Progress and Challenges in the Adjuvant Treatment of Stage II & III Colon Cancer

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Monash Health and Monash University
(with thanks to A/P Jeremy Shapiro)

Melbourne, Australia
Apr 2017
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Submission Information

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adjuvant 5FU/Lev increases survival

5yr OS 71% v 55%

Intergroup 0035 Moertel et al 1990 and Ann Int Med 1995
Meta-analysis of adjuvant therapy in Stage II/III colon cancer (n=3351)

Sargent et al (2001)

5-year DFS 69% v 58%
Risk reduction 32%, p<0.001

5-year OS 71% v 64%
Risk reduction 24%, p<0.001

Recurrence

Death from any cause

Adjuvant therapy better
Surgery alone better

NCCTG
NCCTG intergroup
INT 0035
FFCD
NCIC-CTG
Siena
GIVIO
Overall

Sargen et al (2001)
Adjuvant therapy – slow progress

1990: 1 year 5FU + Levamisole

mid 1997: 6 months of 5FU + Leucovorin as good
no advantage gained by adding levamisole

1998 High dose LV = Low dose LV
Monthly = weekly schedule

2002: Infusional 5FU as good with less side-effects
(but need access and infusor)
Evolution of new standards
2004 – 2005

Can an oral fluoropyrimidine replace IV 5FU?
X-ACT trial in adjuvant treatment of Dukes’ C colon cancer

1° endpoint: disease-free survival (DFS)

2° endpoints
- relapse-free survival (RFS)
- overall survival
- tolerability (NCIC CTG)
- pharmacoeconomics
- QoL

Recruitment 1998–2001

Chemo-naïve Dukes’ C, resection ≤8 weeks

Capecitabine
1250mg/m² twice daily, d1–14, q21d
n = 1004

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

24 weeks

Twelves NEJM 2005
Disease-free survival: 5-year update – median follow-up 6.8 years

Estimated probability

- Capecitabine (n=1004): 60.8%
- 5-FU/LV (n=983): 56.7%

HR = 0.88 (95% CI: 0.77–1.01)
NI margin 1.20

Test of non-inferiority p < 0.0001
Test of superiority p = 0.0682
Overall survival:
5-year update – median follow-up 6.8 years

Estimated probability

- **Capecitabine** (n=1004) 71.4%
- **5-FU/LV** (n=983) 68.4%

HR=0.86 (95% CI: 0.74–1.01)
NI margin 1.14

Test of non-inferiority p=0.000116
Test of superiority p=0.06

ITT population
Improved safety profile versus bolus 5-FU/LV (all grades)

- **Diarrhea**: Capecitabine (n=993) vs. Bolus 5-FU/LV (n=974)
- **Stomatitis**: Capecitabine (n=993) vs. Bolus 5-FU/LV (n=974)
- **Hand-foot syndrome**: Capecitabine (n=993) vs. Bolus 5-FU/LV (n=974)
- **Neutropenia**: Capecitabine (n=993) vs. Bolus 5-FU/LV (n=974)
- **Nausea/vomiting**: Capecitabine (n=993) vs. Bolus 5-FU/LV (n=974)
- **Alopecia**: Capecitabine (n=993) vs. Bolus 5-FU/LV (n=974)

* *= p<0.001
† = Laboratory value

X-ACT study conclusions

- Primary endpoint was met
- Trend to improved DFS and OS supported by
  - superior RFS
  - improved safety
- Capecitabine should replace 5-FU/LV in adjuvant treatment of colon cancer
  - no stage II patients included
  - no Rectal Cancer
Adjuvant Therapy – new agents

Given the increased activity of Oxaliplatin and Irinotecan combinations over 5FU in advanced disease....

what is their role in adjuvant therapy?
MOSAIC: Study Design

Primary end-point: (3 yr) disease-free survival
Secondary end-points: overall survival

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

LV5FU2, Leucovorin 200 mg/m² iv over 2 hrs followed by 5-fluorouracil 400 mg/m² bolus and 5-fluorouracil 600 mg/m² iv over 22 hrs on Days 1 and 2, every 14 days; FOLFOX4, LV5FU2 + oxaliplatin 85 mg/m² iv over 2 hrs on Day 1

FOLFOX4
(LV5FU2 + oxaliplatin 85 mg/m²)

LV5FU2
Adjuvant Oxaliplatin therapy

Improves 3 year DFS by a further 5%

DFS by treatment arm (ITT)

- FOLFOX4 (n=1123) 77.8%
- LV5FU2 (n=1123) 72.9%

Hazard ratio: 0.77 [0.65 – 0.92]  p < 0.01

23% risk reduction in the FOLFOX4 arm

C-07 DFS

- FLOX 272  76.5%
- FULV 332  71.6%

p < 0.004
HR: 0.79 [0.67 – 0.93]
21% risk reduction

Mosaic study NEJM 2004

NSABP C7 ASCO 2005  JCO 2007
Disease-free Survival: ITT all pts

3 yr DFS 78.2% vs 72.9%
p = 0.003

PCPA 2017 Eva Segelov

Data cut-off: June 2006
Disease-free Survival: Stage II & III

Data cut-off: June 2006

<table>
<thead>
<tr>
<th>Stage</th>
<th>HR [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>0.84 [0.62–1.14]</td>
<td>0.258</td>
</tr>
<tr>
<td>Stage 3</td>
<td>0.78 [0.65–0.93]</td>
<td>0.005</td>
</tr>
</tbody>
</table>

