Adjuvant and palliative treatment in colorectal cancer: which drug for what indication?

Falk symposium, May 3 2008
Karen Geboes, MD, PhD
Eric Van Cutsem, MD, PhD
UZ Gasthuisberg Leuven
Where do we come from – where do we go?

Treatment of metastatic CRC

- best supportive care
- 5-FU based chemotherapy (bolus regimen)
- 5-FU / FA / oxaliplatin
- 5-FU / FA / irinotecan
- 5-FU infusional regimen
- capecitabine + oxaliplatin
- sequential therapy with irinotecan and oxaliplatin

- median survival (months)
Where do we come from – where do we go?

Treatment of metastatic CRC

- best supportive care
- 5-FU based chemotherapy (bolus regimen)
- 5-FU / FA / irinotecan
- 5-FU / FA / oxaliplatin
- capecitabine + oxaliplatin
- sequential therapy with irinotecan and oxaliplatin
- cetuximab + irinotecan (3 line)?
- bevacizumab + IFL (1 line)
- bevacizumab + irinotecan (3 line)?
What have we learned with the cytotoxics?

1. Combination treatment is more active than 5-FU/LV

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th></th>
<th>Arm B</th>
<th></th>
<th>P  value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Folfiri (n=109)</td>
<td>Folfox (n=81)</td>
<td>Folfox (n=111)</td>
<td>Folfiri (n=69)</td>
<td></td>
</tr>
<tr>
<td>RR (%)</td>
<td>56</td>
<td>15</td>
<td>54</td>
<td>4</td>
<td>ns</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>8.5</td>
<td>4.2</td>
<td>8.0</td>
<td>2.5</td>
<td>0.26</td>
</tr>
<tr>
<td>PFS (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>OS (months)</td>
<td>21.5</td>
<td></td>
<td>20.6</td>
<td></td>
<td>0.99</td>
</tr>
</tbody>
</table>

2. FOLFOX and FOLFIRI have a similar activity

*Fig 4. Overall survival curves. FOLIRI, 5-fluorouracil and leucovorin; FOLIRI, 5-fluorouracil, leucovorin and oxaliplatin.*


Treatment of metastatic CRC
What have we learned with the cytotoxics?

3. Capecitabine has a similar activity as IV 5-FU/LV
   Capecitabine plus oxaliplatin has a similar activity as FOLFOX

4. The survival is longer if more patients are exposed to all 3 cytotoxic agents: fluoropyrimidines, oxaliplatin and irinotecan


Grothey A., J Clin Oncol 2005; 23: 9441-42

Treatment of metastatic CRC
What have we learned with the cytotoxics?

5. Most patients are treated with combination of 2 cytotoxics, although it is not clear that all patients need upfront combination

CAIRO (n=820):
Sequential therapy: capecitabine followed by irinotecan in 2nd line and capox in third line
Combination therapy: capiri followed by capox
→ No benefit in survival for the use of combination therapy

Koopman et al., Lancet 2007; 370: 135-42
Why then combination therapy in first line?

CAIRO

Importance of objective tumor response
E.g. conversion of unresectable liver metastases to resectable

Koopman et al., Lancet 2007; 370: 135-42
From care to cure?

Liver resection offers the only chance of cure for patients with colorectal liver metastases

5y-survival following resection: 25-40%
5y-survival without resection: 0-5%

Nordlinger B., Eur J Cancer 2007, 43: 2037-2045

Treatment of metastatic CRC
Resection of liver metastases

364 pts with potentially resectable liver metastases

folfox surgery

primary surgery

absolute increase in rate of progression-free survival at 3 years:
7.3% in randomised patients
(28.1 – 35.4%, HR 0.79, p=0.058)

Nordlinger B., Lancet 2008; 371: 1007-16

Treatment of metastatic CRC
Resection of liver metastases

- **Toxicity**
  - Oxaliplatin: vascular lesions
  - Irinotecan: steatohepatitis

Risk of surgical complications ~ number of chemotherapy cycles
Risk of surgical complications is low if not more than 6 cycles are given pre-operatively

- Disappearance of lesions under chemotherapy
  - Close monitoring?

- Progression during preoperative chemotherapy
  - Avoidance of unnecessary surgery
When to use the new ‘targeted’ therapies?

