Adjuvant Therapy for Colon and Rectal Cancer

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DISCLOSURES

Off-Label Usage

• None

Interests

• BMS Imclone
• Roche Genentech
CRC: Demographics and Presentation

- Estimated 2014 U.S. incidence (new cases): 136,830
- Estimated 2014 U.S. mortality: 50,310

Pie chart showing:
- 32.6% stage III
- 24.5% stage II
- 12% stage I
- 18.6% stage IV
US Death Rates in Men & Women: 1975-2008
57,100 in 2003 & 51,690 in 2012
Staging of Colorectal Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of tumor</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No deeper than submucosa</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>B₁</td>
<td>Not through bowel wall</td>
<td>80–85%</td>
</tr>
<tr>
<td>II/B₂</td>
<td>Through bowel wall</td>
<td>70–75%</td>
</tr>
<tr>
<td>III/C₁</td>
<td>Not through bowel wall: lymph node metastases</td>
<td>50–65%</td>
</tr>
<tr>
<td>III/C₂</td>
<td>Through bowel wall: lymph node metastases</td>
<td>25–45%</td>
</tr>
<tr>
<td>D</td>
<td>Distant metastases</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

Adapted from Skarin. *Slide Atlas of Diagnostic Oncology*. Gower Medical Publishing; 1997:Fig 5.98.
The AJCC 6th edition staging manual refined stages II and III of the TNM system:

- Smooth nodules in fat are considered LNs
- Stage II divided into IIA ($T_3$) and IIB ($T_4$)
- Stage III divided into
  - IIIA ($T_{1-2}N_1M_0$)
  - IIIB ($T_{3-4}N_1M_0$)
  - IIIC ($T_{\text{Any}}N_2M_0$)
- $N_2$ denotes metastases to 4 or more regional lymph nodes

5-Year Relative Survival By AJCC 6th Edition 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%

\( p < .001 \)

O’Connell et al., 2004.
CRC: AJCC 7th Edition
Staging Guidelines 2009

• Expanded data sets have shown differential prognosis within T4 lesions based on extent of disease. Accordingly, T4 lesions are subdivided as T4a (tumor penetrates the surface of the visceral peritoneum) and as T4b (tumor directly invades or is histologically adherent to other organs or structures).

• Stage Group II is subdivided into IIA (T3N0), IIB (T4aN0), and IIC (T4bN0).

• The potential importance of satellite tumor deposits is now defined by the new site-specific factor Tumor Deposits (TD) that describe their texture and number. T1-2 lesions that lack regional lymph node metastasis but have tumor deposit(s) will be classified in addition as N1c.
Risk stratification is critical to decision-making in colon cancer

- **Predictive**: explains variability in response to treatment
- **Prognostic**: explains variability irrespective of treatment
Stage II vs. Stage III

Recurrence Rate by 6 mo intervals

Stage 2: 67% of recurrences occur by 3 years

Stage 3: 75% of recurrences occur by 3 years

Sargent, ASCO 2005
May 05, 2004: ODAC recommends 3-year DFS as new regulatory end point for **full** approval in adjuvant colon cancer

\[ p = .90 \]

5-year OS = 0.0002 + 0.998, 3-year DFS

ODAC = FDA Oncology Drugs Advisory Committee; DFS = disease-free survival; OS = overall survival.
Sargent et al., 2005.
History of adjuvant therapy of colon cancer before oxaliplatin

- 5-FU/lev superior to surgery alone
- 5-FU/LV superior to surgery alone
- 5-FU/LV superior to 5-FU/lev
- 6- and 12-month treatment cycles equivalent
- Lev unnecessary
- High-dose and low-dose LV equivalent
- Monthly and weekly treatment equivalent
- LV5FU2 and monthly bolus equivalent

1990

1994

1998

2002
5-FU: Historical Standard in the Adjuvant Setting

- Patients with stage II and III colon cancer

(1) IMPACT Investigators, 1995; (2) Wolmark et al., 1993; (3) QUASAR Group, 2000; (4) André et al., 2003.
Extending Benefit beyond FU/LV in High-risk Stage II/III Colon Cancer

• Can convenience of administration be improved?
  – replace 5-FU with capecitabine

• Do combination therapies offer advantages over 5-FU alone?
  – oxaliplatin-based regimens:
    MOSAIC (infusion), NSABP C0-7 (bolus)
  – irinotecan-based regimens:
    CALGB (bolus), PETACC-3 (infusion), ACCORD-2

• Can we further improve results?
  The role of biologics:
  – anti-EGFR (cetuximab): N0147, PETACC8
  – anti-VEGF (bevacizumab): C-08, AVANT

• Duration of therapy: 3 vs. 6 months (IDEA)
X-ACT Trial Design


- **Chemotherapy-naive stage III colon cancer, Resection < 8 weeks**
  - **Capecitabine**
    - 1,250 mg/m² twice daily,
    - Days 1–14, q21d
    - (n = 1,004)

- **Bolus 5-FU/LV**
  - 5-FU 425 mg/m² plus
  - LV 20 mg/m², Days 1–5,
  - q28d (n = 983)

**End points**
- DFS
- RFS
- Overall survival
- Tolerability (NCIC CTG)
- Pharmacoeconomics
- Quality of life

**24 weeks**

RFS = recurrence-free survival; NCIC CTG = National Cancer Institute of Canada Clinical Trials Group. Twelves et al., 2005.
X-ACT: 5-Year Disease-Free Survival

## Survival Analysis

### Kaplan-Meier Analysis

- **Capecitabine**
  - 5-YES DFS: 60.8%
  - 95% CI: 0.77–1.01
  - HR = 0.88
  - Test of noninferiority, p < .0001
  - Test of superiority, p = .0682

- **5-FU/LV**
  - 5-YES DFS: 56.7%
  - NI margin 1.20

### Median Follow-up

Median follow-up: 6.8 years

**NI = noninferiority.**

Twelves et al., 2007.
MOSAIC: Study Design

<table>
<thead>
<tr>
<th>N = 2,246</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Completely resected colon cancer</td>
</tr>
<tr>
<td>• Stage II: 40%</td>
</tr>
<tr>
<td>• Stage III: 60%</td>
</tr>
<tr>
<td>• Age 18–75 years</td>
</tr>
<tr>
<td>• KPS ≥ 60</td>
</tr>
<tr>
<td>• No prior chemotherapy</td>
</tr>
</tbody>
</table>

Primary end point: 3-yr Disease-free survival
Secondary end points: Safety and overall survival

R = randomize; LV/5-FU2 = leucovorin 200 mg/m² IV over 2 hours followed by 5-FU 400 mg/m² bolus and 5-FU 600 mg/m² IV over 22 hours on Days 1 and 2, every 14 days; FOLFOX4 = LV/5-FU2 + oxaliplatin 85 mg/m² IV over 2 hours on Day 1; KPS = Karnofsky performance status.
de Gramont et al., 2007, JCO 2009
3-yr Disease-Free Survival

$\rho = .003$

Events
- FOLFOX4: 304/1,123 (27.1%)
- LV/5-FU2: 360/1,123 (32.1%)

HR = 0.80 (95% CI: 0.68–0.93)

ITT = intent to treat; HR = hazard ratio; CI = confidence interval.
de Gramont et al., 2007. JCO 2009

Data cut-off: June 2006
Disease-Free Survival: Stage II/III Colon Cancer

Data cut-off: June, 2006.