PCPA 2017 Eva Segelov
Disease-free Survival in Stage III Patients: N1 & N2

Data cut-off: January 16, 2005

- FOLFOX4 – 443 N1
- LV5FU2 – 443 N1
- FOLFOX4 – 229 N2
- LV5FU2 – 232 N2

HR: 0.76
HR: 0.72
Updated Analysis: 6-year OS (2009)

Updated Analysis: 5-year DFS (2009)
### MOSAIC study – 6 yr OS

6 years med f/up – ASCO 2007

<table>
<thead>
<tr>
<th>Prob OS at 6 yrs</th>
<th>5FU</th>
<th>FOLFOX</th>
<th>Net benefit</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>76 %</td>
<td>78.6 %</td>
<td>+ 2.6 %</td>
<td>.057</td>
</tr>
<tr>
<td>Stage II</td>
<td>87 %</td>
<td>87 %</td>
<td>0</td>
<td>.996</td>
</tr>
<tr>
<td>Stage III</td>
<td>69.6%</td>
<td>73 %</td>
<td>+ 4.4 %</td>
<td>.029</td>
</tr>
<tr>
<td>alive with recurrence</td>
<td>7.8 %</td>
<td>6.1 %</td>
<td>+ (1.7%)</td>
<td></td>
</tr>
</tbody>
</table>

- 87 % survival at 5 yrs – much higher than historical data

- No survival benefit at 5 yrs– **can not recommend** Oxaliplatin in Stage II pts
The gain in favour of FOLFOX4 in absolute OS at 6 years is more evident at 10 years (2.2% v 4.6%).

*10-year OS advantage of 8.1% (p=0.016) in the whole population (67.1% v 59.0%),
*6%(p=0.248) with N1 (65.4% v 71.4%)
*12.9% (P=0.013) in N2 (59.5% v 46.6%).
BRAF, MSI MOSAIC

- BRAFV600E mutation was not significantly associated with OS ($P_{965}$)
- pMMR was an independent prognostic factor for a higher risk of death in the final multivariable analysis ($P_{0.014}$). V low rate (9%)
- oxaliplatin provides a significant OS benefit in patients with dMMR tumors and BRAFV600E mutations. However, given the small number of patients, low statistical power
# Mosaic – toxicity data

## Toxicity per Patient (on Treatment)

<table>
<thead>
<tr>
<th>NCI-CTC ≥ grade 3 (% patients)</th>
<th>FOLFOX4</th>
<th>LV5FU2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>41.0 (Gr 4, 12.2)</td>
<td>4.7</td>
</tr>
<tr>
<td>Neutropenia with fever or infection</td>
<td>1.8</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>10.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2.7</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>5.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Allergy</td>
<td>3.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Alopecia (grade 2)</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Neuropathy (grade 3)</td>
<td>12.4</td>
<td>0.0</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

MOSAIC: sensory neuropathy

Months of Follow-up

Grade 0 – no change or symptoms
Grade 1 – mild paresthesia, loss of deep tendon reflexes
Grade 2 – mild or moderate sensory loss, moderate paresthesia
Grade 3 – severe objective sensory loss, paresthesia interfering with function

Patients (%)

During | 1 | 6 | 12 | 18

Months of Follow-up

NEJM 2004 “neuro-toxicity steadily resolves post treatment”
Peripheral Sensory Neuropathy

% of treated patients

- Grade 1
- Grade 2
- Grade 3

During Tx: 48.1
6 months: 31.4
1 year: 30.9
2 years: 22.2
3 years: 14
4 years: 12

27.6, 17.4, 14.2, 11.4

Mosaic – updated neurotoxicity

ASCO 2007
Oxaliplatin Combined With Weekly Bolus Fluorouracil and Leucovorin As Surgical Adjuvant Chemotherapy for Stage II and III Colon Cancer: Results From NSABP C-07

NSABP C7 – similar 3 yr DFS benefit

C-07 DFS

<table>
<thead>
<tr>
<th>Ev #</th>
<th>3yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLOX</td>
<td>272</td>
</tr>
<tr>
<td>FULV</td>
<td>332</td>
</tr>
</tbody>
</table>

p < 0.004
HR: 0.79 [0.67 – 0.93]
21 % risk reduction
## Grade 3/4 Toxicity; C-07

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>FULV Toxicity Grade*</th>
<th>FLOX Toxicity Grade*</th>
<th>$P^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31.6</td>
<td>0.6</td>
<td>36.9</td>
</tr>
<tr>
<td>Dehydration</td>
<td>11.3</td>
<td>0.5</td>
<td>16.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>11.0</td>
<td>0.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7.7</td>
<td>0.7</td>
<td>12.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.3</td>
<td>0.7</td>
<td>4.9</td>
</tr>
<tr>
<td>NCI-Sanofi Neurosensory$^{13}$</td>
<td>0.7</td>
<td>0.0</td>
<td>8.2</td>
</tr>
<tr>
<td>Thrombosis or embolism</td>
<td>3.8</td>
<td>1.1</td>
<td>3.2</td>
</tr>
</tbody>
</table>
Adjuvant XELOX vs 5-FU/LV: NO16968 (XELOXA) phase III trial

- Chemo/radiotherapy-naive stage III colon ≤8 weeks since resection n=1886
- Primary endpoint: superiority of DFS
- Secondary endpoints: RFS, OS, tolerability