<table>
<thead>
<tr>
<th></th>
<th>Monoclonal antibodies (extracellular)</th>
<th>Tyrosine kinase inhibitors (intracellular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>chimeric</td>
<td>EGF</td>
<td>cetuximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gefitinib</td>
</tr>
<tr>
<td></td>
<td>VEGF</td>
<td>sunitinib</td>
</tr>
<tr>
<td>humanized</td>
<td>EGF</td>
<td>panitumumab</td>
</tr>
<tr>
<td></td>
<td>VEGF</td>
<td>bevacizumab</td>
</tr>
</tbody>
</table>
Anti-VEGF antibodies may act against tumours in three ways:

- Regression of existing microvasculature
- Normalisation of remaining tumour vasculature
- Inhibition of new tumour vasculature
When to use the new ‘targeted’ therapies?
Agents targeting the VEGF pathway

- Anti-VEGF antibodies (bevacizumab)
- Soluble decoy VEGF receptors (VEGF-TRAP: aflibercept)
- Anti-VEGFR antibodies (IMC-1121b)
- Small-molecule VEGFR inhibitors (PTK787, AZD2171, sunitinib, …)

VEGF (vascular endothelial growth factor) interacts with VEGFR-1 and VEGFR-2 receptors on endothelial cells. Inhibition of these receptors can block angiogenesis and tumor growth.
When to use the new ‘targeted’ therapies? Bevacizumab

Bevacizumab in first line treatment: pivotal trial with irinotecan

5-FU/FA monotherapy: increased activity in first line
Oxaliplatin based: increased activity in first line

Bevacizumab + bolus 5FU/FA in refractory CRC is not active

Chen H., J Clin Oncol 2006; 24: 3354-3360


Treatment of metastatic CRC
When to use the new ‘targeted’ therapies? BEAT: surgery with curative intent

Overall population: rates of potentially curative hepatic metastasectomy

Patients with liver metastases only: rates of potentially curative hepatic metastasectomy

*Secondary endpoint; **Prospectively assessed


Treatment of metastatic CRC
When to use the new ‘targeted’ therapies?

NO16966: surgery with curative intent

- CAPOX/FOLFOX4 + placebo
- CAPOX/FOLFOX4 + bevacizumab

Patients with liver metastases only

Placebo (n=701) Bevacizumab (n=699)

Placebo (n=178) Bevacizumab (n=177)


Treatment of metastatic CRC
When to use the new ‘targeted’ therapies? Bevacizumab – safety issues

- Bevacizumab does not increase chemotherapy related toxicities
- Bevacizumab has specific side effects:
  - Hypertension
  - Proteinuria
  - Thromboembolic events: arterial
  - Bleeding: minor mucosal (epistaxis) and major hemorrhage (non small cell lung cancer)
  - Gastrointestinal perforation
  - Wound healing/postoperative bleeding
When to use the new ‘targeted’ therapies?
The EGFR Pathway: entryway to multiple intracellular signaling cascades

Treatment of metastatic CRC

Adapted from Mendelsohn and Baselga. Oncogene 2000; 19:6550-6565
When to use the new ‘targeted’ therapies?
Anti-EGFR antibodies in metastatic CRC

| 3rd line          | • BOND: cetuximab ± irinotecan  
|                  | • NCIC C0.17: cetuximab vs BSC  
|                  | • Panitumumab vs BSC (K-ras wild type)  
|                  | Benefit demonstrated |
| 2nd line          | • BOND: cetuximab ± irinotecan  
|                  | • EPIC: irinotecan ± cetuximab  
|                  | Benefit |
| 1st line          | • (randomized) Phase II studies  
|                  | • CRYSTAL: FOLFIRI ± cetuximab  
|                  | • PACCE: chemo/bevacizumab ± panitumumab  
|                  | • Other phase III studies in progress |
When to use the new ‘targeted’ therapies? Cetuximab + irinotecan in refractory CRC

**Response Rate Disease Control (CR+PR+SD)**

<table>
<thead>
<tr>
<th></th>
<th>Percentage</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + irinotecan (n=218)</td>
<td>23</td>
<td>[18-29]</td>
<td>* 0.0074</td>
</tr>
<tr>
<td>Cetuximab (n=111)</td>
<td>11</td>
<td>[6-18]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>[49-62]</td>
<td>** &lt;0.001</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>[24-42]</td>
<td></td>
</tr>
</tbody>
</table>