HR (95% CI)  p Value

Stage II   0.84 (0.62–1.14)  .258
Stage III  0.78 (0.65–0.93)  .005

FOLFOX4 stage II
LV/5-FU2 stage II
FOLFOX4 stage III
LV/5-FU2 stage III

Probability (%)

Time (months)

p = .258
3.8%

p = .005
7.5%

de Gramont et al., 2007 JCO 2009

Data cut-off: June, 2006.
de Gramont et al., 2007 JCO 2009
Kaplan-Meier estimates of disease-free survival (A) by treatment arm and (B) by treatment arm and by stage (intent-to-treat population).

André T et al. JCO 2009;27:3109-3116
MOSAIC: 6 yr results

Kaplan-Meier estimates of overall survival (A) by treatment arm and (B) by treatment arm and by stage (intent-to-treat population).

André T et al. JCO 2009;27:3109-3116
Hazard ratios and 95% CIs for death in stage III patients administered oxaliplatin plus fluorouracil and leucovorin compared with stage III patients administered fluorouracil and leucovorin (FL) according to baseline prognostic factors (intent-to-treat popu...
End point: 3-year DFS

Week 1 2 3 4 5 6 7 8

NSABP C-07

N = 2,407

FU 500
LV 500

OHP 85
2-hr

Week     1        2        3        4        5        6        7       8

RP = Roswell Park regimen; FLOX = oxaliplatin/5-FU/LV; OHP = oxaliplatin.
Wolmark et al., 2005.

Accrual 02/00–11/02
C-07: Disease-Free Survival

\[ p < 0.004 \]
\[ HR = 0.79 \ (0.67 - 0.93) \]

Wolmark et al., 2005, JCO 2007
### Oxaliplatin Benefit: C-07 and MOSAIC

<table>
<thead>
<tr>
<th></th>
<th>3-year DFS(%)</th>
<th>$\Delta$ (%)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-07</td>
<td>76.5</td>
<td>4.9</td>
<td>0.79</td>
</tr>
<tr>
<td>MOSAIC</td>
<td>77.9</td>
<td>5.1</td>
<td>0.77</td>
</tr>
</tbody>
</table>

5-yr OS demonstrated in MOSAIC, not C-07

Wolmark et al., 2005.
CALGB 89803: No Improvement in OS and DFS With IFL in Stage III Colon Cancer

IFL = irinotecan, fluorouracil, and leucovorin.
Saltz et al., 2007.
ACCORD2: No Improvement in DFS With FOLFIRI in High-Risk Colon Cancer

3-Year DFS (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI</td>
<td>60</td>
</tr>
<tr>
<td>LV5FU2</td>
<td>51</td>
</tr>
</tbody>
</table>

Estimated Probability (%)

HR = 1.19
(95% CI: 0.90–1.59)

\[ p = .22 \]

Time (years)

Ychou et al., 2009.
PETACC-3: Study Design

Stratification:
- Stage II vs. III
- Center

Randomization:
F
- Day 1: FA 200 mg/m²
- Day 2: 5-FU bolus 400 mg/m²
- 5-FU CI 600 mg/m²

IF
- Day 1: Irinotecan 180 mg/m²
- Day 2: LV/5-FU² as above

LV/5-FU²
- FA 200 mg/m²
- 5-FU bolus 400 mg/m²
- 5-FU CI 600 mg/m²

Repeat q2w for 12 cycles

CI = continuous infusion.
Van Cutsem et al., 2005;
JCO 2009
PETACC-3: DFS Not Significantly Improved With FOLFIRI in Stage III

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>3-Year DFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI</td>
<td>1,044</td>
<td>63.3</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>1,050</td>
<td>60.3</td>
</tr>
</tbody>
</table>

HR = 0.89  
(95% CI: 0.77–1.11)  
$p = .091$

Van Cutsem et al., 2005; JCO 2009
# 3-year DFS (Stage III): cross-trial comparison

<table>
<thead>
<tr>
<th>Trial</th>
<th>Therapy</th>
<th>3-year DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moertel</td>
<td>Observation</td>
<td>52%</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Observation</td>
<td>44%</td>
</tr>
<tr>
<td>IMPACT</td>
<td>5-FU/LV</td>
<td>62%</td>
</tr>
<tr>
<td>Punt</td>
<td>5-FU/LV</td>
<td>65%</td>
</tr>
<tr>
<td>Fields</td>
<td>5-FU/LV</td>
<td>67%</td>
</tr>
<tr>
<td>André</td>
<td>LV5FU2</td>
<td>61%</td>
</tr>
<tr>
<td>MOSAIC</td>
<td>5-FU/LV</td>
<td>65%</td>
</tr>
<tr>
<td>X-ACT</td>
<td>Capecitabine</td>
<td>64%</td>
</tr>
<tr>
<td>PETACC-3</td>
<td>LV5FU2+IRI</td>
<td>63%</td>
</tr>
<tr>
<td>MOSAIC</td>
<td>FOLFOX4</td>
<td>73%</td>
</tr>
<tr>
<td>NSABP</td>
<td>FLOX</td>
<td>73%</td>
</tr>
</tbody>
</table>

**No therapy**

**Monotherapy**

**Combination therapy**
Adjuvant XELOX vs. 5-FU/LV: XELOXA Phase III trial (NO16968)

Chemo/radiotherapy-naive stage III colon ≤8 weeks since resection N=1886

Primary endpoint: superior 3-yr DFS with XELOX vs. 5-FU

Secondary endpoints: overall survival, tolerability, convenience, medical care use biomarkers, pharmacogenetic information (optional)

Randomization:
- XELOX: capecitabine 1000mg/m² bid d1–14, oxaliplatin 130mg/m² d1, Q3w, 8 cycles
- Bolus 5-FU/LV: Mayo Clinic (24 weeks) or Roswell Park (32 weeks) Institution choice

n=944

n=942
3-yr Disease-free survival: Primary endpoint reached
ESMO 2009

Estimated probability

- **XELOX** (n=944)
- **5-FU/LV** (n=942)

