Konzepte bei der Therapie des metastasierten kolorektalen Karzinoms

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Survival of patients with metastatic CRC over decades

Kopetz et al. JCO 2009
Choices in MCRC

Strategy
- Curative
- Palliative

Therapy
- Chemotherapy
- Biologicals
- Upfront combination
- Sequential
Curative approach

- High response rate
- Conversion chemotherapy
Recession rate of metastases and tumor response

- **Studies incl. selected pats.** (liver metastases only, no extrahepat. disease)
  \[ r = .96, \ p = .002 \]

- **Studies incl. all patients** with metastatic CRC (solid line)
  \[ r = .74, \ p < .001 \]

- **Phase III studies** in metastatic CRC (dashed line)
  \[ r = .67, \ p = .024 \]

Folprecht ... Köhne et al, Ann Oncol 2005
FOLFIRI vs. FOLFOXIRI

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI (122 pts)</th>
<th>FOLFOXIRI (122 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>34%</td>
<td>60%</td>
</tr>
<tr>
<td>PD</td>
<td>24%</td>
<td>11%</td>
</tr>
<tr>
<td>R0</td>
<td>6%* (7 pts)</td>
<td>15%* (18 pts)</td>
</tr>
<tr>
<td>Pts with liver mets only</td>
<td>N=42</td>
<td>N=39</td>
</tr>
<tr>
<td>R0</td>
<td>12%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Falcone et al.  
JCO 2007/ASCO 2007
## NO16966
### Response Rate

<table>
<thead>
<tr>
<th></th>
<th>Chemo+ placebo</th>
<th>Chemo + Bev</th>
<th>FOLFOX+ placebo</th>
<th>FOLFOX + Bev</th>
<th>XELOX+ placebo</th>
<th>XELOX + Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigator report</strong></td>
<td>49% p = 0.90</td>
<td>47%</td>
<td>50% p = 0.88</td>
<td>47%</td>
<td>48% p = 0.91</td>
<td>46%</td>
</tr>
<tr>
<td><strong>IRC data</strong></td>
<td>38% p = 0.99</td>
<td>38%</td>
<td>36% p = 0.49</td>
<td>38%</td>
<td>39% p = 0.48</td>
<td>37%</td>
</tr>
</tbody>
</table>

Saltz, ASCO-GI 2007
Response and R0 resection rates according to treatment

**CRYSTAL**

**KRAS wild-type**

- FOLFIRI: 39.7% response, 2.0% R0 resection
- FOLFIRI + cetuximab: 57.3% response, 5.1% R0 resection

- p<0.001*

**KRAS wild-type LLD**

- FOLFIRI: 44.4% response, 5.6% R0 resection
- FOLFIRI + cetuximab: 70.6% response, 13.2% R0 resection

- p=0.002

**OPUS**

**FOLFOX4**

- FOLFOX4: 34.0% response, 3.1% R0 resection
- FOLFOX4 + cetuximab: 57.3% response, 7.3% R0 resection

- p<0.003*

**FOLFOX4 + cetuximab**

- FOLFOX4: 39.1% response, 4.3% R0 resection
- FOLFOX4 + cetuximab: 76.0% response, 16.0% R0 resection

- p=0.018

**p=0.35*
## CELIM Study: Unresectable liver metastases: Resections and Response Rate

### FOLFOX6 + cetuximab vs FOLFIRI + cetuximab vs All patients

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX6 + cetuximab</th>
<th>FOLFIRI + cetuximab</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>53</td>
<td>53</td>
<td>106</td>
</tr>
<tr>
<td>RR</td>
<td>68% (54-80%)</td>
<td>57% (42-70%)</td>
<td>62% (52-72%)</td>
</tr>
<tr>
<td>RR k-ras wt (n=67)</td>
<td>70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0 resections</td>
<td>38%</td>
<td>30%</td>
<td>34%</td>
</tr>
<tr>
<td>R1-resect / Resect + RFA</td>
<td>2%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>RFA</td>
<td>9%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>R0 / R1 resect. / RFA</td>
<td>49%</td>
<td>43%</td>
<td>46%</td>
</tr>
<tr>
<td>R2 resections</td>
<td>2%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Exploratory lap.</td>
<td>6%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Folprecht...Köhne. Lancet Oncology 2010*
Waterfall plot of resectability at baseline

Votes for “resectable” are in green, for “borderline resectable, surgical exploration recommended” in light green, “chemotherapy preferred” in yellow and for “unresectable” in red.

