Colorectal cancer: Targeted substances in elderly / medically non-fit patients?

Gunnar Folprecht
Survival with colorectal cancer

Kopetz et al, JCO 2009
Overall Survival (%) vs. Time (months)

- 1990-1991
- 1992-1994
- 1995-1997
- 1998-2000
- 2001-2003
- 2004-2006

Kopetz et al, JCO 2009
## Age dependent efficacy of 5-FU

<table>
<thead>
<tr>
<th>age</th>
<th>&lt; 70 y</th>
<th>≥ 70 y</th>
<th>70-74</th>
<th>75-79</th>
<th>≥ 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3,196</td>
<td>629</td>
<td>484</td>
<td>125</td>
<td>20</td>
</tr>
<tr>
<td>OS</td>
<td>11.3</td>
<td>10.8</td>
<td>10.9</td>
<td>9.4</td>
<td>13.4</td>
</tr>
<tr>
<td>(10.9-11.7)</td>
<td>(9.7-11.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>5.3</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>6.4</td>
</tr>
<tr>
<td>(5.1-5.5)</td>
<td>(5.2-5.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/PR</td>
<td>21.1%</td>
<td>23.9%</td>
<td>24%</td>
<td>26%</td>
<td>(11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Folprecht, Ann Oncol 2004
FOLFOX in elderly pts

Progression free survival

< 70 years

≥ 70 years

MOSAIC

1st line
DeGramont
Goldberg

2nd line

Goldberg, JCO 2006
FOLFOX in elderly pts

Overall survival

Goldberg, JCO 2006
5-FU +/- irinotecan (2,691 patients)

Response rate:

<table>
<thead>
<tr>
<th></th>
<th>&lt;70 years</th>
<th>≥70 years</th>
<th>Subgroup: ≥75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-FU</td>
<td>FU</td>
<td>I-FU</td>
<td>FU</td>
</tr>
<tr>
<td>N</td>
<td>745</td>
<td>1218</td>
<td>208</td>
</tr>
<tr>
<td>Response rate</td>
<td>46.6%</td>
<td>29.0%</td>
<td>50.5%</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>P=0.006*</td>
</tr>
</tbody>
</table>

Folprecht, JCO 2008
5-FU +/- irinotecan (2,691 patients)

Response rate

<table>
<thead>
<tr>
<th></th>
<th>&lt;70 years</th>
<th>≥70 years</th>
<th>Subgroup: ≥75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I-FU</td>
<td>FU</td>
<td>I-FU</td>
</tr>
<tr>
<td>N</td>
<td>745</td>
<td>1218</td>
<td>208</td>
</tr>
<tr>
<td>N</td>
<td>60</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>48.3%</td>
</tr>
</tbody>
</table>

Folprecht, JCO 2008
FOCUS II - Studie
„Frail elderly patients“

The regimens

FU

80% standard dose*

(LV 175 mg; FU 320 mg/m² b.i.d.; FU 2240 mg/m² over 46 hr every 2 weeks)

OxFU

80% standard dose*

(Ox 65 mg/m²; LV and FU as above except 1920 mg/m² over 46 hr every 2 weeks)

Cap

80% standard dose

(Capcitabine 1000 mg/m² b.i.d. for 14 days, every 3 weeks)

OxCap

80% standard dose

(Ox 104 mg/m² d1; Cap 800 mg/m² b.i.d. for 14 days, every 3 weeks)

Seymour, ASCO 2007
FOCUS II- Studie
„Frail elderly patients“

Progression-free survival: Overall Survival

For curves, go to ASCO website, please

<table>
<thead>
<tr>
<th>Addition of oxaliplatin</th>
<th>HR=0.83; p=0.06</th>
</tr>
</thead>
<tbody>
<tr>
<td>[FU vs OxFU] + [Cap vs OxCap]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Addition of oxaliplatin</th>
<th>HR=0.94; p=0.61</th>
</tr>
</thead>
<tbody>
<tr>
<td>[FU vs OxFU] + [Cap vs OxCap]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substitution of FU with Cap</th>
<th>HR=1.00; p=0.96</th>
</tr>
</thead>
<tbody>
<tr>
<td>[FU vs Cap] + [OxFU vs OxCap]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substitution of FU with Cap</th>
<th>HR=1.00; p=0.97</th>
</tr>
</thead>
<tbody>
<tr>
<td>[FU vs Cap] + [OxFU vs OxCap]</td>
<td></td>
</tr>
</tbody>
</table>