<table>
<thead>
<tr>
<th>Months</th>
<th>XELOX</th>
<th>5-FU/LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>0.71</td>
<td>0.67</td>
</tr>
<tr>
<td>12</td>
<td>0.44</td>
<td>0.42</td>
</tr>
<tr>
<td>18</td>
<td>0.31</td>
<td>0.29</td>
</tr>
<tr>
<td>24</td>
<td>0.22</td>
<td>0.20</td>
</tr>
<tr>
<td>30</td>
<td>0.16</td>
<td>0.15</td>
</tr>
<tr>
<td>36</td>
<td>0.12</td>
<td>0.11</td>
</tr>
<tr>
<td>42</td>
<td>0.09</td>
<td>0.08</td>
</tr>
<tr>
<td>48</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>54</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>60</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>66</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>72</td>
<td>0.02</td>
<td>0.01</td>
</tr>
</tbody>
</table>

At risk:
- **XELOX**: 944 862 782 720 673 641 613 589 497 362 182 7 0
- **5-FU/LV**: 942 855 753 689 650 606 573 529 438 320 135 2 0

**Event (%)**
- XELOX: 31.3
- 5-FU/LV: 37.5

**Time to event 3-years [95% CI]**
- XELOX: 0.71 [0.68–0.74]
- 5-FU/LV: 0.67 [0.63–0.70]

**HR [95% CI]**
- XELOX: 0.80 [0.69–0.93] (p=0.0045)

**ITT population**
Cross-trial comparison of MOSAIC and XELOXA: OS in stage III disease

NO16968 (XELOXA)*  5-yr OS  6-yr OS
MOSAIC1**  

XELOX (n=944)  77.6%  –
FOLFOX4 (n=672)  –  72.9%

*Median observation time: 57.0 months
**Median follow-up: 81.9 months

ITT population

1. André et al. JCO 2009
## Fluoropyrimidines ± Oxaliplatin Stage III

<table>
<thead>
<tr>
<th>Study</th>
<th>HR for DFS</th>
<th>P value</th>
<th>DFS Delta (%)</th>
<th>HR for OS</th>
<th>P value</th>
<th>OS Delta (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOSAIC (1)</strong></td>
<td>0.78</td>
<td>0.005</td>
<td>7.5%</td>
<td>0.80</td>
<td>0.023</td>
<td>4.2%</td>
</tr>
<tr>
<td></td>
<td>CI, 0.65-0.93</td>
<td>At 5 year</td>
<td>58.9% vs 66.4%</td>
<td>CI, 0.65-0.97</td>
<td>At 6 year</td>
<td>68.7% vs 72.9%</td>
</tr>
<tr>
<td><strong>NSABP C-07 (2)</strong></td>
<td>0.78</td>
<td>0.0007</td>
<td>6.6%</td>
<td>0.85</td>
<td>0.052</td>
<td>2.7%</td>
</tr>
<tr>
<td></td>
<td>CI, 0.68-0.90</td>
<td>At 5 year</td>
<td>57.8% vs 64.4%</td>
<td>CI, 0.72-1.00</td>
<td>At 5 year</td>
<td>73.8% vs 76.5%</td>
</tr>
<tr>
<td><strong>XELOXA (3)</strong></td>
<td>0.80</td>
<td>0.0045</td>
<td>4.4%</td>
<td>0.87</td>
<td>0.1486</td>
<td>3.4%</td>
</tr>
<tr>
<td></td>
<td>CI, 0.69-0.93</td>
<td>At 3 year</td>
<td>66.5% vs 70.9%</td>
<td>CI, 0.72-1.05</td>
<td>At 5 year</td>
<td>ND (57 months FU)</td>
</tr>
</tbody>
</table>

1 André T, J Clin Oncol. 2009  
2 Yothers G, J Clin Oncol 2011  
3 Haller D, J Clin Oncol 2011
FOLFOX as standard treatment arm

CO-8

R  →  mFOLFOX6

R  →  mFOLFOX6 + bevacizumab

AVANT

R  →  FOLFOX4

R  →  FOLFOX4 + bevacizumab

R  →  XELOX + bevacizumab

PETACC-8/ N0147

R  →  FOLFOX

R  →  FOLFOX + cetuximab

= 6 months of chemotherapy; 12 months of bevacizumab
NSABP C-08 Schema

Stage II or III Colon Cancer

Stratification
Number of Positive Lymph Nodes

Randomization

mFOLFOX6

mFOLFOX6 + bevacizumab (12 mo)
<table>
<thead>
<tr>
<th>%</th>
<th>Events</th>
<th>3yDFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFF6+B</td>
<td>291</td>
<td>77.4</td>
</tr>
<tr>
<td>mFF6</td>
<td>312</td>
<td>75.5</td>
</tr>
</tbody>
</table>

HR 0.89
P 0.15
AVANT Study Design

Surgery for high-risk stage II or stage III colon cancer (N=3451)

- FOLFOX4
  - Bev 5 mg/kg q2w

- FOLFOX4 + bevacizumab
  - Bev 7.5 mg/kg q3w

- XELOX + bevacizumab
  - Bev 7.5 mg/kg q3w

- Bevacizumab monotherapy
  - Bev 7.5 mg/kg q3w

Follow-up

24 weeks
DFS (ITT Stage III)

- FOLFOX (N=955)
- FOLFOX4 + Bev (N=960)
- XELOX + Bev (N=952)

HR (95% CI)
- FOLFOX: 1.17 (0.98, 1.39)
- FOLFOX4 + Bev: 1.07 (0.90, 1.28)

Event-free rate

Number at risk
- FOLFOX4: 955, 890, 823, 779, 740, 708, 609, 451, 282, 121, 32, 0, 0
- FOLFOX4 + Bev: 960, 921, 868, 791, 728, 695, 586, 436, 280, 123, 33, 1, 0
- XELOX + Bev: 952, 900, 865, 784, 722, 688, 580, 415, 268, 110, 28, 0, 0

Time (months)
- 0, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72
DFS: Cumulative Hazard Ratio (ITT Stage III)

Hazard ratio

Time from randomization (years)

FOLFOX4 + Bev
XELOX + Bev
There is some transient benefit to adding Bev to FOLFOX, but this is dependent upon the longer duration of Bevacizumab therapy.