Actual R0 resected cases are marked with “|”, R+ resected cases and patients with radiofrequency ablation “-”

Folprecht....Köhne . Lancet Oncology 2010
Waterfall plot of resectability after chemotherapy

Votes for “resectable” are in green, for “borderline resectable, surgical exploration recommended” in light green, “chemotherapy preferred” in yellow and for “unresectable” in red.

Actual R0 resected cases are marked with “|”, R+ resected cases and patients with radiofrequency ablation “-”

Resectability according to imaging increased by 28% (32% → 60%) p<0.01

Folprecht....Köhne . Lancet Oncology in press 2009
Curative approach

Combination CTx plus EGFR Ab

Both Irinotecan and Oxaliplation are valid options
Poor performance status
Agressive disease

• High response rate

• PFS and OS
OS – Infusional Combo by PS

- Other ~ PS 0-1 (median = 15.5 mos)
- Infusional Combo ~ PS 0-1 (median = 18.8 mos)
- Other ~ PS 2 (median = 6.4 mos)
- Infusional Combo ~ PS 2 (median = 11.8 mos)

p-value < 0.0001
HR: 0.84 (0.78-0.91)

Interaction p-value = 0.004

Goldberg, Köhne et al, JCO 2008
CRYSTAL trial: PFS time subgroup analyses

All ITT subjects (n=1198)

Subgroup (number of patients)
Age
< 65 years (n=751)
≥ 65 years (n=446)
ECOG Performance Status
0,1 (n=1156)
2 (n=42)
Involved disease sites
≤ 2 (n=1016)
> 2 (n=166)
Liver metastases only
Yes (n=256)
No (n=942)
Prior adjuvant therapy
Yes (n=243)
No (n=955)
Leucocytes
> 10000/mm³ (n=214)
≤ 10000/mm³ (n=943)
Alkaline Phosphatase
≥ 300 U/L (n=151)
< 300 U/L (n=986)
LDH
> UNL (n=540)
≤ UNL (n=516)

HR [95% CI]

0.851 [0.726 - 0.998]
0.775 [0.634 - 0.948]
0.989 [0.759 - 1.288]
0.839 [0.713 - 0.998]
1.187 [0.551 - 2.556]
0.862 [0.724 - 1.026]
0.794 [0.520 - 1.211]
0.637 [0.432 - 0.941]
0.913 [0.765 - 1.088]
0.816 [0.574 - 1.161]
0.858 [0.716 - 1.027]
0.765 [0.531 - 1.101]
0.874 [0.728 - 1.050]
0.819 [0.537 - 1.249]
0.836 [0.698 - 0.999]
0.790 [0.625 - 0.999]
0.956 [0.745 - 1.226]
### Panitumumab KRAS wt: subgroup analyses for PFS