Randomization:
- XELOX (6 months)
  - capecitabine 1000mg/m² bid d1-14
  - oxaliplatin 130mg/m² d1 q3w
  - 8 cycles
- Bolus 5-FU/LV (6 months)
  - Mayo Clinic [n=664]
  - or
  - Roswell Park [n=278]

Haller et al. ECCO-ESMO 2009; Abstract 5LBA
5-year DFS: benefit with XELOX maintained and increased over time

Haller et al. ECCO-ESMO 2009; Abstract 5LBA
# Irinotecan: adjuv studies in colon cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>CALGB C89803</th>
<th>ACCORD-2</th>
<th>PETACC-3</th>
<th>HCOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>Irinotecan + bolus 5-FU/LV vs bolus 5FU/LV (Roswell Pk)</td>
<td>Irinotecan + LV5FU2 vs LV5FU2</td>
<td>Irinotecan + LV5FU2 vs LV5FU2: Weekly iri and 2\textsuperscript{nd} weekly: de Gram and AIO</td>
<td>Weekly iri (80/m\textsuperscript{2}) + FU/LV v bolus FU</td>
</tr>
<tr>
<td>n</td>
<td>1264</td>
<td>400</td>
<td>3278</td>
<td>873</td>
</tr>
<tr>
<td>Stage</td>
<td>3</td>
<td>High-risk 3</td>
<td>2 and 3</td>
<td>2 and 3</td>
</tr>
<tr>
<td>Results</td>
<td>NEGATIVE (Trend to Inferiority)</td>
<td>NEGATIVE (Trend to Inferiority)</td>
<td>NEGATIVE (+ve on 2\textsuperscript{o} endpt) 3yr RFS</td>
<td>NEGATIVE</td>
</tr>
</tbody>
</table>

Also negative RCT of FOLFIRI v FU post liver metastatectomy.
Benefit of adjuvant therapy for stage II patients not always clear

- Relatively few stage II patients have been randomized
- Lower risk of recurrence
- Contradictory meta-analyses
  - IMPACT meta-analysis concluded no advantage in 1025 patients\(^1\)
  - NSABP pooled data analysis showed improved event-free and overall survival in 1,565 patients\(^2\)

\(^1\)IMPACT. J Clin Oncol 1999;17:1356–63
QUASAR Trial Design

Complete resection of colon or rectal cancer

Doctor and patient decide

Either: ‘Clear Indication’ for chemotherapy (4320 patients)

Randomise (2x2)

5-fluorouracil (370mg/m²) + high or low-dose folinic acid (in either a 6 x 5-day, 4-weekly or 30 x once-weekly schedule)
levamisole or placebo

Or: ‘Uncertain indication’ for chemotherapy (3239 patients)

Randomise

Observation only (n=1617)

Chemotherapy as for Clear Indication (n=607)
After Oct 1997
5FU+low dose FA (n=1015)
QUASAR: recurrence

5-year recurrence

Chemotherapy: 22.2%
Observation: 26.2%

Relative risk = 0.78 (CI 0.67-0.91)

Number still at risk
- Chemotherapy: 1622, 1350, 1127, 904, 735, 564, 394, 216, 81, 11
- Observation: 1617, 1318, 1040, 844, 690, 511, 349, 214, 84, 6

Years from randomisation

Events, O-E, Var
- Chemotherapy: 288, -40.3, 159.6
- Observation: 351
QUASAR: survival by allocated treatment

5-year survival: 80.3% for Chemotherapy, 77.4% for Observation
Relative risk = 0.83 (CI 0.71-0.97)

p = 0.02

Deaths, O-E, Var for Chemotherapy: 281, -28.5, 152.2
Deaths, O-E, Var for Observation: 328
Dutch trial of 5-FU/LEV suggested improved OS for stage II

Overall survival (%)

Years

5-FU/LEV (n=233)

Control (n=235)

Reasonable to routinely offer high-risk stage II patients adjuvant chemotherapy

- high-risk patients – conventional prognostic factors
  - obstruction or perforation
  - venous or lymphatic invasion
  - perineural invasion
  - tumor adherence
  - less than 10 nodes

- Better prognostic factors could aid in patient selection
  - Biomarker data collection incorporated in most ongoing studies
Is it reasonable to routinely offer high-risk St II patients adjuvant chemotherapy?

➢ Must present benefit accurately and clearly

- 3-5% absolute risk reduction (probably less)

(not 20% reduction in risk of recurrence)
Role of Oxaliplatin in Stage II CRC
Yothers, # 3507

NSABP Meta-analysis c5-8 trials
3000 stage II pts (2009 5FU, 991 Oxali)
5 yr OS “high risk” 90 v 87 %

=> outcomes excellent, oxali had minimal benefit, at most 2-3%
Is Oxali effective in stage II?

- OS HR = 0.95 (0.75-1.21), p = 0.67
- DFS HR = 0.86 (0.71-1.04), p = 0.11
- TTR HR = 0.81 (0.62-1.05), p = 0.10

- No definitive evidence that Oxali is effective in stage II disease
  - relative effect (hazard ratio) may not differ from 1.0
Is there a role for single agent capecitabine in Stage III colon cancer?
MOSAIC trial demonstrated efficacy of FOLFOX4 vs. LV5FU2 is not maintained in patients ≥65 years

<table>
<thead>
<tr>
<th>Prognostic factor (n)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>≥65 (463)</td>
<td></td>
</tr>
<tr>
<td>&lt;65 (884)</td>
<td></td>
</tr>
</tbody>
</table>

André, T et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27(19):3109-3116. Reprinted with permission. © 2009 American Society of Clinical Oncology. All rights reserved.
Capecitabine for Stage III patients?