- If so, bevacizumab should be administered longer?
- But.....there are issues!
  - How much longer?
  - How much will it cost?
  - What are the long term adverse events?
  - Is this feasible?
- Discussion no longer underway in NSABP/Genentech/Roche to compare 2+ years of bevacizumab to one year.
Final Design for N0147 – June 2008

Stage 3 Colon Cancer (N = 3768)

K-ras WT

Centralized K-ras analysis

K-ras Mut

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 (95% CI)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX N=902</td>
<td>75.8% (72.1%-79.6%)</td>
<td>1.2 (0.96-1.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>FOLFOX + Cmab N=945</td>
<td>72.3% (68.5%-76.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Forest Plot for DFS

- Low Histology
- High Histology

- Female
- Male

- Stage T3
- Stage T4

- Age < 60
- Age > 60

- Age < 65
- Age > 65

- Age < 70
- Age > 70

- 1-3 Nodes
- ≥ 4 Nodes

Favors FOLFOX alone
Possible Explanations and Implications

1. Antibody Dependent Cellular Cytotoxicity (ADCC): not relevant with cetuximab
2. EGFR Signaling is complicated
   - Robust EGFR resistance networks
3. EGFR is not a relevant target in colon cancer micro metastasis (how to select biologics for future adjuvant trials?)
4. Increased toxicity with antibody, especially in >70 yrs, led to early discontinuations and reduced toxicity

NB: PETACC-8 reported at ESMO GI June 2012…also negative
Current trial(s): IDEA (International Duration Evaluation in Adjuvant) colon cancer, a prospective pooled analysis

- Worldwide effort to address duration question of oxaliplatin (3 vs 6 mos)
IDEA: International Duration Evaluation in Adjuvant colon cancer

- Participating groups:
  - GISCAD/GONO (Italy – TOSCA) – (bevacizumab)
  - SCOT (UK, Australia) – only 3 vs 6
  - CALGB/SWOG (US - C80702) – also ± celecoxib
    - c/w negative VICTOR trial with rofecoxib (JCO Oct 20, 2010:4575-4580)
  - GERCOR/PRODIGE (France) – only 3 vs 6
  - HORG (Greece) – only 3 vs 6

- Pooling only stage III colon cancer
- Total numbers of patients pooled: >10,500
  - Non-inferiority margin of 2.5%
- Extension to stage II patients ongoing
Adjuvant Therapy for Stage II Colon Cancer

Surgery
NCDB Results for Stage II Patients

- 31,551 patients with T3N0 disease
  - Median number of nodes removed = 9
  - 5-yr survival if 1-2 nodes examined ~ 64% (similar to T3N1 [stage IIIA])
  - 5-yr survival if >20 nodes examined ~ 87% (similar to T2N0 [stage I])
- Is the number of nodes a reflection of the surgeon, the pathologist or the patient?
Stage II survival vs. lymph nodes examined: a secondary analysis of INT-089 (all treated)

- >20 lymph nodes examined
- 11–20 lymph nodes examined
- 1–10 lymph nodes examined

Percentage survival over months from surgery.
Nodes in High-Risk Colon Cancer

- More taken/examined is better
  - ? Better surgery
  - ? Better pathology
    - Stage migration
  - ? Better biology

- LN staging and traditional clinical-pathologic markers of prognosis are available today, before molecular staging techniques...
Existing Tools for Selecting Stage II Patients for Treatment Are Inadequate

Recurrence Risk
- Bowel obstruction or perforation
- T-Stage
- # of nodes assessed
- Tumor grade
- Lymphatic/vascular invasion
- Margin status
- Mismatch repair status (MMR)
- Perineural invasion

Treatment Benefit
- dMMR

According to Current Guidelines\(^1,\)\(^2\)
- No molecular markers have been routinely established in clinical practice for stage II colon cancer
- Treatment decisions are based on the expectation that higher risk stage II patients derive larger absolute benefit with adjuvant chemotherapy
Adjuvant Chemotherapy for Stage II Colon Cancer With Poor Prognostic Features
O’Connor et al, et al  JCO July 2011

Patients and Methods: 43,032 Medicare beneficiaries who underwent colectomy for stage II and III primary colon adenocarcinoma diagnosed from 1992 to 2005 were identified from the SEER-Medicare database.

Results: Of the 24,847 patients with stage II cancer, 75% had one or more poor prognostic features. Adjuvant chemotherapy was received by 20% of patients with stage II disease. 5-year survival benefit from chemotherapy was observed only for patients with stage III disease (hazard ratio [HR], 0.64; 95% CI, 0.60 to 0.67). No survival benefit was observed for patients with stage II cancer with no poor prognostic features (HR, 1.02; 95% CI, 0.84 to 1.25) or stage II cancer with any poor prognostic features (HR, 1.03; 95% CI, 0.94 to 1.13).

Limitation: Medicare database
Molecular markers in colon cancer have a stage-specific prognostic value. Results of the translational study on the PETACC 3 - EORTC 40993 -SAKK 60-00 trial.

A. D. Roth, S. Tejpar, P. Yan, R. Fiocca, D. Dietrich, M. Delorenzi, R. Labianca, D. Cunningham, E. Van Cutsem, F. Bosman
## Marker Alteration Rate per stage

<table>
<thead>
<tr>
<th>Marker</th>
<th>Stage II (n=420)</th>
<th>Stage III (n=984)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI-H</td>
<td>22%</td>
<td>12%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TS</td>
<td>43%</td>
<td>29%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p53</td>
<td>30%</td>
<td>37%</td>
<td>0.01</td>
</tr>
<tr>
<td>SMAD4</td>
<td>18%</td>
<td>23%</td>
<td>0.03</td>
</tr>
<tr>
<td>18qLOH</td>
<td>63%</td>
<td>70%</td>
<td>0.04</td>
</tr>
<tr>
<td>hTERT</td>
<td>41%</td>
<td>48%</td>
<td>0.06</td>
</tr>
<tr>
<td>KRAS</td>
<td>35%</td>
<td>37%</td>
<td>0.81</td>
</tr>
<tr>
<td>BRAF</td>
<td>8%</td>
<td>8%</td>
<td>0.90</td>
</tr>
</tbody>
</table>

* Test of equal proportions
PETACC 3: RFS according to MSI or 18qLOH in stage II colon cancer

**MSI**

- Stage II (RFS)
- Estimated relapse-free survival probability
- Time (years)
- # at risk

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>306</td>
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<td>85</td>
<td>85</td>
<td>82</td>
<td>80</td>
<td>78</td>
<td>68</td>
<td>17</td>
<td>2</td>
</tr>
</tbody>
</table>

- p = 0.00219

**18qLOH**

- Stage II (RFS)
- Estimated relapse-free survival probability
- Time (years)
- # at risk

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>98</td>
<td>95</td>
<td>92</td>
<td>87</td>
<td>80</td>
<td>65</td>
<td>15</td>
<td>4</td>
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<td>166</td>
<td>158</td>
<td>140</td>
<td>130</td>
<td>123</td>
<td>102</td>
<td>30</td>
<td>3</td>
</tr>
</tbody>
</table>

- p = 0.0274

- no LOH
- LOH
Defective MMR in Colon cancer

- Characterized by presence of MSI & loss of MLH1, MSH2, MSH6 or PMS2 expression
- ~15% of Sporadic CC, >90% loss of MLH1
- Clinical Correlations: Right-sided, Female, Early stage, Better prognosis
- Tumors: Poorly differentiated, signet-ring-cell, lymphocytic infiltration
- dMMR (MSI-high) cells resistant to 5-FU\textsuperscript{1,2}
(A) Disease-free survival (DFS) in all untreated patients by DNA mismatch repair (MMR) status. (B) DFS in treated patients by MMR. dMMR, defective DNA mismatch repair; pMMR, proficient DNA mismatch repair.
(A) Disease-free survival (DFS) in patients with stage II disease and defective DNA mismatch repair (dMMR) by treatment status.