<table>
<thead>
<tr>
<th>Factors</th>
<th>n</th>
<th>Favours: pmab</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized</td>
<td>656</td>
<td></td>
<td>0.80</td>
<td>0.66-0.97</td>
</tr>
<tr>
<td>Primary: colon</td>
<td>430</td>
<td></td>
<td>0.79</td>
<td>0.62-1.00</td>
</tr>
<tr>
<td>Primary: rectal</td>
<td>226</td>
<td></td>
<td>0.83</td>
<td>0.59-1.16</td>
</tr>
<tr>
<td>Liver mets: yes</td>
<td>566</td>
<td></td>
<td>0.78</td>
<td>0.64-0.96</td>
</tr>
<tr>
<td>Liver mets: no</td>
<td>90</td>
<td></td>
<td>0.91</td>
<td>0.54-1.54</td>
</tr>
<tr>
<td>Liver mets only: yes</td>
<td>116</td>
<td></td>
<td>0.82</td>
<td>0.50-1.34</td>
</tr>
<tr>
<td>Liver mets only: no</td>
<td>540</td>
<td></td>
<td>0.81</td>
<td>0.65-1.00</td>
</tr>
<tr>
<td>Met sites: &lt;3</td>
<td>363</td>
<td></td>
<td>0.85</td>
<td>0.65-1.11</td>
</tr>
<tr>
<td>Met sites: ≥3</td>
<td>290</td>
<td></td>
<td>0.76</td>
<td>0.57-1.02</td>
</tr>
<tr>
<td>ECOG: 0</td>
<td>369</td>
<td></td>
<td>0.68</td>
<td>0.52-0.90</td>
</tr>
<tr>
<td>ECOG: 1</td>
<td>248</td>
<td></td>
<td>0.92</td>
<td>0.68-1.24</td>
</tr>
<tr>
<td>ECOG: 2</td>
<td>38</td>
<td></td>
<td>1.99</td>
<td>0.96-4.15</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>261</td>
<td></td>
<td>1.02</td>
<td>0.75-1.38</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>395</td>
<td></td>
<td>0.70</td>
<td>0.54-0.89</td>
</tr>
<tr>
<td>Men</td>
<td>421</td>
<td></td>
<td>0.71</td>
<td>0.55-0.90</td>
</tr>
<tr>
<td>Women</td>
<td>235</td>
<td></td>
<td>1.00</td>
<td>0.73-1.39</td>
</tr>
</tbody>
</table>

**Hazard ratio (pmab / no pmab)**

Douillard JY, *et al.* Eur J Cancer 2009;7(3suppl):10LBA, oral presentation
Poor performance status

Combination Ctx
Plus VEGF ?
Cave EGFR AB

Rapidly progressive disease

No data available (subgroup FOCUS / CAIRO)
Combination CTx + EGFR (?) / + VGFR ?
Slow tumor progression
Low tumor burden

• Maintain QoL

• Improve PFS and OS
Slow tumor progression
Low tumor burden

Sequential ?
Stopp and Go ?
LIFE, FOCUS und CAIRO: N = 3663
No benefit for „upfront combination“

LIFE Study: Overall Survival (ITT)

- Oxaliplatin/5-FU arm: median OS 15.2 months
- 5-FU arm: median OS 15.9 months

HR [95% CI] = 0.93 [0.78 – 1.10]
P = 0.155 (NS)

Overall survival (1556 events)

- Staged combination B(irt) + B(ox)
- 1st-line combination C(irt) + C(ox)
- Single-agent A

OPTIMOX2-Study

R

Folfox7 – LV5FU2 – Folfox7 – etc..

Folfox7 – PAUSE – Folfox7 – etc..

Overall Survival

Overall Survival  Poor Prognostic

Overall Survival  Good Prognostic

p=0.0549

p=0.105

p=0.11

OPTIMOX1 median 26 months

OPTIMOX2 median 19 months

OPTIMOX1 median 17 months (n=54)

OPTIMOX2 median 15 months (n=53)

OPTIMOX1 median NA months (n=45)

OPTIMOX2 median 29 months (n=50)

Maindrault-Goebel, ASCO 2007
Slow tumor progression
Low tumor burden

Sequential not suitable for all pts. !

