Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3

A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients

FIRE-3 study design

- Primary endpoint: Overall response rate (RECIST 1.0)
- **592** patients enrolled from 2007 - 2012
- 150 active centers in Germany and Austria
FIRE-3 study results

Overall survival

- Cetuximab + CT (FOLFIRI) (n=297)
- Bevacizumab + CT (FOLFIRI) (n=295)

Δ = 3.7 months

HR=0.77 p=0.017

<table>
<thead>
<tr>
<th></th>
<th>Cetuximab + CT</th>
<th>Bevacizumab + CT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>62%</td>
<td>58%</td>
<td>0.183</td>
</tr>
<tr>
<td>(primary endpoint not met)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>10.0 months</td>
<td>10.3 months</td>
<td>0.547</td>
</tr>
</tbody>
</table>

Heinemann V, et al. ASCO 2013 (Abstract No. LBA3506)
Consort Diagram

N=752
mCRC 1st-line
unselected patients

N=592
KRAS exon 2 wild-type
ITT population

N=407 (69%)
RAS evaluable population

N=342
RAS wild-type

N=171
FOLFIRI + Cetuximab

N=171
FOLFIRI + Bevacizumab

N=65 (16%)
‘New’ RAS mutant

N=34
FOLFIRI + Cetuximab

N=31
FOLFIRI + Bevacizumab

N=113
KRAS exon 2 mutant
population*

N=58
FOLFIRI + Cetuximab

N=55
FOLFIRI + Bevacizumab

## Comparability of Evaluated Groups

### Response Parameters

<table>
<thead>
<tr>
<th></th>
<th>ITT, KRAS wt exon 2 population</th>
<th>RAS evaluable population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=592</td>
<td>N=407</td>
</tr>
<tr>
<td>FOLFIRI Cetuximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=297</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFIRI Bevacizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=295</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td>58%</td>
<td>59.4%</td>
</tr>
<tr>
<td>Progression-free survival (median, months)</td>
<td>10.0</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>9.9</td>
<td>10.3</td>
</tr>
<tr>
<td>Overall survival (median, months)</td>
<td>28.7</td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td>28.7</td>
<td>24.9</td>
</tr>
</tbody>
</table>
Frequency of Mutations in the EGFR Pathway

**KRAS**

<table>
<thead>
<tr>
<th>EXON 1</th>
<th>EXON 2</th>
<th>EXON 3</th>
<th>EXON 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>12, 13</td>
<td>wt</td>
<td>61</td>
<td>146</td>
</tr>
<tr>
<td>4.3%</td>
<td>4.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NRAS**

<table>
<thead>
<tr>
<th>EXON 1</th>
<th>EXON 2</th>
<th>EXON 3</th>
<th>EXON 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>12, 13</td>
<td>59, 61</td>
<td>117, 146</td>
<td></td>
</tr>
<tr>
<td>3.8%</td>
<td>2%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

**KRAS:** Kirsten-RAS  
**NRAS:** Neuroblastoma-RAS  
**BRAF:** proto-oncogene B-RAF  
**PIK3CA:** Phosphatidylinositol 3-kinase  
**AKT:** Protein Kinase B
## Evaluation of ORR

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI + Cetuximab</th>
<th>FOLFIRI + Bevacizumab</th>
<th>Odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>%</td>
<td>95%-CI</td>
<td>%</td>
<td>95%-CI</td>
</tr>
<tr>
<td>KRAS exon 2 WT ITT population (N= 592)</td>
<td>62.0</td>
<td>56.2 – 67.5</td>
<td>58.0</td>
<td>52.1 – 63.7</td>
</tr>
<tr>
<td>RAS WT (N= 342)</td>
<td>65.5</td>
<td>57.9 – 72.6</td>
<td>59.6</td>
<td>51.9 – 67.1</td>
</tr>
<tr>
<td>RAS MT (N= 65)</td>
<td>38.2</td>
<td>22.2 – 56.4</td>
<td>58.1</td>
<td>39.1 – 75.5</td>
</tr>
<tr>
<td>KRAS exon 2 MT and RAS MT (N= 178)</td>
<td>38.0</td>
<td>28.1 – 48.8</td>
<td>51.2</td>
<td>40.1 – 62.1</td>
</tr>
</tbody>
</table>

\( p = \text{"one-sided Fisher’s exact test; \text{" two-sided Fisher’s exact test}"

\( \text{Stintzing S. et al ECC 2013 (Abstract No. LBA17)} \)
Evaluation of PFS

KRAS exon 2 wild-type (N=592)

<table>
<thead>
<tr>
<th>Events n/N (%)</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>— FOLFIRI Cetuximab</td>
<td>250/297 (84.2%)</td>
<td>10.0</td>
</tr>
<tr>
<td>— FOLFIRI Bevacizumab</td>
<td>242/286 (82.0%)</td>
<td>10.3</td>
</tr>
</tbody>
</table>