(C) DFS in patients with stage II disease and proficient MMR (pMMR) by treatment status.
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: OS in patients with “no clear indication for chemo” (mostly stage II)  
5-FU/LV vs surgery alone

5-year OS, Observation = 77.4% vs Chemotherapy = 80.3%
Relative risk = 0.83 (95% CI, 0.71-0.97)

$P = .02$

QUASAR group, Lancet 2007
The 12-Gene Colon Cancer Recurrence Score (RS) Predicts Recurrence Following Surgery in Stage II Colon Cancer (QUASAR)

Prospectively-Defined Primary Analysis in Stage II Colon Cancer (n=711)

- **STROMAL**
  - FAP
  - INHBA
  - BGN

- **CELL CYCLE**
  - Ki-67
  - C-MYC
  - MYBL2

- **REFERENCE**
  - ATP5E
  - GPX1
  - PGK1
  - UBB
  - VDAC2

RS = 0.15 x Stromal Group - 0.30 x Cell Cycle Group + 0.15 x GADD45B

Kerr et al., ASCO 2009, #4000
QUASAR Results: Recurrence Score® Result, T Stage, and MMR Deficiency Are Key Independent Predictors of Recurrence in Stage II Colon Cancer

Rare patients (2% of all patients) with T4, MMR-D tumors had estimated recurrence risks that approximated (with large confidence intervals) those for patients with T3 stage, MMR-P tumors and were not included in this figure.


The Recurrence Score predicts recurrence risk in stage II and III colon cancer.

The Recurrence Score enables better discrimination of absolute treatment benefit as a function of risk.

Oncotype DX for colon cancer leads to a change in treatment recommendations in 45% of patients (ASC0 GI 2013).

Incorporating the Recurrence Score result with traditional factors may better inform adjuvant therapy decisions.

### Resected Colon Cancer

#### Stage II
- **T-Stage**
- **MMR Status**
  - T3 & MMR-D: Low Risk
  - T3 & MMR-P: Standard Risk
  - T4 & MMR-P: High Risk

  - Consider Observation

#### Stage III
- **IIIA/B**
  - Oxi-containing Chemotherapy; 5FU/LV or Capecitabine

- **IIIC**
  - Consider Chemotherapy

MMR-D, mismatch repair deficient; MMR-P, mismatch repair proficient

*Patients not considered candidates for oxaliplatin
Onco
type DX® Colon Cancer Assay

• Prospective study to evaluate the impact of Recurrence Score results on treatment recommendations. The analysis included 141 patients with stage II, T3, mismatch repair-proficient (MMR-P) colon cancer.

• Prior to and after receiving these results, physicians completed surveys indicating their planned treatments. The results indicated that the use of the Oncotype DX® Colon Cancer test changed treatment decisions 45 percent of the time.

• Treatment intensity decreased for more than 33 percent of patients (from chemotherapy to observation or from oxaliplatin-containing to non-oxaliplatin containing regimens) and increased for more than 11 percent of patients (from observation to any chemotherapy or from non-oxaliplatin containing to oxaliplatin-containing treatment).

• Possible cost-savings; ? Impact on DFS/OS

Stage II colon cancer

Surgery

Tumor block risk assessment based on biology (18q/MSI)

High-risk (MSS and 18q LOH)

Arm A mFOLFOX6

Arm B mFOLFOX6 + bevacizumab 5mg/kg

Low-risk (MSI or no loss of 18q LOH)

Observation

> 2400 accrued

NB: patients with <8 LNns excluded
What is the Standard Adjuvant Therapy in Colon Cancer?

- FOLFOX (or XELOX) is standard adjuvant therapy in
  - most stage III and
  - can be considered in high-risk stage II colon cancer
  - very consistent results for oxaliplatin across trials
- Capecitabine (or 5FU/LV) for
  - patients who are not considered candidates for oxaliplatin (elderly, IIIA?)
  - unselected stage II, pMMR
- Irinotecan, bevacizumab, and cetuximab have failed!
- Less is more: IDEA
- More is better: FOLFIRINOX for high-risk stage III
ACCENT Database: Adjuvant Results over Time

• Improved time from recurrence to death (TRD) in newer trials supports the premise that more aggressive intervention (oxaliplatin- and irinotecan-based chemotherapy and/or surgery for recurrent disease) improves OS for patients previously treated in the adjuvant setting.

• Lower recurrence rates with identical treatments in those with stage II disease enrolled onto newer-era trials reflect stage migration over time, calling into question historical data related to the benefit of FU-based adjuvant therapy in such patients.

JCO Oct 10, 2013:3656-3663
ACCENT Database: Age

- 11,953 patients age < 70 and 2,575 age ≥ 70 years from seven adjuvant therapy trials
- Statistically significant interactions were not observed between treatment arm and age (P interaction = .09 for DFS, .05 for OS, and .36 for TTR), although the stratified point estimates suggested limited benefit from the addition of oxaliplatin in elderly patients (DFS hazard ratio [HR], 0.94; 95% CI, 0.78 to 1.13; OS HR, 1.04; 95% CI, 0.85 to 1.27).
- Comorbidities important; Among patients on clinical trials, younger (<40 yo) and older patients with stage II and III colon cancer had similar RFI and adjuvant therapy benefit. Younger patients have longer OS and DFS, which is likely primarily because of fewer competing causes of death.

McCleary et al; JCO Jul 10, 2013:2600-2606; Hubbard et al; JCO Jul 1, 2012:2334-2339
Follow-Up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer: ASCO Clinical Practice Guideline Endorsement

- Surveillance should be guided by presumed risk of recurrence and functional status of the patient (important within the first 2 to 4 years).
- Medical history, physical examination, and carcinoembryonic antigen testing should be performed every 3 to 6 months for 5 years. Patients at higher risk of recurrence should be considered for testing in the more frequent end of the range. A computed tomography scan (abdominal and chest) is recommended annually for 3 years, in most cases.
- A surveillance colonoscopy should be performed 1 year after the initial surgery and then every 5 years, dictated by the findings of the previous one. If a colonoscopy was not performed before diagnosis, it should be done after completion of adjuvant therapy (before 1 year).
- If a patient is not a candidate for surgery or systemic therapy because of severe comorbid conditions, surveillance tests should not be performed.