* p=0.0074; ** p<0.001; [] = 95% CI

Cunningham D., N Engl J Med 2004; 351: 337-345
When to use the new ‘targeted’ therapies?
Cetuximab in first line

Cetuximab in first line treatment: CRYSTAL

EGFR Expressing mCRC

<table>
<thead>
<tr>
<th>N=540: cetuximab + folfiri</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=540: folfiri</td>
</tr>
</tbody>
</table>

- Primary end-point: progression free survival
When to use the new ‘targeted’ therapies? Cetuximab in first line

When to use the new ‘targeted’ therapies? CRYSTAL: surgery with curative intent

Surgery with curative intent
No residual tumor after resection

Percenta (\%) $\text{\%}$

CMH test $p=0.0034^*$

odds ratio 3.0
[95\% CI: 1.4 - 6.5]

FOLFIRI alone Cetuximab + FOLFIRI

ITT population (pre-planned)
Liver metastases only (exploratory)

No residual tumor in patients with liver metastases
n=134/n=122

Treatment of metastatic CRC

When to use the new ‘targeted’ therapies?

BOSS-trial
Resectable liver metastases

Folfox + cetuximab + avastin
Folfox + cetuximab

surgery

Folfox + cetuximab + avastin
Folfox + cetuximab

Treatment of metastatic CRC
When to use the new ‘targeted’ therapies?

EGFR-inhibitors - toxicity

**Acne-like rash**

Post inflammatory effects

**Dry skin**

**Fissura**

**Paronychia**

**Pruritus**

Description of severe cases

**THERAPY SUGGESTIONS**

- Topical anti-acne creams (drying effect)
- +/- tetracyclines
- +/- antihistamines
- Pulse dye laser
- Emollients
- Hydrocolloid dressing or
- Propylene glycol +/- acetylsalicyl
- Anti-septic soaks
- Silver nitrate (pyogenic granuloma)

**Treatment of metastatic CRC**

S Segaert & E Van Cutsem, Ann Oncology 2005
When to use the new ‘targeted’ therapies?  
EGFR-inhibitors - toxicity

Figure 1: Changes in serum magnesium concentrations from baseline over time during EGFR-targeting antibody treatment for colorectal cancer. Solid lines represent the individual linear regression line of the data points for each individual patient. × denotes end of treatment.

Figure 2: Kaplan-Meier curve of estimated proportion of patients maintaining a serum magnesium concentration in normal range (i.e., >0.65 mmol/L) during treatment with EGFR-targeting antibodies for colorectal cancer.
When to use the new ‘targeted’ therapies? EGFR and prediction of response

No correlation of antitumor efficacy with EGFR expression

Correlation with skin toxicity

<table>
<thead>
<tr>
<th>Skin toxicity (NCI-CTC)</th>
<th>Cetuximab monotherapy RR (%)</th>
<th>Combination therapy RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Grade 1</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>Grade 2</td>
<td>20</td>
<td>34</td>
</tr>
</tbody>
</table>

Cunningham D., Proc Am Soc Clin Oncol 2003; abstr 1012

Treatment of metastatic CRC
When to use the new ‘targeted’ therapies? EGFR and prediction of response

- Skin reaction grade 0 or 1, n=244
- Skin reaction grade 2, n=243
- Skin reaction grade 3*, n=112