Stopp and Go:
with irinotecan not a relevant question
Slow tumor progression
Low tumor burden

Integration of biologicals
HR = 0.83 [97.5% CI 0.72–0.95] (ITT)
\( p = 0.0023 \)

FOLFOX+placebo/XELOX+placebo
N=701; 547 events

FOLFOX+bevacizumab/XELOX+bevacizumab
N=699; 513 events

Saltz et al. JCO 2008
PFS CTx+ bevacizumab: XELOX and FOLFOX subgroups

Cassidy et al. ASCO 2007; Saltz et al. JCO 2008
Bevacizumab beyond progression

Grothey et al. JCO 2008

Ondansetron beyond progression

Kopetz et al. JCO 2009
# Bevacizumab in first line mCRC randomized studies

**Discrepancy between marketing and scientific evidence**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Δ RR</th>
<th>Δ PFS</th>
<th>HR</th>
<th>Δ OS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>FU/LV + bev (pooled data)</td>
<td>10.8</td>
<td>3.7</td>
<td>0.5*</td>
<td>3.3*</td>
<td>0.74</td>
</tr>
<tr>
<td>Capecitabine + bev</td>
<td>7.8</td>
<td>2.8</td>
<td>0.63*</td>
<td>0</td>
<td>0.86</td>
</tr>
<tr>
<td>IFL + bev</td>
<td>10.0*</td>
<td>4.4</td>
<td>0.54*</td>
<td>4.7*</td>
<td>0.66</td>
</tr>
<tr>
<td>FU/FA/Iri+- Bev</td>
<td>1.6</td>
<td>n.a.</td>
<td>n.a.</td>
<td>-3.0</td>
<td>n.a.</td>
</tr>
<tr>
<td>XELOX/FOLFOX4 + bev</td>
<td>-2</td>
<td>1.4</td>
<td>0.83*</td>
<td>1.4</td>
<td>0.89</td>
</tr>
<tr>
<td>FOLFOX + Bev</td>
<td>-3</td>
<td>0.8</td>
<td>0.89</td>
<td>0.9</td>
<td>0.94</td>
</tr>
<tr>
<td>CapeOx + Bev</td>
<td>-2</td>
<td>1.9</td>
<td>0.77*</td>
<td>2.2</td>
<td>0.84</td>
</tr>
</tbody>
</table>

* $P<0.05$
## Randomised trials of EGFR antibodies – 1st line

### 1st Line mCRC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Therapy</th>
<th>ORR</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRYSTAL</strong> <em>(n=666)</em></td>
<td>FOLFIRI +/- Cetux*</td>
<td>40% vs. 57%</td>
<td>8.4 vs. 9.9</td>
<td>20.0 vs. 23.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR = 0.696</td>
<td>HR = 0.796</td>
</tr>
<tr>
<td><strong>OPUS</strong>  <em>(n=197)</em></td>
<td>FOLFOX +/- Cetux*</td>
<td>34% vs. 57%</td>
<td>7.2 vs. 8.3</td>
<td>18.5 vs. 22.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR = 0.567</td>
<td>HR = 0.855</td>
</tr>
<tr>
<td><strong>COIN</strong>   <em>(n=729)</em></td>
<td>XELOX/ FOLFOX +/- Cetux*</td>
<td>57% vs. 64%</td>
<td></td>
<td>17.9 vs. 17.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR = 0.959</td>
<td>HR = 1.038</td>
</tr>
<tr>
<td><strong>PRIME</strong>  <em>(n=656)</em></td>
<td>FOLFOX +/- Pani*</td>
<td>48% vs. 55%</td>
<td>9.6 vs. 8.0</td>
<td>19.7 vs. 23.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR = 0.80</td>
<td>HR = 0.83</td>
</tr>
<tr>
<td><strong>NORDIC</strong> <em>(n=194)</em></td>
<td>FLOX +/- Cetux</td>
<td>47% vs. 46%</td>
<td></td>
<td>22.0 vs. 21.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8.7 vs. 7.9</td>
<td>HR = 1.14</td>
</tr>
</tbody>
</table>

* sig. diff;  – no sig. diff  * KRAS wt population
Coin trial: CapeOX or FOLFOX +/- Cetuximab

Interaction: OS and PFS by Fluoropyrimidine regimen

KRAS\textsuperscript{wt}

Xelox
OxMdG
Interaction

KRAS\textsuperscript{mut}

OS

PFS

MRC Medical Research Council
Relating KRAS status to Efficacy
FOLFOX +/- Panitumumab 1st line