Meyerhardt et al JCO Dec 10, 2013:4465-4470
Data from Observational Studies for Stage I-III Disease

- Decreased risk of recurrence
  - Physical activity (NCIC trial)
  - Avoidance of Western pattern diet
  - Avoidance of class II/III obesity (BMI > 35 kg/m2)
  - Aspirin or COX-2 inhibitor (mutated-PIK3CA)
  - Higher vitamin D levels

- No association with recurrence to date
  - Weight change (gain or loss)
  - Smoking status or history
  - Multivitamin
Rectal Cancer

Portion of Rectum

Upper 1/3

Middle 1/3

Lower 1/3

Cm. from anal verge

15

11

7

2

Left upper valve of Houston

Right middle valve of Houston

Peritoneum

Left lower valve of Houston

Anal verge

Endpoints in Clinical Trials in Rectal Cancer

- Overall Survival
- Disease-free survival
- Distant failure
- Local failure
- R0 margin
- Circumferential margin
- pCR rate
- Downstaging (T,N)
- Toxicity/morbidity (acute/late)
- Sphincter preservation (late function)
Z6051: Laparoscopic Rectal Cancer Trial

Eligible pt with stage II-III primary rectal adenocarcinoma by ERUS or MRI staging

Randomization

Open rectal resection  Laparoscopic rectal resection

Accrual completed; results pending
# ADJUVANT RECTAL CANCER POOLED ANALYSIS

## Impact of TN Stage on Overall Survival

<table>
<thead>
<tr>
<th>Classification (TN stage)</th>
<th>No.</th>
<th>5-Yr (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-2 N1</td>
<td>355</td>
<td>79</td>
<td>0.001</td>
</tr>
<tr>
<td>N2</td>
<td>226</td>
<td>67</td>
<td>–</td>
</tr>
<tr>
<td>T3 N0</td>
<td>1060</td>
<td>75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N1</td>
<td>887</td>
<td>60</td>
<td>–</td>
</tr>
<tr>
<td>N2</td>
<td>935</td>
<td>44</td>
<td>–</td>
</tr>
<tr>
<td>T4 N0</td>
<td>111</td>
<td>65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N1</td>
<td>62</td>
<td>35</td>
<td>–</td>
</tr>
<tr>
<td>N2</td>
<td>108</td>
<td>37</td>
<td>–</td>
</tr>
</tbody>
</table>

*Gunderson, JCO 2004*
ADJUVANT RECTAL CANCER
POOLED ANALYSIS
Conclusions - Impact of Treatment

- **Intermediate risk patients** (T1-2N1, T3N0)
  - Tri-modality adjuvant therapy for all patients may be excessive treatment, based on OS of >80% with surgery + chemotherapy

- **Moderately-high risk patients** (T1-2N2, T3N1, T4N0)
  - 5-yr OS ranges from 20-80%
  - Improvement in OS should be feasible since some treatment arms had DFS of only 20-50%

- **High-risk patients** (T3N2, T4N1, T4N2)
  - 5-yr OS was <50% in most groups of patients
  - More aggressive postoperative, preoperative or targeted therapy is indicated
Adjuvant Therapy of Rectal Cancer: The Mayo/NCCTG Trial

204 patients with T3-4, N1-2 rectal cancer Postoperative

- XRT 5040 cGy
- 5-FU + MeCCNU
  - bolus 5-FU + XRT
  - 5-FU + MeCCNU
NCCTG 79-47-51: CTX/XRT vs: XRT Alone

Recurrence-free Survival

Overall Survival

Pre-operative adjuvant therapy in rectal cancer

- Emphasis on curative resection in addition to sphincter preservation
  - pre-operative staging
  - pre-operative tumor down-staging
  - surgical technique (TME)
  - accurate pathological staging (R0)
  - reduce acute and late toxicities

CRM = circumferential resection margin; TME = total mesorectal excision
Phase III Preop vs. Postop Chemoradiation

- **Intergroup 0147**
  - 53 Pts; Closed Early Secondary to Poor Accrual

- **NSABP R-03**
  - Scheduled to Accrue 900 Pts; Closed at 200; Underpowered to Answer Survival Endpoints

- **German CAO/ARO/AIO-94 Study**
German CAO/ARO/AIO-94 Study

CAO/ARO/AIO 94

805 patients
EUS T3, T4 or node positive

RANDOMIZE

Arm 1 / TME
Surgery

Arm 2
50.4 Gy RT
+ 5-FU, CI

50.4 Gy RT
+ 5.4 Gy boost
with 5-FU, CI
to start within
4 weeks of surgery

pT1-2N0
Observe

5 cycles of bolus 5-FU

4-6 weeks after completion of RT and 5-FU
<table>
<thead>
<tr>
<th>Pathohistologic Tumor Stage</th>
<th>Postoperative RCT n= 394</th>
<th>Preoperative RCT n = 405</th>
</tr>
</thead>
<tbody>
<tr>
<td>No tumor</td>
<td>0.7%</td>
<td>7.7%</td>
</tr>
<tr>
<td>UICC- I</td>
<td>18 %</td>
<td>25 %</td>
</tr>
<tr>
<td>UICC-II</td>
<td>28 %</td>
<td>29 %</td>
</tr>
<tr>
<td>UICC-III</td>
<td>39 %</td>
<td>26 %</td>
</tr>
<tr>
<td>UICC-IV</td>
<td>7 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Missing</td>
<td>6 %</td>
<td>6 %</td>
</tr>
</tbody>
</table>

P < 0.0001
Preoperative vs Postoperative Therapy of Rectal Cancer

German Rectal Cancer Study

CAO/ARO/AIO-94, NEJM 2004

- Decreased acute and delayed toxicities with preoperative therapy
- Sphincter preservation in 43 (39%) vs 17 (20%) in those declared to require APR at randomization
- Locoregional failure: 6% vs 12%
- No difference in distant metastases, DFS or OS
Prognostic factors – ypT/ypN

Disease-free survival after R0-resection (n=344)

- ypT1
- ypT0
- ypT2
- ypT3
- ypT4
- ypNO
- ypN1
- ypN2

p=0.001

p<0.0001
Forest plot analysis of local recurrences after macroscopically complete local tumor resection for different subgroups of patients who actually received chemoradiotherapy (CRT).