There were no grade 4 skin reactions

CRYSTAL trial: Subgroup analysis of PFS time by on-study skin reactions

When to use the new ‘targeted’ therapies? EGFR and prediction of response

<table>
<thead>
<tr>
<th>Reference</th>
<th>Anti-EGFR</th>
<th>No. of patients (mutant: wild-type)</th>
<th>Objective response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liévre et al. JCO 2008</td>
<td>Cetuximab ± irinotecan-based CTx</td>
<td>114 (36:78)</td>
<td>0 (0) 34 (43.6)</td>
</tr>
<tr>
<td>Benvenuti et al. Cancer Res 2007</td>
<td>Panitumumab or cetuximab or cetuximab + CTx</td>
<td>48 (16:32)</td>
<td>1 (6) 10 (31)</td>
</tr>
<tr>
<td>De Roock, VanCutsem, Tejpar. Ann Oncol 2008</td>
<td>Cetuximab ± irinotecan</td>
<td>113 (46:67)</td>
<td>0 (0) 27 (40)</td>
</tr>
<tr>
<td>Finocchiaro et al. ASCO 2007</td>
<td>Cetuximab ± CTx</td>
<td>81 (32:49)</td>
<td>2 (6) 13 (27)</td>
</tr>
<tr>
<td>Di Fiore et al. Br J Cancer 2007</td>
<td>Cetuximab + CTx</td>
<td>59 (16:43)</td>
<td>0 (0) 12 (28)</td>
</tr>
<tr>
<td>Khambata-Ford et al. JCO 2007</td>
<td>Cetuximab</td>
<td>80 (30:50)</td>
<td>0 (0) 5 (10)</td>
</tr>
</tbody>
</table>

Treatment of metastatic CRC
When to use the new ‘targeted’ therapies?
EGFR and prediction of response

Correlation with KRAS-status

De Roock W., Ann Oncol 2008; 19: 508-515
When to use the new ‘targeted’ therapies? 
EGFR and prediction of response

Panitumumab vs BSC in 3° line mCRC: Objective Tumor Response (Central Radiology)

<table>
<thead>
<tr>
<th></th>
<th>All Evaluable n (%)</th>
<th>Mutant n (%)</th>
<th>Wild-type n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td><strong>Pmab</strong> (N = 208)</td>
<td><strong>Pmab</strong> (N = 84)</td>
<td><strong>Pmab</strong> (N = 124)</td>
</tr>
<tr>
<td></td>
<td><strong>BSC</strong> (N = 219)</td>
<td><strong>BSC</strong> (N = 100)</td>
<td><strong>BSC</strong> (N = 119)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>21 (10)</td>
<td>0 (0)</td>
<td>21 (17)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>52 (25)</td>
<td>10 (12)</td>
<td>42 (34)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>104 (50)</td>
<td>59 (70)</td>
<td>45 (36)</td>
</tr>
<tr>
<td><strong>CR, PR, SD</strong></td>
<td>73 (35)</td>
<td>10 (12)</td>
<td>63 (51)</td>
</tr>
</tbody>
</table>

Pmab, panitumumab; BSC, best supportive care; CR, complete response; PR partial response; SD, stable disease; PD, disease progression

*Treatment of metastatic CRC*  
*Amado R, Van Cutsem E et al, J Clin Oncol 2008*
When to use the new ‘targeted’ therapies? EGFR and prediction of response

Panitumumab vs BSC in 3° line mCRC

Wild-type K-ras

Fig 4. Waterfall plots showing maximum percent decrease in target lesions (blinded central radiology). (A) Patients receiving panitumumab, mutant KRAS. (B) Patients receiving panitumumab, wild-type (WT) KRAS. (C) Best supportive care (BSC) patients, mutant KRAS. (D) BSC patients, WT KRAS. Percentages are best response within each KRAS group, excluding missing or nonassessable postbaseline tumor assessments. PR, partial response; SD, stable disease; PD, progressive disease.
Biologics as first-line therapy in advanced CRC: PFS (overall) from key randomised trials

- Bevacizumab Placebo
- Bevacizumab Placebo
- Bevacizumab Placebo
- Bevacizumab Placebo
- Cetuximab Control
- Panitumumab Bevacizumab
- Bevacizumab

Kabbinavar et al. JCO 2005
Hurwitz et al. NEJM 2004
Saltz et al. JCO. 2008
Bokemeyer et al. ECCO 2007
Van Cutsem et al. ASCO 2007
Hecht et al. ASCO GI 2008

Treatment of metastatic CRC
Treatment algorithms…
The integration of the biologicals in the continuum of care of CRC

1st line cytotoxic → 2nd line cytotoxic → 3rd line cytotoxic

How to start? How to select?

At progression change chemo, biologic or both?

Independent sequences?

1st biologic → 2nd biologic

Treatment of metastatic CRC
Mod. from Van Cutsem E. Editorial J Clin Oncol 2006
Treatment algorithms…

The questions remain the same:
Combination of all therapies or sequential therapy?
Continuous or intermittent therapy?
If a break in chemotherapy is considered, should patients be continued on a biological agent?