**WT KRAS**

<table>
<thead>
<tr>
<th>Events n (%)</th>
<th>Median (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab + FOLFOX4</td>
<td>199 / 325 (61)</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>215 / 331 (65)</td>
</tr>
</tbody>
</table>

HR = 0.80 (95% CI: 0.66 – 0.97)
Log-rank p-value = 0.02

**MT KRAS**

<table>
<thead>
<tr>
<th>Events n (%)</th>
<th>Median (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab + FOLFOX4</td>
<td>167 / 221 (76)</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>157 / 219 (72)</td>
</tr>
</tbody>
</table>

HR = 1.29 (95% CI: 1.04 – 1.62)
Log-rank p-value = 0.02
Relating KRAS Status to Efficacy

FOLFIRI + Panitumumab 2\textsuperscript{nd} line

**WT KRAS**

- **Events n (%)**
  - Panitumumab + FOLFIRI: 178/ 303 (59)
  - FOLFIRI: 203/ 294 (69)

- **Median (95% CI) months**
  - Panitumumab + FOLFIRI: 5.9 (5.5 - 6.7)
  - FOLFIRI: 3.9 (3.7 - 5.3)

- HR = 0.73 (95% CI: 0.59, 0.90)
- Log-rank p-value = 0.004

**MT KRAS**

- **Events n (%)**
  - Panitumumab + FOLFIRI: 162/ 238 (68)
  - FOLFIRI: 161/ 248 (65)

- **Median (95% CI) months**
  - Panitumumab + FOLFIRI: 5.0 (3.8 - 5.6)
  - FOLFIRI: 4.9 (3.6 - 5.6)

- HR = 0.85 (95% CI: 0.68, 1.06)
- Log-rank p-value = 0.14
Phase III Trials of Combined Biologic Therapy with Negative Impact on PFS

CAIRO2
CapeOx/Bev +/- Cetux

PACCE
FOLFOX/Bev +/- Pan

HR = 1.21 (95% CI: 1.03-1.45)
\( P = .018 \)

HR = 1.44 (95% CI: 1.13-1.85)
\( P = .004 \)

9.6 vs. 10.7 M

FOLFOX/Bev
9.6 vs. 11.1 M

Hecht et al; World GI Cancer, Barcelona, 2007
OS according to treatment in CRYSTAL and OPUS study patients with non-LLD

FOLFIRI vs FOLFIRI + ERBITUX
- Number of events: 233 (FOLFIRI), 196 (FOLFIRI + ERBITUX)
- Median OS, months: 17.4 (FOLFIRI), 22.5 (FOLFIRI + ERBITUX) [95% CI: 15.6–20.2 vs 20.0–25.7]
- HR*: 0.79 [0.65–0.95] (FOLFIRI vs FOLFIRI + ERBITUX)
- p-value†: 0.013

FOLFOX4 vs FOLFOX4 + ERBITUX
- Number of events: 57 (FOLFOX4), 41 (FOLFOX4 + ERBITUX)
- Median OS, months: 16.4 (FOLFOX4), 19.8 (FOLFOX4 + ERBITUX) [95% CI: 14.1–19.9 vs 16.6–24.1]
- HR*: 0.80 [0.54–1.21] (FOLFOX4 vs FOLFOX4 + ERBITUX)
- p-value†: 0.29

*Stratified HR for LLD vs non-LLD; †stratified log-rank test

Number of patients at risk
- FOLFIRI: 278, 244, 188, 128, 92, 67, 48, 35, 13, 20
- FOLFIRI + ERBITUX: 248, 217, 180, 151, 109, 82, 63, 47, 18, 30

Number of patients at risk
- FOLFOX4: 74, 62, 47, 30, 17, 11, 20000
- FOLFOX4 + ERBITUX: 57, 50, 37, 32, 19, 11, 20000

Van Cutsem……Köhne et al. ASCO GI 2011, Abstract No. 472
# Biologicals for Palliation