- Age
- medically unsuitable for oxaliplatin
- unwilling to receive more intensive Rx
- Prefer oral therapy
- to some patients, the toxicity and inconvenience of oxaliplatin will outweigh the added 5-6 % 3 yr DFS benefit
- Low N
More recent history of Adjuvant therapy for Colorectal Cancer

Adjuvant chemo +/- biologic trials

2007 – 2010
NSABP C-08

- mFF6 q2wk X 6 mo
- Bev* q2wk X 1 yr

Allegra JCO 2011
NSABP C-08 DFS

Disease-free survival (%)

Years

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5

0 20 40 60 80 100

mFF6+B 291 77.4
mFF6 312 75.5

Ev 3y DFS

HR 0.89
P 0.15
AVANT study

Primary endpoint: 3 y DFS
Secondary endpoints: OS and safety

Surgery for high risk stage 2/3 colon cancer (n=3,450)

- FOLFOX4
- FOLFOX4 + bev
- XELOX + bev

Duration of treatment:
- FOLFOX4: Observation
- FOLFOX4 + bev: bev alone q3 weeks
- XELOX + bev: bev alone q3 weeks

Duration: 24 weeks
➢ Why was this a negative trial?
➢ Early stopping of bev when chemo stopped?
➢ Interaction between oxali and bev (or cape-bev)

Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial

Rachel S Kerr, Sharon Love, Eva Segelov, Elaine Johnstone, Beverly Falcon, Peter Hewett, Andrew Weaver, David Church, Claire Scudder, Sarah Pearson, Patrick Julier, Francesco Pezzella, Ian Tomlinson, Enric Domingo, David J Kerr

Summary

Background Antiangiogenic agents have established efficacy in the treatment of metastatic colorectal cancer. We investigated whether bevacizumab could improve disease-free survival in the adjuvant setting after resection of the primary tumour.

Methods For the open-label, randomised, controlled QUASAR 2 trial, which was done at 170 hospitals in seven countries, we recruited patients aged 18 years or older with WHO performance status scores of 0 or 1 who had undergone potentially curative surgery for histologically proven stage III or high-risk stage II colorectal cancer. Patients were randomly assigned (1:1) to receive eight 3-week cycles of oral capecitabine alone (1250 mg/m² twice daily for 14 days followed by a break for 7 days) or the same regimen of oral capecitabine plus 16 cycles of 7·5 mg/kg bevacizumab by intravenous infusion over 90 min on day 1 of each cycle. Randomisation was done by a computer-generated schedule with use of minimisation with a random element stratified by age, disease stage, tumour site, and country. The study was open label and no-one was masked to treatment assignment. The primary endpoint was 3-year disease-free survival, assessed in the intention-to-treat population. Toxic effects were assessed in patients who received at least one dose of randomised treatment. This trial is registered with the ISRCTN registry, number ISRCTN45133151.

Findings Between April 25, 2005, and Oct 12, 2010, 1952 eligible patients were enrolled, of whom 1941 had assessable data (968 in the capecitabine alone group and 973 in the capecitabine and bevacizumab group). Median follow-up was 4·92 years (IQR 4·00–5·16). Disease-free survival at 3 years did not differ between the groups (75·4%, 95% CI 72·5–78·0 in the capecitabine and bevacizumab group vs 78·4%, 75·7–80·9 in the capecitabine alone group; hazard ratio 1·06, 95% CI 0·89–1·25, p=0·54). The most common grade 3–4 adverse events were hand–foot syndrome (201 [21%] of 963 in the capecitabine alone group vs 257 [27%] of 959 in the capecitabine and bevacizumab group) and diarrhoea (102 [11%] vs 104 [11%]), and, with the addition of bevacizumab, expected increases were recorded in all-grade hypertension (320 [33%] vs 75 [8%]), proteinuria (197 [21%] vs 49 [5%]), and wound healing problems (30 [3%] vs 17 [2%]). 571 serious adverse events were reported (221 with capecitabine alone and 350 with capecitabine and bevacizumab). Most of these were gastrointestinal (n=245) or cardiovascular (n=169). 23 deaths within 6 months of randomisation were classified as being related to treatment, eight in the capecitabine alone group and 15 in the capecitabine and bevacizumab group.

Interpretation The addition of bevacizumab to capecitabine in the adjuvant setting for colorectal cancer yielded no benefit in the treatment of an unselected population and should not be used.
- dMMR or pMMR with high free CD31 expression had a bev DFS benefit

- pMMR with low free CD31 (endothelial cell marker; angiogenesis) had reduced DFS with bev
Phase III Clinical Trial of FOLFOX with or without Cetuximab in Resected *K-ras wild type* Stage 3 Colon Cancer:

Cooperative Group Trial N0147
(NCCTG*, CALGB, ECOG, NCIC, NSABP, SWOG)

*: Coordinating group
Final Design for N0147 – June 2008

Stage 3 Colon Cancer (N = 3768)

- Pre-register

K-ras WT

- Centralized K-ras analysis

K-ras Mut

Randomize

Arm A
mFOLFOX6

Arm D
mFOLFOX6 + Cetuximab

Arm G
- Adjuvant therapy per primary oncologist
- Report therapy given
- Annual status through year 8
Disease Free Survival (N=1847)

