
- Stomach
- Pancreas
- Ovary
- Non-Hodgkin Lymphoma
- Uterus
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

Genetic Changes:
- APC loss
- K-ras mutation
- Chrom 18 loss
- p53 loss

Stages:
- Normal Epithelium
- Hyperproliferation
- Early Adenoma
- Intermediate Adenoma
- Late Adenoma
- Cancer
Fecal Occult Blood Test
Colorectal Cancer (CRC)

- **Sporadic (average risk)** (65%–85%)
- **Family history** (10%–30%)
- **HNPCC** (5%)
- **FAP** (1%)
- **Rare syndromes** (<0.1%)
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 such as liver or lungs
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

T4a: perf. visceral peritoneum
T4b: invasion of organs

Regional lymph nodes (N)

- **N0**: No regional lymph node metastases
- **N1**: Metastases in 1–3 regional lymph nodes
- **N2**: Metastases in 4 or more regional lymph nodes

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.**
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
       1  Avastin negative
       2  Cetuximab negative
BCCA Adjuvant Chemotherapy

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

- **Stage II**
  - Low Risk: Capecitabine
    - If treatment deemed necessary / Rule out MSI
  - High Risk T4: FOLFOX
BCCA Adjuvant Chemotherapy

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

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

n=2246

Enrollment:
Oct 1998–Jan 2001 (146 centres; 20 countries)

- Completely resected colon cancer
- Stage II, 40%; Stage III, 60%
- Age 18–75 years
- KPS ≥60
- No prior chemotherapy

FOLFOX4
(LV5FU2 + oxaliplatin 85 mg/m²)

LV5FU2

(n=1123)

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

Disease-free survival (months)

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

Data cut-off: June 2006

**HR [95% CI]** | **p-value**
--- | ---
Stage II | 0.84 [0.62–1.14] | 0.258
Stage III | 0.78 [0.65–0.93] | 0.005

- **FOLFOX4 stage II**
- **LV5FU2 stage II**
- **FOLFOX4 stage III**
- **LV5FU2 stage III**

*Probability*

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<th>Months</th>
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<td>66</td>
<td>0.20</td>
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<tr>
<td>72</td>
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*3.8% (p=0.258)*

*7.5% (p=0.005)*
XELOXA Trial

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

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

ITT population
BCCA Adjuvant Chemotherapy

- **Stage III: N1+**
  - FOLFOX
  - CAPOX: Funding October 1 2011
  - Capecitabine: Elderly or Unfit

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

Chemo-naïve
Stage III
resection ≤8 weeks

6 months

CAPECITABINE
1250mg/m² BID, d1–14, q21d
n = 1004

BOLUS 5-FU 425mg/m²
LV 20mg/m², d1–5, q28d
n = 983

Cassidy NEJM 352:2696-2704, 2005
Primary endpoint met and trend to superior DFS (ITT)

- Capecitabine (n=1004): 64.2%
- 5-FU/LV (n=983): 60.6%

HR = 0.87 (95% CI: 0.75–1.00)
p = 0.0528
What about Stage II
DFS: Stage II and Stage III Patients

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<td>0.7</td>
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<td>6</td>
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<td>0.3</td>
<td>6</td>
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- p=0.258
- p=0.005

UNDERPOWERED for Stage II

3.8%
7.5%
BCCA Adjuvant Chemotherapy

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

- **Stage II**
  - Low Risk: Capecitabine if treatment deemed necessary (R/O MSI)
  - High Risk T4: FOLFOX
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-FU\textsuperscript{1,2}

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

N = 55

N = 47

Untreated 93%
Treated 75%

5 yr OS

HR: 3.15 (1.07-9.29)
p=0.03
BCCA Adjuvant Chemotherapy

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

- **Stage II**
  - Low Risk: Capecitabine if treatment deemed necessary (R/O MSI)
  - High Risk T4: FOLFOX
5-Year Relative Survival By AJCC Stage

Percentage of Patients (%)

Stage I (T_{1-2}N_0) 93
Stage IIA (T_3N_0) 85
Stage IIB (T_4N_0) 72
Stage IIIA (T_{1-2}N_1) 83
Stage IIIB (T_{3-4}N_1) 64
Stage IIIC (T_{any}N_2) 44
Stage IV (M_1) 8

p < .001

O'Connell et al., 2004.
MOSAIC: DFS
High-risk Stage II

Disease-free survival (months)

FOLFOX4 n=286
LV5FU2 n=290

HR: 0.74; (CI): 0.52–1.06

7.2%
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

R

3 mos

6 mos

FOLFOX or XELOX
Decision-making for Adjuvant Rx

Online resources

• www.mayoclinic.com/calcs/colon/input.cfm
• www.adjuvantonline.com/colon.jsp
Adjuvant Treatment for Rectal Cancer
Radiation and Surgery

1970s

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

1980s

Total Mesorectal Excision established as the superior surgery

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
Rectal Cancer: Short Course XRT