<table>
<thead>
<tr>
<th>KRAS mut</th>
<th>Goal</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
<th>QoL</th>
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</thead>
<tbody>
<tr>
<td>KRAS mut</td>
<td>Goal</td>
<td>RR</td>
<td>PFS</td>
<td>OS</td>
<td>QoL</td>
</tr>
<tr>
<td>FU or Cape +B</td>
<td>Yes</td>
<td>Yes</td>
<td>(no)</td>
<td></td>
<td>HFS</td>
</tr>
<tr>
<td>FOLFOX+B</td>
<td>No</td>
<td>no</td>
<td>No</td>
<td></td>
<td>Neuro</td>
</tr>
<tr>
<td>FOLFIRI+B</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td></td>
<td>Allop</td>
</tr>
<tr>
<td>CapeOx+B</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>HFS/Neuro</td>
</tr>
<tr>
<td>KRAS wt (KRA mut)</td>
<td>Goal</td>
<td>(no)</td>
<td></td>
<td></td>
<td>Skin/Neuro</td>
</tr>
<tr>
<td>FOLFOX+C</td>
<td>Yes</td>
<td>Yes</td>
<td>(no)</td>
<td></td>
<td>Skin/Neuro</td>
</tr>
<tr>
<td>FOLFOX+P</td>
<td>No</td>
<td>Yes</td>
<td>(no)</td>
<td></td>
<td>Skin/Neuro</td>
</tr>
<tr>
<td>FOLFIRI+C</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Skin/Allop</td>
</tr>
</tbody>
</table>
Patient groups in mCRC

Group 1
Potentially resectable metastases

Group 2
non-resectable metastases, high tumor burden, tumor-related symptoms

Group 3
non-resectable metastases, asymptomatic and less aggressive disease

Intensive therapy

2010-ESMO Guidelines

Less intensive therapy
Patient groups in mCRC

**Group 1**
Potentially resectable metastases

**Group 2**
non-resectable metastases, high tumor burden, tumor-related symptoms

**Group 3**
on-resectable metastases, asymptomatic and less aggressive disease

K-ras wt* justified on stand alone CRYSTA data?

K-ras mut

Intensive therapy

Less intensive therapy
Conclusions

- Data of chemotherapy combined with „targeted agents“ have become less clear.
- In KRAS wt tumors EGFR Ab improve activity of Irinotecan in first or later lines. Best strategy is unknown. Stand alone CRYSTAL data in first line.
- For EGFR Ab the chemo-backbone probably matters. Data with capecitabine and oxaliplatin are unclear.
- Role of bevacizumab has become unclear. Stand alone 2nd line data.
- Depending on the patients needs, tumor biology and treatment strategy biological may be chosen.
Using biomarkers to optimize clinical outcome

Identified 60% of patients (KRAS wt) treated with tailored therapy

KRAS wild-type (wt) population

Overall survival estimate

0.0 0.2 0.4 0.6 0.8 1.0

Time (months)

ERBITUX + FOLFIRI (n=316)
FOLFIRI (n=350)

HR=0.80

Overall patient population

HR=0.93

Personalized treatment is a better approach than ‘one treatment fits all’

### Clinical efficacy by KRAS/BRAF tumor mutation status

<table>
<thead>
<tr>
<th></th>
<th>KRAS wt (n=845)</th>
<th>KRAS wt/BRAF wt (n=730)</th>
<th>KRAS wt/BRAF mt (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFIRI (n=447)</td>
<td>Cetuximab + FOLFIRI (n=398)</td>
<td>FOLFIRI (n=381)</td>
</tr>
<tr>
<td><strong>Median OS months</strong></td>
<td>19.5</td>
<td>23.5</td>
<td>21.1</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>0.81</td>
<td>0.84</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.0062</td>
<td>0.0479</td>
<td>0.0764</td>
</tr>
<tr>
<td><strong>Median PFS months</strong></td>
<td>7.6</td>
<td>9.6</td>
<td>7.7</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>0.66</td>
<td>0.64</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.2301</td>
</tr>
</tbody>
</table>

_Bokemeyer, Köhne et al. ASCO 2010_
First line strategy of metastatic CRC

Does the patient need (or desire) aggressive therapy?