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>Preoperative CRT v Postoperative CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CRT patients</td>
<td>646</td>
<td>1.57 (0.9 to 2.85)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td>335</td>
<td>1.28 (0.6 to 2.86)</td>
</tr>
<tr>
<td>&gt; Median</td>
<td>311</td>
<td>2.0 (0.8 to 4.91)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>451</td>
<td>1.84 (0.9 to 3.76)</td>
</tr>
<tr>
<td>Female</td>
<td>195</td>
<td>1.1 (0.4 to 3.29)</td>
</tr>
<tr>
<td>Distance, cm²</td>
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<tr>
<td>&lt; 5</td>
<td>175</td>
<td>1.65 (0.7 to 3.97)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>449</td>
<td>1.7 (0.7 to 4.19)</td>
</tr>
<tr>
<td>(L)AR</td>
<td>422</td>
<td>1.01 (0.4 to 2.85)</td>
</tr>
<tr>
<td>APR or ISR</td>
<td>223</td>
<td>2.24 (1.1 to 4.71)</td>
</tr>
<tr>
<td>(y)Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/I/II</td>
<td>352</td>
<td>1.45 (0.4 to 4.83)</td>
</tr>
<tr>
<td>III/IV</td>
<td>291</td>
<td>0.95 (0.5 to 1.95)</td>
</tr>
<tr>
<td>R0</td>
<td>627</td>
<td>1.4 (0.7 to 2.63)</td>
</tr>
<tr>
<td>R1</td>
<td>12</td>
<td>1.59 (0.2 to 15.4)</td>
</tr>
</tbody>
</table>

Sauer R et al. JCO 2012; 30:1925-1933
CAO/ARO/AIO-94: 11-yr results

(A) Overall survival and (B) cumulative incidence of distant recurrences in the intention-to-treat population.

Sauer R et al. JCO 2012;30:1926-1933
STAR TRIAL
Aschele, ASCO 2009

RT 50.4 Gy
FU 225 mg/m²/day PVI

RT 50.4 Gy
FU 225 mg/m²/day PVI
OXA 60 mg/m² weekly x 6

FU/LV (bolus or CI, center choice)

6-8 wks

• stage
• center

pathologic CR

<table>
<thead>
<tr>
<th></th>
<th>patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FU/RT</td>
</tr>
<tr>
<td></td>
<td>(n= 379)</td>
</tr>
<tr>
<td>ypT0N0</td>
<td>16</td>
</tr>
<tr>
<td>(95% cl)</td>
<td>(13-20)</td>
</tr>
</tbody>
</table>
NSABP R-04

Stratification: gender; tumor stage (II vs. III); intended surgery (sphincter saving vs. other)

RT (45Gy in 25 fractions)*
Capecitabine 825mg/m² b.i.d. x5d/w continuously during RT

oxaliplatin

No oxali

RT (45Gy in 25 fractions)*
CI 5-FU 225mg/m²/day during RT

oxaliplatin

No oxali

Surgery

Pathologic Complete Response by Treatment 5-FU vs Capecitabine

<table>
<thead>
<tr>
<th>pCR Status</th>
<th>5-FU</th>
<th>Cape</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>without pCR</td>
<td>584</td>
<td>550</td>
<td>1134</td>
</tr>
<tr>
<td>with pCR</td>
<td>135</td>
<td>157</td>
<td>292</td>
</tr>
<tr>
<td>Total Patients</td>
<td>719</td>
<td>707</td>
<td>1426</td>
</tr>
</tbody>
</table>

pCR Rate (%)

<table>
<thead>
<tr>
<th>5-FU</th>
<th>Cape</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.8</td>
<td>22.2</td>
</tr>
</tbody>
</table>

95% CI

<table>
<thead>
<tr>
<th>5-FU</th>
<th>Cape</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.0-21.8</td>
<td>19.2-25.5</td>
</tr>
</tbody>
</table>

P-value

| 0.12 |
### Pathologic Complete Response by Treatment

**Oxaliplatin vs None**

<table>
<thead>
<tr>
<th>pCR Status</th>
<th>No Oxali</th>
<th>Oxali</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>without pCR</td>
<td>469</td>
<td>457</td>
<td>926</td>
</tr>
<tr>
<td>with pCR</td>
<td>111</td>
<td>121</td>
<td>232</td>
</tr>
<tr>
<td>Total Patients</td>
<td>580</td>
<td>578</td>
<td>1158</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>pCR Rate (%)</th>
<th>95% CI</th>
<th>No Oxali</th>
<th>Oxali</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.1</td>
<td>16.0-22.6</td>
<td>20.9</td>
<td>17.7-24.5</td>
<td>0.46</td>
</tr>
</tbody>
</table>
NSABP R-04
Conclusions

• Administration of capecitabine with preoperative RT achieved rates similar to continuous infusion 5-FU for
  – Surgical downstaging
  – Sphincter saving surgery
  – Pathologic complete response

• Addition of oxaliplatin did not improve outcomes (sphincter-saving) and added significant toxicity

• Longer follow up will be needed to assess local-regional tumor relapse, DFS and OS
Preoperative chemoradiotherapy and postoperative chemotherapy with 5-FU and oxaliplatin versus 5-FU alone in locally advanced rectal cancer

Results of the CAO/ARO/AIO-04 randomized phase III trial


German Rectal Cancer Study Group

ASCO 2014
Phase III: CAO/ARO/AIO-04

**Best arm of CAO/ARO/AIO-94:**

RT 50.4 Gy + 5-FU
1000 mg/m² days 1-5 + 29-33

**Based on phase I/II trials:**

RT 50.4 Gy + 5-FU/OX
Oxaliplatin: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35
Note: Chemo gap during 3rd week of RT

**5-FU**
500 mg/m² d 1-5, q29
4 cycles (4 months)

**mFOLFOX6**
Oxaliplatin: 100 mg/m² d1,q15
Folinic acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)
**Primary Endpoint DFS**

Median Follow-up: 50 months (range, 0.3 – 73)  
Intention-to-treat  
Time between randomisation and the first of the following events:

<table>
<thead>
<tr>
<th>Event</th>
<th>5-FU Arm n=623</th>
<th>5-FU/Ox Arm n=613</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete local resection (R2)</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Locoregional recurrence after R0/R1 resection (+/- distant metastases)</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Distant metastases/Progression</td>
<td>149</td>
<td>115</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>106</td>
<td>96</td>
</tr>
<tr>
<td>Cancer-/treatment related/surgical mortality</td>
<td>69/4/6</td>
<td>54/7/4</td>
</tr>
<tr>
<td>Unrelated</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>First events for DFS (total)</td>
<td>198</td>
<td>159</td>
</tr>
</tbody>
</table>
Disease-free Survival: Intention-to-treat analysis

Mixed-effects Cox Model:
HR = 0.79; 95% CI = (0.64, 0.98)
P-value = 0.030
3-year DFS: 71.2% vs. 75.9%
5-year DFS: 64.3% vs. 68.8%