Seymour, ASCO 2007
Quality of Life improvement (1)

**EORTC QLQ-C30 global scale**: Percentage of patients with improvement in between baseline and week 12:

- 0%
- 10%
- 20%
- 30%
- 40%
- 50%
- 60%
- 70%
- 80%

For graphs, go to ASCO website, please

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Improvement Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substitution of FU with Cap</td>
<td>55% vs 56%; p=0.89</td>
<td></td>
</tr>
<tr>
<td>[FU vs Cap] + [OxFU vs OxCap]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addition of oxaliplatin</td>
<td>62% vs 49%; p=0.04</td>
<td></td>
</tr>
<tr>
<td>[FU vs OxFU] + [Cap vs OxCap]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Seymour, ASCO 2007
FOCUS- trial

2100 Pts. not suitable for neoadjuv. therapy

1. line 2. line 3. line

A 5-FU/FA Irinotecan OxCape

B₁ 5-FU/FA FOLFIRI OxCape
B₂ 5-FU/FA FOLFOX IriCape

C₁ FOLFIRI OxCape
C₂ FOLFOX IriCape

Pts receiving all 3 drugs

16%
19%
33%

Seymour, Lancet 2007
FOCUS- trial

Seymour, Lancet 2007
Overall survival

< 70 y.
\( n = 2745 \)

69%

71%

64%

> 70 y.
\( n = 506 \)

62%

69%

Overall survival

Freedom from recurrence

Sargent, NEJM 2001
QUASAR

A

![Graph showing survival rates and number of patients at risk for chemotherapy and observation groups.](image)

B

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Chemotherapy</th>
<th>Observation</th>
<th>O-E</th>
<th>Var</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td>20/185</td>
<td>23/185</td>
<td>-17</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td>(10.8%)</td>
<td>(12.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59 years</td>
<td>63/428</td>
<td>83/427</td>
<td>-10.1</td>
<td>36.4</td>
</tr>
<tr>
<td></td>
<td>(14.7%)</td>
<td>(19.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69 years</td>
<td>133/678</td>
<td>171/673</td>
<td>-23.2</td>
<td>75.9</td>
</tr>
<tr>
<td></td>
<td>(19.5%)</td>
<td>(25.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70+ years</td>
<td>95/331</td>
<td>93/332</td>
<td>0.8</td>
<td>47.0</td>
</tr>
<tr>
<td></td>
<td>(28.7%)</td>
<td>(28.0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity between four groups \( \chi^2 = 3.3; p = 0.35 \)

Test for trend over four groups \( \chi^2 = 1.2; p = 0.28 \)
Adjuvant: FOLFOX +/- Bevacizumab

For curves, go to ASCO website, please

Disease free survival: HR 0.89
p = 0.15

Wolmark, ASCO 2009
Forest Plots of Hazard Ratios
Overall Survival

Hazard Ratio

Oxaliplatin

Irinotecan

Overall

Age < 70
Age >= 70

McCleary, ASCO 2009
Cetuximab vs. BSC

K-RAS mut

K-RAS wildtype

HR = 0.55 (0.41-0.74)

p < 0.001

Karapetis NEJM 2008
FOLFIRI +/- Cetuximab

For curves, go to ECCO website, please

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI (n=350)</th>
<th>+FOLFIRI (n=316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Events</td>
<td>288</td>
<td>242</td>
</tr>
<tr>
<td>Median OS [95% CI]</td>
<td>20.0 [17.4–21.7]</td>
<td>23.5 [21.2–26.3]</td>
</tr>
<tr>
<td>HR (95%):</td>
<td>0.796 [0.670–0.946]</td>
<td></td>
</tr>
<tr>
<td>p-value:</td>
<td>0.0094 (log-rank)</td>
<td></td>
</tr>
</tbody>
</table>
Cetuximab vs. BSC

**K-RAS mut**

- Cetuximab plus best supportive care
- Best supportive care alone
- HR = 0.89
- P = 0.89