YES ~ 85%

KRAS

Unavailable

Doublet

WT

Doublet +/- cetuximab

MUT

Doublet

NO ~15%

5FU/Cape ± bev

Expert discussion, ESMO/ Lugano 2010 modified
FOLFOX +/- Bevacizumab (10mg/kg) 2nd line Overall Survival

HR = 0.76
A vs B: p = 0.0018
B vs C: p = 0.95

5 FU/LV +/- Bevacizumab: a combined analysis of 3 trials

Median survival (months): 14.6 vs 17.9
HR=0.74, p=0.0081

Kabbinavar et al. J Clin Oncol 2005
Bevacizumab in combination with 5 FU/LV patients with metastatic CRC: a combined analysis

AVF2107
Patient eligibility: metastatic CRC (n=313)

Arm 1 IFL/placebo (n=100)

Arm 2 IFL/Bev 5mg (n=103)

Arm 3 5-FU/LV/Bev 5mg (n=110)

AVF0780
Patient eligibility: metastatic CRC (n=104)

5-FU/LV (n=36)

5-FU/LV/Bev 5mg (n=35)

5-FU/LV/Bev 10mg (n=33)

AVF2192
Patient eligibility: metastatic CRC (not optional candidates for first-line irinotecan, n=209)

5-FU/LV/Placebo (n=105)

5-FU/LV/Bev 5mg (n = 104)

Capecitabine +/- Bevacizumab: Progression-free survival

- **Capecitabine**
- **Capecitabine + Bevacizumab**
- **Capecitabine + Bevacizumab + Mitomycin C**

**Median PFS**
- **C**: 5.7 months
- **CB**: 8.5 months
- **CBM**: 8.4 months

**Hazard ratios**
- **C vs CB**: 0.63, *P* < 0.001
- **C vs CBM**: 0.59, *P* < 0.001

**Number at Risk:**
- **C**: 156
  - 67
  - 22
  - 4
- **CB**: 157
  - 106
  - 38
  - 15
  - 5
- **CBM**: 158
  - 104
  - 40
  - 20
  - 6

NHMRC Clinical Trials Centre, University of Sydney, Australia
Australasian Gastro-Intestinal Trials Group
Capecitabine +/- Bevacizumab: Overall survival

- **Median OS**
  - C: 18.9 months
  - CB: 18.9 months
  - CBM: 16.4 months

- **Hazard ratios**
  - C vs CB: 0.86, \(P=0.2\)
  - C vs CBM: 1.00, \(P>0.9\)

**Number at Risk**
- C: 156, 125, 102, 80, 44, 11
- CB: 157, 133, 113, 81, 46, 20
- CBM: 158, 143, 103, 72, 37, 20

**Months from randomisation**
0 6 12 18 24 30

**Proportion surviving**
0.0 0.2 0.4 0.6 0.8 1.0

NHMRC Clinical Trials Centre, University of Sydney, Australia
Australasian Gastro-Intestinal Trials Group
**Efficacy in LLD: CRYSTAL and OPUS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CRYSTAL LLD</th>
<th>OPUS LLD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT</td>
<td>CT + ERBITUX</td>
</tr>
<tr>
<td></td>
<td>n=72</td>
<td>n=68</td>
</tr>
</tbody>
</table>

| PFS      | Median, months | 9.2 | 11.8 | 7.9 | 11.9 |
|          | HR             | 0.56 | 0.64 |     |     |
|          | [95% CI]       | [0.32–0.97] | [0.23–1.79] |     |     |
|          | p-value†       | 0.035 | 0.39 |     |     |

| OS       | Median, months | 27.7 | 27.8 | 23.9 | 26.3 |
|          | HR             | 0.85 | 0.93 |     |     |
|          | [95% CI]       | [0.57–1.28] | [0.44–2.00] |     |     |
|          | p-value†       | 0.44 | 0.86 |     |     |

*Stratified hazard and odds ratios are for CT + ERBITUX vs CT alone groups; †stratified log-rank test.
CI, confidence interval; CT, chemotherapy; HR, hazard ratio; LLD, liver-limited disease; OS, overall survival; PFS, progression-free survival.