Try to identify reliably patients who are most likely to respond or to encounter toxicity

Performance status and physiological age

Strong upfront therapy in young patients with potentially resectable liver metastases
→ try to identify best therapy


*Table 4. Examples of promising predictive and prognostic markers for improved survival [36]*

<table>
<thead>
<tr>
<th>Marker</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS gene expression</td>
<td>5-FU</td>
</tr>
<tr>
<td>DPD gene expression</td>
<td>5-FU</td>
</tr>
<tr>
<td>ERCC1 gene expression</td>
<td>Oxaliplatin</td>
</tr>
<tr>
<td>UGT1A1 polymorphism</td>
<td>Irinotecan toxicity</td>
</tr>
<tr>
<td>DPD polymorphisms</td>
<td>5-FU toxicity</td>
</tr>
<tr>
<td>VEGF gene expression</td>
<td>Cetuximab</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; DPD, dihydropyrimidine dehydrogenase; ERCC1, excision repair cross-complementing rodent repair deficiency, complementation group 1; OPRT, orotidine phosphoribosyl transferase; TS, thymidylate synthase; VEGF, Vascular endothelial growth factor.
Treatment of metastatic CRC

FOLFOX / Xelox + bevacizumab¹

FOLFIRI + bevacizumab¹

FOLFOX / Xelox + bevacizumab¹

Capecitabine (5-FU/FA) ± bevacizumab¹

FOLFOX / Xelox

FOLFIRI

Irinotecan + cetuximab

Irinotecan + cetuximab

FOLFOX / Xelox

FOLFOX / Xelox

FOLFIRI

¹ if no cardiovascular contraindications
Adjuvant therapy in CRC

Aims:
- After surgery with curative intent
- To decrease mortality related to CRC recurrence
- Patients with high risk of recurrence

- Effective and well tolerated
- Good compliance and quality of life

<table>
<thead>
<tr>
<th>T stage</th>
<th>N stage</th>
<th>5y survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (T1 or T2)</td>
<td>N0</td>
<td>93.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IIa (T3)</td>
<td>N0</td>
<td>84.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IIb (T4)</td>
<td>N0</td>
<td>72.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IIIa (T1 or T2)</td>
<td>N1</td>
<td>83.4&lt;sup&gt;a&lt;/sup&gt; – 59.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>IIIb (T3 or T4)</td>
<td>N1</td>
<td>64.1&lt;sup&gt;a&lt;/sup&gt; – 42.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>IIIc (any T)</td>
<td>N2</td>
<td>44.3&lt;sup&gt;a&lt;/sup&gt; – 27.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>


Adjuvant treatment of CRC
Adjuvant therapy in CRC: 5FU

- 5FU/LEV and 5FU/FA are superior to control
- 5FU/low dose FA for 6 months is the optimal schedule
- Infusional 5FU is as efficacious and safer than bolus FU/FA


Adjuvant treatment of CRC
Adjuvant therapy in CRC: Oxaliplatin

3y DFS
- Folfox: 78.2%
- LV5FU2: 72.9%
  
  HR: 0.77
  
  p = 0.002

5y DFS
- Folfox: 73.3%
- LV5FU2: 67.4%

Stage III: folfox 72.2% vs LV5FU2 65.5%
  
  HR: 0.76 (0.62 – 0.92)

Stage II: folfox 87.0% vs LV5FU2 84.4%
  
  HR: 0.80 (0.56 – 1.15)

Stage III: folfox 66.4% vs LV5FU2 58.9%

*Adjuvant treatment of CRC*

*André T., N Eng J Med 2004; 350: 2343-51*
## Adjuvant therapy in CRC: Irinotecan

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>n</th>
<th>Regimen</th>
<th>DFS (%)</th>
<th>HR/p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3y</td>
<td>5y</td>
</tr>
<tr>
<td>CALGB-C89803</td>
<td>III</td>
<td>1264</td>
<td>Bolus 5FU/FA</td>
<td>69</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFL</td>
<td>66</td>
<td>59</td>
</tr>
<tr>
<td>ACCORD-2</td>
<td>High-risk</td>
<td>400</td>
<td>LV5FU2</td>
<td>60</td>
<td>1.19; NS</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td></td>
<td>IF</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>PETACC-3</td>
<td>III</td>
<td>2111</td>
<td>LV5FU2</td>
<td>60.3</td>
<td>0.89; 0.091</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IF</td>
<td>63.3</td>
<td></td>
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<tr>
<td></td>
<td>II/III</td>
<td>3005</td>
<td>LV5FU2</td>
<td>66.8</td>
<td>0.88; 0.050</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IF</td>
<td>69.6</td>
<td></td>
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</table>

*Adjuvant treatment of CRC*
Can capecitabine replace IV 5FU?