<table>
<thead>
<tr>
<th>Arm</th>
<th>3 Year Rates</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX</td>
<td>75.8% (72.1%-79.6%)</td>
<td>1.2</td>
<td>0.22</td>
</tr>
<tr>
<td>N=902</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX + Cmab</td>
<td>72.3% (68.5%-76.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=945</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% Alive and Disease Free

- FOLFOX
- FOLFOX + Cmab
Overall Survival (N=1847)

<table>
<thead>
<tr>
<th>Arm</th>
<th>3 Year Rates (95% CI)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX N=902</td>
<td>87.8% (84.7%-90.9%)</td>
<td>1.3 (0.96-1.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>FOLFOX + Cmab N=945</td>
<td>83.9% (80.3%-87.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Disease Free Survival
Age $\geq$ 70 (N=258)

<table>
<thead>
<tr>
<th>Arm</th>
<th>3 Year Rates (95% CI)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX</td>
<td>80.9% (73.0%-89.8%)</td>
<td>1.79 (1.01-3.18)</td>
<td>0.03</td>
</tr>
<tr>
<td>N=112</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX + Cmab</td>
<td>66.1% (56.8%-77.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=146</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PETACC-8

Fully resected stage III colon cancer
Planned n=2000
Primary endpoint: DFS

R

FOLFOX4 + cetuximab
Treatment will be administered for 6 months
FOLFOX4
Figure 2: Kaplan-Meier curves for disease-free survival according to study treatment
(A) In patients in the KRAS exon 2 wild-type intention-to-treat population.
(B) In patients with KRAS exon 2 wild-type and BRAF wild-type tumours.
(C) In patients with KRAS exon 2-mutated tumours. DFS=disease-free survival. HR=hazard ratio.
What results are coming for adjuvant therapy for CRC?
Duration of Adjuvant Chemotherapy

- Can adjuvant chemo be shortened? (SAFFA TRIAL)
- 6 months bolus 5FU v 12 weeks PVI 5FU

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5-year survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus 5-FU/LV</td>
<td>71.5% (66.4-75.9%)</td>
</tr>
<tr>
<td>PVI 5-FU</td>
<td>75.7% (70.8-79.9%)</td>
</tr>
</tbody>
</table>

Log rank p=0.0833
HR: 0.79; 95% CI: 0.61-1.03

Chau et al. Ann Oncol. 2005
Duration of Adjuvant Chemotherapy: Phase 3 Studies

SCOT Trial

Resected high risk stage 2 and 3 Colon Cancer n= 9500

6 months
XELOX or FOLFOX

3 months
XELOX or FOLFOX

Italian 3 versus 6 Trial

Resected Stage 3 Colon Cancer

6 months
FOLFOX

3 months
FOLFOX
ASCO 2017

• IDEA metaanalysis

• SCOT

• Will a new standard change recommendations for rectal ca?
Biomarkers in Adjuvant therapy for Colorectal Cancer
Prognostic and Predictive markers

**Prognostic** - identifying pts at higher risk for recurrence

- MSI (dMMR) - increased survival
- Allelic loss of 18 q - ? decreased survival
- High TS levels in primary - ? decreased survival
- BRAF, KRAS + MSS - shorter TTR, SAR (surv after rel), OS
- BRAF, KRAS + MSI - no correlation

**Predictive** - identifying pts who benefit from adjuvant Rx

- dMMR - No benefit with 5FU in stage II
- Low TS/DPD/TP - ? better response to chemo
- ? Markers for bev benefit

Phase III adjuvant trial in high-risk stage II colon cancer (E5202)

Stage II patients

MSS LOH 18q “unfavorable”
- mFOLFOX6
- mFOLFOX6 Avastin

MSI normal 18q “favorable”
- No therapy
CDX2 as a Prognostic Biomarker in Stage II and Stage III Colon Cancer

Piero Dalerba, M.D., Debashis Sahoo, Ph.D., Soonmyung Paik, M.D., Xiangqian Guo, Ph.D., Greg Yothers, Ph.D., Nan Song, Ph.D., Nate Wilcox-Fogel, M.S., Erna Forgó, M.D., Pradeep S. Rajendran, B.S., Stephen P. Miranda, B.A., Shigeo Hisamori, M.D., Ph.D., Jacqueline Hutchison, Tomer Kalisky, Ph.D., Dalong Qian, M.D., Norman Wolmark, M.D., George A. Fisher, M.D., Ph.D., Matt van de Rijn, M.D., Ph.D., and Michael F. Clarke, M.D.

ABSTRACT

BACKGROUND
The identification of high-risk stage II colon cancers is key to the selection of patients who require adjuvant treatment after surgery. Microarray-based multigene-expression signatures derived from stem cells and progenitor cells hold promise, but they are difficult to use in clinical practice.

METHODS
We used a new bioinformatics approach to search for biomarkers of colon epithelial differentiation across gene-expression arrays and then ranked candidate genes according to the availability of clinical-grade diagnostic assays. With the use of subgroup analysis involving independent and retrospective cohorts of patients with stage II or stage III colon cancer, the top candidate gene was tested for its association with disease-free survival and a benefit from adjuvant chemotherapy.