Van Cutsem…Köhne et al. ASCO GI 2011, Abstract No. 472
OPTIMOX1-Study

R

- Folfox4
- Folfox7 – 5-FU/FA – Folfox7 – etc.

Progression free survival

- FOLFOX4 median 9.0 months
- FOLFOX7 median 8.7 months

Survival

- FOLFOX4 median 19.3 months
- FOLFOX7 median 21.2 months

Tournigand, JCO 2006
Curative and palliative treatment strategies in cancer treatment

Köhne et al. EJC 2008
## Bevacizumab in first line mCRC randomized studies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Δ RR</th>
<th>Δ PFS</th>
<th>HR</th>
<th>Δ OS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>FU/LV + bev (pooled data)</td>
<td>10.8</td>
<td>3.7</td>
<td>0.5*</td>
<td>3.3*</td>
<td>0.74</td>
</tr>
<tr>
<td>Capecitabine + bev</td>
<td>7.8</td>
<td>2.8</td>
<td>0.63*</td>
<td>0</td>
<td>0.86</td>
</tr>
<tr>
<td>IFL + bev</td>
<td>10.0*</td>
<td>4.4</td>
<td>0.54*</td>
<td>4.7*</td>
<td>0.66</td>
</tr>
<tr>
<td>FU/FA/Iri+- Bev</td>
<td>1.6</td>
<td>n.a.</td>
<td>n.a.</td>
<td>-3.0</td>
<td>n.a.</td>
</tr>
<tr>
<td>XELOX/FOLFOX4 + bev</td>
<td>-2</td>
<td>1.4</td>
<td>0.83*</td>
<td>1.4</td>
<td>0.89</td>
</tr>
<tr>
<td>FOLFOX + Bev</td>
<td>-3</td>
<td>0.8</td>
<td>0.89</td>
<td>0.9</td>
<td>0.94</td>
</tr>
<tr>
<td>CapeOx + Bev</td>
<td>-2</td>
<td>1.9</td>
<td>0.77*</td>
<td>2.2</td>
<td>0.84</td>
</tr>
</tbody>
</table>

* *P* < 0.05
<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI (n=32)</th>
<th>Cetuximab + FOLFIRI (n=35)</th>
<th>Hazard/odds ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>50.0 [31.9–68.1]</td>
<td>77.1 [59.9–89.6]</td>
<td>3.456 [1.140–10.472]</td>
<td>0.025a</td>
</tr>
</tbody>
</table>

Van Cutsem, Köhne in press
### CELIM Study: Unresectable liver metastases: Resections and Response Rate

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX6 + cetuximab</th>
<th>FOLFIRI + cetuximab</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>53</td>
<td>53</td>
<td>106</td>
</tr>
<tr>
<td>RR</td>
<td>68% (54-80%)</td>
<td>57% (42-70%)</td>
<td>62% (52-72%)</td>
</tr>
</tbody>
</table>

#### RR k-ras wt (n=67)

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX6 + cetuximab</th>
<th>FOLFIRI + cetuximab</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 resections</td>
<td>38%</td>
<td>30%</td>
<td>34%</td>
</tr>
<tr>
<td>R1-resect / Resect + RFA</td>
<td>2%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>RFA</td>
<td>9%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>R0 / R1 resect. / RFA</td>
<td>49%</td>
<td>43%</td>
<td>46%</td>
</tr>
<tr>
<td>R2 resections</td>
<td>2%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Exploratory lap.</td>
<td>6%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Blinded surgical review

Blinded surgical review performed for CT/MRI at baseline and at 4 months

CT/MRI scans

CT scans were evaluated without knowing when the scan was taken (before or after chemotherapy) and without clinical data