N at risk
5-FU  623  509  441  363  233  114  1
5-FU/OX 613  522  447  364  230  110  1
## Subgroup Analysis of DFS: Pathological factors

**Intention-to-treat**

<table>
<thead>
<tr>
<th>Variable</th>
<th>5-FU Events/n</th>
<th>5-FU/OX Events/n</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ypT-category</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT0-1</td>
<td>13/122</td>
<td>21/153</td>
<td>1.36 (0.68, 2.72)</td>
</tr>
<tr>
<td>ypT2</td>
<td>41/183</td>
<td>29/160</td>
<td>0.77 (0.48, 1.24)</td>
</tr>
<tr>
<td>ypT3</td>
<td>120/278</td>
<td>92/260</td>
<td>0.78 (0.60, 1.03)</td>
</tr>
<tr>
<td>ypT4</td>
<td>17/26</td>
<td>9/17</td>
<td>0.76 (0.34, 1.70)</td>
</tr>
<tr>
<td><strong>ypN-category</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypN0</td>
<td>94/423</td>
<td>75/416</td>
<td>0.78 (0.58, 1.06)</td>
</tr>
<tr>
<td>ypN1</td>
<td>53/131</td>
<td>45/133</td>
<td>0.82 (0.55, 1.22)</td>
</tr>
<tr>
<td>ypN2</td>
<td>44/60</td>
<td>30/42</td>
<td>1.09 (0.65, 1.81)</td>
</tr>
<tr>
<td><strong>TNM stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>30/176</td>
<td>19/148</td>
<td>0.72 (0.40, 1.28)</td>
</tr>
<tr>
<td>Stage II</td>
<td>48/148</td>
<td>40/154</td>
<td>0.74 (0.49, 1.13)</td>
</tr>
<tr>
<td>Stage III</td>
<td>71/169</td>
<td>57/154</td>
<td>0.89 (0.63, 1.28)</td>
</tr>
<tr>
<td>ypT0ypN0</td>
<td>6/81</td>
<td>9/104</td>
<td>1.19 (0.43, 3.36)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>198/623</strong></td>
<td><strong>159/613</strong></td>
<td><strong>0.79 (0.64, 0.98)</strong></td>
</tr>
</tbody>
</table>

5-FU/OX better than 5-FU
Overall Survival: Intention-to-treat analysis

Mixed-effects Cox model:
HR = 0.96; 95% CI = (0.72, 1.26)
P-value = 0.752
3-year OS: 88.0% vs. 88.7%
5-year OS: 78.3% vs. 78.0%

N at risk
- 5-FU: 623, 572, 530, 446, 286, 142, 2
- 5-FU/OX: 613, 559, 512, 430, 268, 123, 1
Conclusions: CAO/ARO/AIO-04

• Preop 5-FU/OX-CRT with one week chemo gap
  - well tolerated, high compliance
  - increased pCR-rate

• Quality assurance program
  - Optimal TME quality 76-77%
  - Lymph nodes examined per specimen 15 (median)

• Oxaliplatin included both pre- and postop
  - 78% started adjuvant CTx (of whom 79% completed all cycles)

• Primary endpoint: DFS after 50 months f/u
  - 71.2% in 5-FU arm vs. 75.9% in 5-FU/OX arm at 3 years (HR 0.79; p=0.03)
The image shows a CONSORT diagram of patients with clinical stage II/III rectal cancer and administration of adjuvant chemotherapy. The flowchart starts with all patients with colorectal cancer (N = 8,366) and then delineates into patients with rectal cancer (n = 2,073) and who had 9 months follow-up and surgery (n = 1,647). It then further divides into patients who did not receive neoadjuvant therapy (n = 454; 28%) and those who did receive neoadjuvant therapy (n = 1,193; 72%).

The diagram continues to break down further into patients who did not receive adjuvant therapy (n = 203; 17%) and received adjuvant therapy (n = 990; 83%). It then splits again, comparing those not seen by Med Onc (n = 40; 20%) with those seen by Med Onc (n = 136; 67%), and those who are unknown (n = 27; 13%).

The final branches focus on chemo: those who received chemo (n = 74; 54%), those who recommended chemo but didn’t discuss it (n = 50; 37%), and those whose status is unknown (n = 12; 9%).

The source of the data is Khrizman P et al. JCO 2013;31:30-38.

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Where do we go in adjuvant therapy of Rectal Cancer?

- Patient selection
- Drug selection
- Do all patients need (adjuvant) chemotherapy?
- Do all patients need radiation therapy?
  - T3N0 high rectal lesions
- Do all patients need surgery?
Rectal Cancer: ACOSOG Z6092 / CALGB 81001: Can XRT be deleted in low risk, high rectal tumors? (PROSPECT trial)

Protocol Schema

Clinical Stage T1N1, T2N1, T3N0, T3N1 Rectal cancer
Candidate for LAR Surgeon is TME credentialed

Randomize

Intervention

Neoadjuvant mFOLFOX6 x 6

Restage

Stable Disease

Progression

Low Anterior Rectal Resection with TME

Pre-op 5FUCMT

Outcomes: R0 rate and Path CR

Post-Op Rx:
- If path=R1/2, & no preop XRT, then 5FUCMT
- FOLFOXx6 if no 5FUCMT
- FOLFOXx8 if pre-op 5FUCMT

Outcomes: LRR & DFS
Rectal Cancer: ACOSOG Z6092 / CALGB 81001

Intervention Arm

Randomize to Selective Arm

- Neoadjuvant mFOLFOX6 x 6
- Restage

- Clinical Evidence of Primary Tumor Progression
  - Pre-op 5FUCMT
  - Low Anterior Rectal Resection with TME
  - Post-Op

- No Clinical Evidence of Primary Tumor Progression
  - R0 Surgical Resection
    - Suggest: Adjuvant mFOLFOX6 x6
    - Post-Op: Selective Arm
  - R1 or R2 Surgical Resection
    - Suggest: Post-op 5FUCMT, then mFOLFOX4

Post Treatment Surveillance
  (starting at 1 yr +/- one month from date of primary resection):
  - CEA: q6 month x3 years
  - Endoscopic exam of anastomosis: q6x2; q12x2
  - CT scan (Chest/abd/pel) q 12 months x 3 years
Twenty-one patients with cCR were included in the wait-and-see policy group. Mean follow-up was 25 ± 19 months. One patient developed a local recurrence and had surgery as salvage treatment. The other 20 patients are alive without disease. The control group consisted of 20 patients with a pCR after surgery who had a mean follow-up of 35 ± 23 months. For these patients with a pCR, cumulative probabilities of 2-year disease-free survival and overall survival were 93% and 91%, respectively.