- Radiation
  - 1 week

- Surgery

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

1 week

6-8 weeks
Rectal Cancer: Long Course

- Chemo-radiation
  - 5 weeks

- Surgery

- Chemo
  - N: Imaging
  - N1 FOLFOX 4 mo
  - N0 Cape 4 mo

6 weeks → 6-8 weeks → 6 weeks
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 solitary/oligo- hepatic metastases
Metastatic Colorectal Carcinoma
Lines of Therapy Today BCCA

• First Line
  - FOLFIRI + Bevacizumab
  - Capecitabine PS 2

• Second Line
  - FOLFOX

• Third Line
  - Kras 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-aza-uracil. 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-otic acid (II Ro 2-9945) exert considerable anti-tumour activity against transplanted tumours in rats and mice, whereas 5-fluorocytosine (III Ro 2-9915)

Nature, March 30, 1957
FOLFOX or FOLFIRI?
Irinotecan

- Topoisomerase I inhibitor, causes DNA double strand breaks and S-phase specific cytotoxicity
- Toxicities are GI (diarrhea, nausea, vomiting) and neutropenia

Irinotecan

Converted by carboxylesterase to the active metabolite: 7-ethyl-10-hydroxycamptothecin (SN38)

SN38

Topo1

SN38

Stabilization of the cleavable complex of topoisomerase I and DNA

Topo1

SN38

Interference with DNA replication fork

DNA double strand break
Oxaliplatin

A complex of 1,2-diaminocyclohexane, an oxalate group and platinum

- Formation of DNA adducts: interstrand, intrastrand or DNA protein cross-links
- Interference with DNA replication and transcription
- Apoptosis

- Third generation platinum compound
- Causes inter- and intra-strand crosslinks in DNA, inhibiting DNA synthesis and proliferation
- Only platinum active in CRC
- Cold sensitive Cumulative peripheral neuropathy is the major toxicity

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<tr>
<th>Lesions per Mbp</th>
<th>Mono-adducts</th>
<th>Interstrand</th>
<th>Protein cross-links</th>
<th>Breaks</th>
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<td>Oxaliplatin</td>
<td>118</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Cisplatin</td>
<td>371</td>
<td>23</td>
<td>4</td>
<td>0</td>
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</table>
FOLFOX 6 vs FOLFIRI

226 Patients Randomized (Tournigand et al)

Arm A
- FOLFIRI
- CPT-11 180 mg/m² IV
- + simplified LV5FU
- until progression

Arm B
- FOLFOX6
- L-OHP 100 mg/m² IV
- + simplified LV5FU
- until progression

R
- until progression
- 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

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

Estimated probability

Months

1.0
0.8
0.6
0.4
0.2
0.0

15.6
20.3

IFL + Avastin

IFL + placebo

ITT population

Hurwitz et al. NEJM 2004
How long do you treat for in first line?

Drug Holidays or Treatment to Progression?
OPTIMOX 2

Maindrault-Goebel et al, ASCO 2006
Lesson from OPTIMOX2: Complete chemo free intervals may not be ideal
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
Kras Wild Type: EGFR Inhibitors
Nomenclature

No mutation in Kras=

Wild type Kras=

Treatment with EGFR MOA
Distribution of mutations in mCRC

- KRas Wild Type (60%)
- KRas Mutations
  - KRAS mt (40%)
  - KRAS WT
408 Phase III Study
Panitumumab Monotherapy in Chemorefractory Patients With mCRC

**PFS**
- HR 0.45; (95% CI: 0.34–0.59), p < 0.0001
- Proportion event free (%)
- Time (weeks)

**OS**
- HR 0.99; (95% CI: 0.75–1.29)
- Survival probability (%)
- Time (months)

**THIRD LINE**

NCIC CO.17 Phase III Study **KRAS WT**
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

All Metastatic CRC referred to BCCA: 2009

New Diagnosis mCRC, N=443
1st Line Chemo, N=321
KRAS Test, N=164
2nd Line Chemo, N=117
3rd Line EGFR Therapy, N=49

Any change within 3 months

4th Line Trial Non-evidence based Tx

Should have been 160
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)

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<th>N (Events)</th>
<th>PFS (m) Median</th>
<th>95% CI</th>
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<td>Chemo + Bev</td>
<td>559 (498)</td>
<td>10.8</td>
<td>9.7-11.4</td>
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<tr>
<td>Chemo + Cetux</td>
<td>578 (499)</td>
<td>10.4</td>
<td>9.6-11.3</td>
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P = 0.55
HR 1.04 (0.91 - 1.17)
CALGB/SWOG 80405: Overall Survival

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<th>Arm</th>
<th>N (Events)</th>
<th>OS (m) Median</th>
<th>95% CI</th>
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<tr>
<td>Chemo + Cetux</td>
<td>578 (375)</td>
<td>29.9</td>
<td>27.0-32.9</td>
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<tr>
<td>Chemo + Bev</td>
<td>559 (371)</td>
<td>29.0</td>
<td>25.7-31.2</td>
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P = 0.34
HR 0.925 (0.78-1.09)
BEST BIOLOGIC FIRST LINE?