RESULTS
The transcription factor CDX2 ranked first in our screening test. A group of 87 of 2115 tumor samples (4.1%) lacked CDX2 expression. In the discovery data set, which included 466 patients, the rate of 5-year disease-free survival was lower among the 32 patients (6.9%) with CDX2-negative colon cancers than among the 434 (93.1%) with CDX2-positive colon cancers (hazard ratio for disease recurrence, 3.44; 95% confidence interval [CI], 1.60 to 7.38; P=0.002). In the validation data set, which included 314 patients, the rate of 5-year disease-free survival was lower among the 38 patients (12.1%) with CDX2 protein-negative colon cancers than among the 276 (87.9%) with CDX2 protein-positive colon cancers (hazard ratio, 2.42; 95% CI, 1.36 to 4.29; P=0.003). In both these groups, these findings were independent of the patient's age, sex, and tumor stage and grade. Among patients with stage II cancer, the difference in 5-year disease-free survival was significant both in the discovery data set (49% among 15 patients with CDX2-negative tumors vs. 87% among 191 patients with CDX2-positive tumors, P=0.003) and in the validation data set (51% among 15 patients with CDX2-negative tumors vs. 80% among 106 patients with CDX2-positive tumors, P=0.004). In a pooled database of all patient cohorts, the rate of 5-year disease-free survival was higher among 23 patients with stage II CDX2-negative tumors who were treated with adjuvant chemotherapy than among 25 who were not treated with adjuvant chemotherapy (91% vs. 56%, P=0.006).

CONCLUSIONS
Lack of CDX2 expression identified a subgroup of patients with high-risk stage II colon cancer who appeared to benefit from adjuvant chemotherapy. (Funded by the National Comprehensive Cancer Network, the National Institutes of Health, and others.)

From the Herbert Irving Comprehensive Cancer Center, the Department of Pathology and Cell Biology, and the Department of Medicine, Division of Digestive and Liver Diseases, Columbia University, New York (P.D.); Institute for Stem Cell Biology and Regenerative Medicine (P.D., D.S., P.S.R., S.P.M., S.H., J.H., D.Q., M.F.C.) and the Departments of Pathology (X.G., E.F., M.R.) and Medicine, Division of Oncology (N.W.-F., G.A.F., M.F.C.), Stanford University, Stanford, and the Departments of Pediatrics and Computer Science and Engineering, University of California San Diego, San Diego (D.S.) — both in California; Faculty of Engineering, Bar-Ilan University, Ramat Gan, Israel (T.K.); the National Surgical Adjuvant Breast and Bowel Project, NBG Oncology (S.P., G.Y., N.S., N.W.) and the Allegheny Cancer Center at Allegheny General Hospital (N.W.) — both in Pittsburgh; Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, South Korea (S.P.); and the Department of Biochemistry and Molecular Biology, Medical School of Henan University, Kaifeng, China (X.G.). Address reprint requests to Dr. Dalerba at the Herbert Irving Comprehensive Cancer Center, Columbia University, Irving Cancer Research Center, 1310 St. Nicholas Ave., Rm. 509A, New York, NY 10032, or at pdd2109@columbia.edu; or to Dr. Clarke at the Institute for Stem Cell Biology and Regenerative Medicine, Stanford University, Lorry I. Lokey Stem Cell Research Bldg., 265 Campus Dr., Rm. G2021A, Mail Code 5461, Stanford, CA 94305, or at mclarke@stanford.edu.

*Drs. Dalerba and Sahoo contributed equally to this article.

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Deficient Mismatch Repair as a Predictive Marker for Lack of Benefit from 5-FU based Chemo in Adjuvant Colon Cancer
Ribic NEJM 2003:
Controls better than chemo in MSI-H pts!

P-value = 0.100
HR : 2.17 (0.84-5.55)

Ribic, NEJM 2003
dMMR and FU

- Very low numbers
- Definition <50 for Lynch
- HR 0.67 for pMMR;
- 1.10 for dMMR
- 2.96 (1.02-8.54) for StII dMMR
- May be differential benefit in germline v sporadic
ACCENT database - 1

• With homage to Dan Sargent
• Adjuvant Colon Cancer End Points group (ACCENT)
• Individual patient data from 18 trials in US, Canada, Australia, Europe testing FP -based adjuvant therapy for 20,898 pts with St II/III colon ca
• Major conclusions:
  • 2 or 3 y DFS HRs are highly predictive of 5 and 6 years OS HRs in stage III but not stage II.
  • In all patients the DFS/OS association is stronger for 6 year OS, thus need at least 6 year follow-up for OS
  • Age >70 years had reduced benefit from adding oxaliplatin although no stat signif effect; FP retained their efficacy (11,000 pts)
Compared to pMMR, dMMR was strongly associated with improved OS (HR=0.27, p=0.01) and TTR (HR=0.27, p=0.01) in stage II pts treated with surgery alone. MMR was prognostic although of attenuated impact in 5FU treated stage II, III with significance confined to 5FU-treated stage III pts (HR=0.80, p=0.02 for TTR; HR=0.79, p=0.02 for OS).
When I get a headache I take two aspirin and keep away from children, just like the bottle says.
Aspirin and COX-2i

• Numerous observational studies and RCTs

• Demonstrates efficacy of aspirin against development of colorectal adenomas and cancer through inhibition of COX-2 pathway

• Pathway overexpressed in 80-85% of CRCs
Primary prevention in CRC

- Aspirin use reduces the risk of colorectal adenomas and cancer.
- Randomised trials evaluating cardiovascular benefits showed that aspirin use resulted in a 24% reduction in CRC incidence and a 35% reduction in CRC mortality.

### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reimers/2014</td>
<td>0.64 (0.49-0.83)</td>
</tr>
<tr>
<td>Cardwell/2014</td>
<td>1.06 (0.94-1.19)</td>
</tr>
<tr>
<td>McCowan/2013</td>
<td>0.67 (0.57-0.79)</td>
</tr>
<tr>
<td>Domingo/2013</td>
<td>0.88 (0.53-1.47)</td>
</tr>
<tr>
<td>Walker/2014</td>
<td>0.91 (0.82-1.00)</td>
</tr>
<tr>
<td>Bastiaanet/2012</td>
<td>0.87 (0.82-0.92)</td>
</tr>
<tr>
<td>Chan/2009</td>
<td>0.79 (0.65-0.97)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>0.84 (0.75-0.94)</strong></td>
</tr>
</tbody>
</table>

**Fig 1.** Meta-analysis of aspirin use postdiagnosis of CRC vs mortality.27

### Reference

- Flossman [10] Overview of 2 RCTs; 7,588 patients; 23 yrs
  - HR 0.74 (95% CI 0.56-0.97, p= 0.02) for CRC incidence; Absolute risk reduction (ARR) 0.9%

- Rothwell [11] Overview of 8 RCTs; 25,570 patients; 20 yrs
  - HR 0.60 (95% CI 0.45-0.81, P=0.007) for CRC death; HR 0.76 (95% CI 0.60-0.96, p=0.02) for CRC incidence

- Algra [12] Overview of 6 RCTs; 19,692 patients
  - OR 0.58 (95% CI 0.44-0.78, p=0.0002) for CRC death; ARR 0.8%

- Rothwell [7] Overview of 5 RCTs; 17,285 patients; 12 yrs
  - HR 0.26 (95% CI 0.11-0.57, p=0.0008) for CRC Metastases

- Rothwell [13] Overview of 51 RCTs; 69,224 patients; 10 yrs
  - OR 0.58 (95% CI 0.38-0.89, p= 0.008) for CRC death

Aspirin in randomised vascular prevention trials and incidence of CRC
PIK3Ca story

• 964 pts CRC Nurses Health Study & Health Prof Followup Study who had data on aspirin use after diagnosis

• Examined PTGS2, phosphorylated AKT, KRAS, BRAF, MSI, CIMP,

VICTOR: Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime

- Recurrence-free survival of regular low-dose aspirin users and nonusers in the VICTOR trial according to (A) absence or (B) presence of tumour PIK3CA mutation.

**Graphs:**

**A**
- Aspirin use: Red line
- No aspirin use: Blue dashed line
- Log-rank $P = 0.710$

**B**
- Aspirin use: Red line
- No aspirin use: Blue dashed line
- Log-rank $P = 0.036$
Mortality among Patients with Colorectal Cancer, According to Regular Use or Nonuse of Aspirin after Diagnosis and PIK3CA Mutation Status; Nurse Health study.

Patients with Stage II/III colon cancer (or) Rectal cancer subgroups

Surgery
(Complete resection of tumour)

Standard therapy
(at least 3 months of Chemotherapy + Radiotherapy)

Aspirin
200 mg OD for 3 years
3 monthly follow-up for 3 years then
6 monthly follow-up for 2 years

Placebo
200 mg OD for 3 years
3 monthly follow-up for 3 years then
6 monthly follow-up for 2 years
## Other adjuvant aspirin CRC trials

clinicaltrials.gov on 14.7.16

<table>
<thead>
<tr>
<th>Trial acronym</th>
<th>Aspirin dose</th>
<th>Sample size / Special population</th>
<th>Start / Complete recruitment</th>
<th>Primary outcome</th>
<th>Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOLT</td>
<td>200</td>
<td>1200 / No</td>
<td>2013 - 2017</td>
<td>3y DFS</td>
<td>Tissue, blood</td>
</tr>
<tr>
<td>ACC</td>
<td>100</td>
<td>185 / PI3KCAmut</td>
<td>2015 - 2018</td>
<td>3y DFS</td>
<td>Tissue</td>
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<tr>
<td>AddAspirin</td>
<td>100 / 300</td>
<td>2600 CRC / No</td>
<td>2015 - 2021</td>
<td>3y DFS</td>
<td>N/A</td>
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<tr>
<td>APREMEC</td>
<td>100 / 200</td>
<td>3000 / No</td>
<td>2015 - 2022</td>
<td>3y DFS</td>
<td>N/A</td>
</tr>
<tr>
<td>ASPIRIN</td>
<td>80</td>
<td>1588 / Age&gt; 45y</td>
<td>2014 - 2022</td>
<td>5y OS</td>
<td>N/A</td>
</tr>
<tr>
<td>ALASCCA</td>
<td>160</td>
<td>408 / PI3KCAmut</td>
<td>2021 - 2014</td>
<td>3y DFS</td>
<td>Tissue</td>
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</tbody>
</table>

Agreement for metaanalysis with ASCOLT
Molecular predictors of relapse and need for adjuvant therapy

- Circulating Tumour DNA Analysis Informing Adjuvant Chemotherapy in Stage III Colon Cancer: A Multicentre Randomised Study (DYNAMIC-III)
  - Other ctDNA markers
  - Prognostic v predictive
only 1 mutation identified in each patient’s tumor tissue was analyzed in our study, yielding a sensitivity of 48% in detecting residual disease and predicting recurrence
What hasn’t been done