**K-RAS wildtype**

- Cetuximab plus best supportive care
- Best supportive care alone
- HR = 0.55 (0.41-0.74)
- p < 0.001
- 4.8 vs. 9.5 months

Karapetis NEJM 2008
Panitumumab vs. BSC

**k-ras**
- *mutiert*
- *Wildtyp*

**Amado JCO 2008**
Cross-trial: EGFR-AB mono vs. 5-FU (PFS)

De Gramont 1998 / Amado JCO 2008
First-line single-agent cetuximab in patients with advanced colorectal cancer

A. Pessino¹, S. Artale², S. Sciallero¹, A. Guglielmi¹, G. Fornarini¹, I. C. Andreotti², S. Mammoliti¹, D. Comandini¹, F. Caprioni¹, E. Bennicelli¹, V. Andretta¹, S. Siena² & A. Sobrero¹*

Response rate 11%
TTP 2 mo, OS 12.3 mo.
TTD-06-01: Cetuximab/Capecitabin

Cetuximab 400/250 / Capecitabine 2500 or 1900mg/m²
amendment:
Cetuximab 400/250 / Capecitabine 2000 or 1500mg/m²

Karnofsky PS $\geq$ 80%
$\geq$ 70 years and
- Dependency in ADL or
- $\geq$ 3 comorbidities or
- geriatric syndroms

Cohort 1: Median PFS: 5.9 m
Cohort 2: Median PFS: 7.1 m
Log rank p=0.92

For curves, go to ECCO website, please

Rivera, ESMO/ECCO 2009
Elderly pts: Cetuximab/Capecitabine

66 pts, phase II
Response rate: 33%

**Progression free**
**Overall survival**

Median PFS: 7.1 m  
(95% CI: 6.5-8.7 m)  
Median OS: 15.6 m

For curves, go to ECCO website, please

Rivera, ESMO/ECCO 2009
Elderly pts: Cetuximab/Capecitabine

Response rate (subgroup 55 pts)
KRAS wildtype: 48%, mut: 24%

**Progression free**
- KRAS wt
  - Median PFS: 8.4 m
  - HR: 0.53
  - p 0.02
- KRAS mut
  - Median PFS: 6 m

**Overall survival**
- KRAS wt
  - Median OS: 18.8 m
  - HR: 0.58
  - p 0.11
- KRAS mut
  - Median OS: 13.5 m

For curves, go to ECCO website, please

Rivera, ESMO/ECCO 2009
Bevacizumab (VEGF- Antibody)

IFL+Bevacizumab

IFL+Placebo

5-FU+Bevacizumab

1st line, CRC

Hurwitz, NEJM 2004
Bevacizumab (VEGF- Antibody)

**Inclusion:**
- An age of at least 18 years
- An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- A life expectancy of more than three months

**Exclusion:**
- Clinically significant cardiovascular disease
- Clinically detectable ascites
- Pregnancy or lactation
- Regular use of aspirin (more than 325 mg per day) or other nonsteroidal antiinflammatory agents
- Preexisting bleeding diatheses or coagulopathy
- The need for full-dose anticoagulation
- Known central nervous system metastases

<table>
<thead>
<tr>
<th>Overall Survival (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFL+bevacizumab</td>
<td>IFL+bevacizumab</td>
<td>IFL+placebo</td>
<td>IFL+placebo</td>
<td>IFL+placebo</td>
</tr>
<tr>
<td>No. at Risk</td>
<td>402</td>
<td>362</td>
<td>320</td>
<td>178</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Hurwitz, NEJM 2004
## Arterial thromboembolic events

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients with Event, Number of Patients</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>50, 1745</td>
<td>1.98</td>
<td>1.05, 3.74</td>
<td></td>
</tr>
<tr>
<td>AVF2107G</td>
<td>25, 897</td>
<td>2.66</td>
<td>0.99, 7.12</td>
<td></td>
</tr>
<tr>
<td>AVF2192G</td>
<td>15, 204</td>
<td>1.77</td>
<td>0.6, 5.21</td>
<td></td>
</tr>
<tr>
<td>AVF0757G</td>
<td>4, 98</td>
<td>1.39</td>
<td>0.14, 13.37</td>
<td></td>
</tr>
<tr>
<td>AVF0780G</td>
<td>4, 102</td>
<td>1.47</td>
<td>0.15, 14.17</td>
<td></td>
</tr>
<tr>
<td>AVF2119G</td>
<td>2, 444</td>
<td>0.85</td>
<td>0.05, 13.53</td>
<td></td>
</tr>
</tbody>
</table>