VEGF MoA

EGFR MoA
What's New?
New

- **Triplets**: FOLFOXIRI
- **Biomarker**: RAS
- **New drugs**: Regorafenib
New

• **Triplets:** FOLFOXIRI
TRIBE TRIAL

Study Design

1st line unresectable mCRC pts
stratified by
✓ center
✓ PS 0/1-2
✓ adjuvant CT

R 1:1

FOLFIRI + bev*
- Bev 5 mg/kg ev g1
- Irinotecan 180 mg/sqm ev g1
- L-LED 200 mg/sqm ev g1
- 5-FU 400 mg/sqm ev g1 bolus
- 5-FU 2400 mg/sqm ev gg1→3

FOLFOXIRI + bev*
- Bev 5 mg/kg ev g1
- Irinotecan 165 mg/sqm ev g1
- Oxaliplatin 85 mg/sqm ev g1
- L-LED 200 mg/sqm ev g1
- 5-FU 3200 mg/sqm ev gg1→3
Primary endpoint: PFS

FOLFIRI + bev, PFS: 9.7 mos
FOLFOXIRI + bev, PFS: 12.2 mos

HR: 0.73 [0.60-0.88]  
p=0.0012
New

• Biomarker: RAS
mCRC: Approximately 60% KS WT vs 40% KRAS MT

KRAS exon 2 wild-type subset
Other RAS Mutations

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<th>Exon</th>
<th>KRAS</th>
<th>NRAS</th>
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<tr>
<td>4</td>
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</table>

- **KRAS**: Mutations at positions 12 and 13 in exon 2, and 61 in exon 3.
- **NRAS**: Mutations at positions 12 and 13 in exon 2, 59 and 61 in exon 3, and 117 and 146 in exon 4.
PRIME study RAS analysis
OS (primary analysis)

MT RAS

HR = 1.25 (95% CI, 1.02–1.55)
P = 0.034

Detriment OS
Significant

- Panitumumab + FOLFOX4 (n = 272)
  187 (69) 15.6 (13.4–17.9)
- FOLFOX4 (n = 276)
  175 (63) 19.2 (16.7–21.8)

MT RAS, MT in any KRAS or NRAS exon 2, 3, or 4
(excludes 7 patients harbouring KRAS/NRAS codon 59 mutations)
EGFR (Epidermal Growth Factor Receptor)

Cell Membrane

PI3 kinase

Akt

PTEN

Ras

MAPK/ERK

Proliferation

Apoptosis

Angiogenesis

Invasion & metastasis

STATs

EGFR (Epidermal Growth Factor Receptor)

Panitumumab

Cetuximab

P

P

TK

TK

EGFR

(Epidermal Growth Factor Receptor)
Distribution of mutations in mCRC

- Super Wild Type: ~50%
- RAS Mutation: ~40%
- New RAS mt: ~10%
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
mCRC after standard therapy

2:1

Primary Endpoint: OS

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

Placebo + BSC
3 weeks on, 1 week off

CORRECT
## Response

<table>
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<th>Best response, %</th>
<th>Regorafenib N=505</th>
<th>Placebo N=255</th>
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<td>Complete response</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Partial response</td>
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<td>Stable disease</td>
<td>43.8</td>
<td>14.9</td>
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<tr>
<td>Progressive disease</td>
<td>49.5</td>
<td>80.0</td>
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**Disease control rate, %**

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<thead>
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<th></th>
<th>Regorafenib N=505</th>
<th>Placebo N=255</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>44.8</td>
<td>15.3</td>
</tr>
</tbody>
</table>

*DCR = PR + SD; p<0.000001*
Overall survival

<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>

Survival distribution function

Days from randomization

Survival distribution function

Placebo N=255
Regorafenib N=505
Conclusion
BCCA Adjuvant Chemotherapy

- **Stage III: N1+**
  - FOLFOX
  - CAPOX (XELOX)
  - Capecitabine: Elderly or Unfit

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

• First Line
  • FOLFIRI + Bevacizumab
  • Capecitabine PS 2

• Second Line
  • FOLFOX or FOLFIRI

• Third Line
  • Ras WT: Panitumumab or Cetuximab
CALGB/SWOG 80405: Overall Survival

Presented by Alan Venook at 2014 ASCO Annual Meeting

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>OS (m) Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Cetux</td>
<td>578 (375)</td>
<td>29.9</td>
<td>27.0-32.9</td>
</tr>
<tr>
<td>Chemo + Bev</td>
<td>559 (371)</td>
<td>29.0</td>
<td>25.7-31.2</td>
</tr>
</tbody>
</table>

P=0.34
HR 0.925 (0.78-1.09)
Colorectal Cancer: 20 Years Later
meta-analysis 1992
80405 results

CALGB/SWOG 80405
30 months

Fig 2. Overall survival.  J Clin Oncol, 1992
IT’S COMPLICATED!
Thank you

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