➢ No adjuvant trial of irinotecan + cetux in extended RAS wt
➢ Little appetite for trials in absence of biomarker
➢ 67 open studies
➢ Neoadjuvant chemo
Body mass index at diagnosis and survival among colon cancer patients enrolled in clinical trials of adjuvant chemotherapy

A. Time-to-Recurrence in Men

B. Time-to-Recurrence in Women

C. Overall Survival in Men

D. Overall Survival in Women
Exercise AFTER surgery for Colon cancer
Meyerhardt et al JCO Aug 2006

2 prospective observational studies:
- 573 women with resected Stage I-III colon cancer
- 832 with resected Stage III colon cancer enrolled on CALGB adj study
  - MET [metabolic equivalent task] < 3 versus > 18 per wk
    (NB 9 MET = 4 x 30 min brisk walk per wk)

Results:
- Exercise AFTER surgery reduced cancer-specific + overall mortality by 50%!
  [HR 0.4, 0.5 in the 2 studies]
When should we start treatment?

- Trials mandate initiation of chemotherapy within 6 to 8 weeks
- No randomised trials
- Several retrospective studies – conflicting data
- 2 meta-analyses
- Systematic review and meta-analysis
  - 10 studies, 15 000 patients
  - 4 week delay in time beyond 8 weeks associated
    - Increase mortality (HR=1.14, 95%CI 1.10-1.17)
    - Increase disease relapse (HR=1.14, 95%CI 1.10-1.18)

Abstract

Background

The Australian National Bowel Cancer Screening Program (NBCSP) has been offering age-based faecal occult blood testing since 2006. With the rapid expansion of this programme, the NBCSP will ultimately offer biennial screening to all 50–74 years old by 2020. Participation rates remain low. Previous reports have described an increased proportion of earlier stage cancers in patients with NBCSP-detected tumours.

Methods

Data on consecutive patients enrolled into a prospective, comprehensive, multidisciplinary database at six Victorian hospitals were examined. Clinicopathologic and outcome data were compared for NBCSP and symptomatic presentation patients.

Results

We identified 3743 patients that presented with colorectal cancer (CRC) at participating hospitals since May 2006. Of 1930 patients aged between 50 and 70 years, 141 (7.3%) had a NBCSP detected cancer, 1441 (74.7%) presented with symptoms and 266 (13.8%) were diagnosed through screening outside of the NBCSP. Based on the American Society of Anaesthesiology score, the NBCSP patients were fitter. They had an earlier stage of diagnosis and were more likely to be female and less likely to have lymphovascular invasion or to present as an emergency. NBCSP detected patients had a lower rate of recurrence (HR 0.17, \( P = 0.0001 \)) and fewer deaths (HR 0.19, \( P = 0.005 \)).

Conclusions

Patients with NBCSP-detected CRC have a markedly reduced risk of CRC recurrence and death compared with patients with a symptomatic presentation. The dominant driver of this appears to be earlier stage at diagnosis. Increased promotion of the impact of the NBCSP, including data related to the survival impact, should be undertaken to increase participation rates and achieve further survival gains.
Hard cases

- Young pts with stage II pMMR
- Pts with Stage III dMMR >70y
- RECTAL CANCER (after neoadj CRT)
- “adjuvant’ post metastatectomy
Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology

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Abstract

This portion of the NCCN Guidelines for Colon Cancer focuses on the use of systemic therapy in metastatic disease. Considerations for treatment selection among 32 different monotherapies and combination regimens in up to 7 lines of therapy have included treatment history, extent of disease, goals of treatment, the efficacy and toxicity profiles of the regimens, KRAS/NRAS mutational status, and patient comorbidities and preferences. Location of the primary tumor, the BRAF mutation status, and tumor microsatellite stability should also be considered in treatment decisions.

Footnotes

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently available data. However, the above guidelines should not be construed as dictating an exclusive course of treatment or as being followed in every situation. The actual treatment regimen selected will be dependent upon the clinical situation as opposed to any research data presented. Any clinician seeking to apply or consult this guideline for a particular case is advised to refer to and become familiar with the complete text of the guidelines available at NCCN.org. The complete NCCN Guidelines are the product of the NCCN Guidelines Working Group. Copyright © 2017 National Comprehensive Cancer Network, Inc. All rights reserved.
Conclusions (1)

➢ Oxaliplatin based regimens superior to 5FU-based Rx in Stage III colon cancer, and has become the standard of care (neuropathy problematic); relatively small additional gain and not in pts >70

➢ For patients receiving fluropyrimidines alone, capecitabine or bolus 5FU/LV
The role of adjuvant therapy in stage 2 colon cancer remains unclear and is at most of small benefit but should be considered in high-risk patients.

- Oxaliplatin can not be recommended.
- Must quote absolute benefit (3-5%) not relative risk reduction (eg 20-25%).
- Test for MSI-H (15-20%) if you are considering Rx, and avoid it if found.
Conclusions (3)

➢ Lack of progress since MOSAIC trial reported in 2003

➢ Drugs active in advanced disease do not always work in adjuvant Rx (and we don’t know why)

➢ Await current trials
  – Duration of chemotherapy
  – Biomarker enrichment designs
  – Aspirin, exercise

➢ Search for better prognostic and predictive factors