Scappaticci, JNCI 2007
Bevacizumab (VEGF- Antibody)

IFL+Bevacizumab

IFL+Placebo

5-FU+Bevacizumab

1st line, CRC

Hurwitz, NEJM 2004
## Chemotherapy +/- Bevacizumab

Pooled analysis of 2 trials: IFL, 5-FU/FA, +/- Bev

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Treatment</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 65 years</td>
<td>CTx+Bev</td>
<td>34%</td>
<td>9.2</td>
<td>19.3</td>
</tr>
<tr>
<td>439 pts</td>
<td>CTx</td>
<td>29%</td>
<td>6.2</td>
<td>14.3</td>
</tr>
<tr>
<td>≥ 70 years</td>
<td>CTx+Bev</td>
<td>31%</td>
<td>9.2</td>
<td>18.7</td>
</tr>
<tr>
<td>276 pts</td>
<td>CTx</td>
<td>26%</td>
<td>6.2</td>
<td>12.6</td>
</tr>
</tbody>
</table>

ATE 7.6 vs. 2.8%, wound healing 2.4 vs 0%, more GI perforation (data not provided),

Kabbinavar, JCO 2009
Yet another pooled analysis...

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;65 years</td>
</tr>
<tr>
<td>Pooled analysis</td>
<td>0.77 (0.69–0.86)</td>
</tr>
<tr>
<td>IFL ± bev</td>
<td>0.77 (0.63–0.94)</td>
</tr>
<tr>
<td>5-FU/FA ± bev</td>
<td>0.51 (0.22–1.15)</td>
</tr>
<tr>
<td>FOLFOX or Xelox ± bev</td>
<td>0.81 (0.69–0.96)</td>
</tr>
<tr>
<td>2nd line FOLFOX ± bev</td>
<td>0.72 (0.58–0.90)</td>
</tr>
<tr>
<td>First-line studies</td>
<td>0.79 (0.69–0.89)</td>
</tr>
</tbody>
</table>

Cassidy, et al. ESMO 2008
Chemo ± Bevacizumab

Cassidy, et al.
ESMO 2008
Bevacizumab

BRITE – observational study (1953 pts, Bev + chemo)

no clear inclusion / exclusion criteria
("No exclusion criteria were specified. To reduce selection bias, sites were instructed to recruit all eligible patients")

- median age: 63.6 y.
- PS 0-1: 85 %
  PS 2: 7 %
  unknown: 8 %

- Diabetes 12 %
- Arterial history 18 % (incl. peripheral arterial disease, stroke, myocard. infarct., also atrial fibrill.)

Kozloff, Oncologist 2009
Bevacizumab

≥ 75 years: 363 pts
- more arterial thrombotic events:
  ≥ 75 y.: 15/363 pts, 4.1%
  < 75 y.: 25/1590 pts, 1.6%
- no difference in other AE

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 y.</td>
<td>1057</td>
<td>10.2</td>
<td>26.0</td>
</tr>
<tr>
<td>65...75 y.</td>
<td>533</td>
<td>9.6</td>
<td>21.1</td>
</tr>
<tr>
<td>≥ 75 y</td>
<td>363</td>
<td>9.7</td>
<td>19.2</td>
</tr>
<tr>
<td>≥ 80 y*</td>
<td>161</td>
<td>9.2</td>
<td>16.2</td>
</tr>
</tbody>
</table>

Kozloff, Oncologist 2009
* Kozloff, ASCO 2008
Antibodies in elderly pts with colorectal cancer

**Limited data:**
- No 1st line FOLFOX/FOLFIRI data with EGFR AB
- No Bevacizumab data on frail patients
  limited data for “real” comorbidities
  in selected patients slightly increased tox.
- 5-FU /Beva good option (if no comorbidity?)
- 5-FU/cetuximab seems interesting

**Endpoints:** PFS, independence, pharmacoeconomics, ORR, OS