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Can capecitabine replace IV 5FU?</strong></td>
</tr>
</tbody>
</table>

![Graph showing survival rates over time for X-act, 5FU/FA, and capecitabine.](image)

### Table: 3y DFS and 3y survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>3y DFS</th>
<th>3y survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-act N=1987 5FU/FA</td>
<td>60.6</td>
<td>77.6</td>
</tr>
<tr>
<td>X-act N=1987 capecitabine</td>
<td>64.2</td>
<td>81.3</td>
</tr>
</tbody>
</table>

### Biologicals in adjuvant therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETACC-8</td>
<td>2000</td>
<td>Stage III colon</td>
<td>Folfox 4 +/- cetuximab</td>
</tr>
<tr>
<td>Intergroup 0147</td>
<td>2300</td>
<td>Stage III colon</td>
<td>Folfox 6 +/- cetuximab</td>
</tr>
<tr>
<td>AVANT</td>
<td>3450</td>
<td>High risk stage II/III colon</td>
<td>Folfox 4&lt;br&gt;Folfox 4 + bevacizumab&lt;br&gt;Xelox + bevacizumab</td>
</tr>
<tr>
<td>NSABP C-08</td>
<td>2700</td>
<td>Stage II/III colon</td>
<td>Folfox 6 +/- bevacizumab</td>
</tr>
<tr>
<td>QUASAR 2</td>
<td>2240</td>
<td>High risk stage II/III colon</td>
<td>Capecitabine +/- bevacizumab</td>
</tr>
</tbody>
</table>

*Adjuvant treatment of CRC*
Adjuvant therapy in stage II?

Relative risk of death from any cause
chemotherapy <> observation
0.82 (0.70-0.95, p=0.008)

Relative risk of recurrence
chemotherapy <> observation
0.78 (0.67-0.91, p=0.001)

Absolute improvement of survival: 3.6%

Quasar collaborative group, Lancet 2007; 370: 2020-2029

Adjuvant treatment of CRC
Adjuvant therapy in stage II?

High risk stage II

? Molecular markers: LOH, MSI,…

Table 2. Univariate and multivariate analysis of patient and tumor factors with disease-specific survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>5-yr disease-specific survival (95% CI)</th>
<th>Log rank P value</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T stage</td>
<td>T3</td>
<td>92% (89-95)</td>
<td>0.04</td>
<td>2.7 (1.1-6.2)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>69% (51-88)</td>
<td></td>
<td>2.1 (1.1-4.1)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>≤5</td>
<td>93% (89-97)</td>
<td>0.04</td>
<td>2.1 (1.1-4.1)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>&gt;5</td>
<td>87% (78-95)</td>
<td></td>
<td>2.1 (1-4.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Preoperative CEA (ng/ml)</td>
<td>≤5</td>
<td>93% (89-97)</td>
<td>0.04</td>
<td>2.1 (1.1-4.1)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>&gt;5</td>
<td>87% (78-95)</td>
<td></td>
<td>2.1 (1-4.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lymphovascular or perineural invasion</td>
<td>Absent</td>
<td>92% (89-95)</td>
<td>0.02</td>
<td>2.1 (1-4.4)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>80% (68-92)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CEA=carcinoembryonic antigen; CI=confidence interval.

Surviving Fraction

0.8

0.6

0.4

0.2

0 12 24 36 48 60 72 84

Months from Surgery

Quah H, Dis Colon Rectum 2008
Adjuvant therapy?

Adjuvant treatment of 6 months of folfox for patients with stage III colon cancer

Need to demonstrate the role of capecitabine in combination regimens

Need for better selection of high-risk versus low-risk stage II colon cancer

Need to demonstrate the role of the novel targeted therapies