HR 1.06 (95% CI: 0.88 – 1.26)  p (log-rank)= 0.547

RAS* wild-type (N= 342)

<table>
<thead>
<tr>
<th>Events n/N (%)</th>
<th>Median (months)</th>
<th>96% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>— FOLFIRI Cetuximab</td>
<td>144/171 (84.2%)</td>
<td>10.4</td>
</tr>
<tr>
<td>— FOLFIRI Bevacizumab</td>
<td>143/171 (83.8%)</td>
<td>10.2</td>
</tr>
</tbody>
</table>

HR 0.93 (95% CI: 0.74 – 1.17) p (log-rank)= 0.54
Evaluation of OS

KRAS exon 2 wild-type (N=592)

Δ = 3.7 months

HR = 0.77
p = 0.017

No. at risk: 297, 218, 214
Events: 111, 47, 18, 10

— FOLFIRI + Cetuximab: 158/297 (53.2%)
Median (months): 28.7
95% CI: 24.0 – 36.6

— FOLFIRI + Bevacizumab: 185/295 (62.7%)
Median (months): 28.0
95% CI: 22.7 – 27.8

RAS* wild-type (N= 342)

Δ = 7.5 months

HR = 0.70
p = 0.011

No. at risk: 171, 128, 137
Events: 71, 39, 29, 8

— FOLFIRI + Cetuximab: 191/171 (53.2%)
Median (months): 33.1
95% CI: 24.5 – 39.4

— FOLFIRI + Bevacizumab: 110/171 (64.3%)
Median (months): 25.6
95% CI: 22.7 – 28.6

HR 0.70 (95% CI: 0.53 – 0.92)
p (log-rank) = 0.011

RAS* wild-type: KRAS61/146; NRAS Exon2, NRAS Exon3
Summary RAS mutations

• In patients with all-RAS wild-type tumors ORR and PFS were comparable between both treatment arms

• OS was markedly superior (Δ = 7.5 months, HR 0.70) in all-RAS wild-type patients receiving 1st-line therapy with cetuximab

• No benefit was observed when patients with RAS-mutant tumors were treated with FOLFIRI plus cetuximab as compared to FOLFIRI plus bevacizumab
Frequency of Mutations in the EGFR Pathway

BRAF
- EXON 11: 0%
- EXON 15: 10%

PIK3CA
- EXON 9: 5.3%
- EXON 20: 2.0%

AKT
- E17K: 0.9%

KRAS: Kirsten-RAS
NRAS: Neuroblastoma-RAS
BRAF = proto-oncogene B-RAF
PIK3CA = Phosphatidylinositol 3-Kinase
AKT = Protein Kinase B
Distribution of Mutations in the EGFR Pathway

- KRAS (exon 2) wild-type-ITT (n=592)
  - RAS status not evaluable (n=185)
  - RAS mutant (n=65)
    - BRAF mutant (n=48)
      - n=1
      - n=47
    - PIK3CA 9 mutant (n=27)
      - n=2
      - n=7
    - PIK3CA 20 mutant (n=11)
      - n=1
      - n=7
  - RAS wild-type (n=342)
    - AKT E17K mutant (n=3)
      - n=3
Distribution of Mutations in the EGFR Pathway

KRAS (exon 2) wild-type-ITT (n=592)

- **RAS mutant (n=65)**
  - BRAF mutant (n=48)
    - n=1
  - PIK3CA 9 mutant (n=27)
    - n=2
    - n=7
  - PIK3CA 20 mutant (n=11)
    - n=1
- **RAS wild-type (n=342)**
- **RAS status not evaluable (n=188)**

*16 double mutations (15%) in RAS-mut group

AKT E17K mutant (n=3)
Distribution of Mutations in the EGFR Pathway

**KRAS (exon 2) wild-type-ITT (n=592)**

- **RAS mutant (n=65)**
  - **BRAF mutant (n=48)**
    - n=1
    - n=47
  - **PIK3CA 9 mutant (n=27)**
    - n=2
    - n=5
    - n=15
- **PIK3CA 20 mutant (n=11)**
  - n=2
  - n=1
  - n=7
- **AKTE17K mutant (n=3)**
  - n=3

**RAS wild-type (n=342)**

- 72 mutant tumors (21%) in RAS-wt group

RAS status not evaluable (n=186)
## BRAF mutant population

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI + Cetuximab</th>
<th>FOLFIRI + Bevacizumab</th>
<th>Odds ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR %</td>
<td>95% CI</td>
<td>ORR %</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>KRAS exon 2 WT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT population</td>
<td>62.0</td>
<td>56.2 – 67.5</td>
<td>58.0</td>
<td>52.1 – 63.7</td>
</tr>
<tr>
<td>(N= 592)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RAS WT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N= 342)</td>
<td>65.5</td>
<td>57.9 – 72.6</td>
<td>59.6</td>
<td>51.9 – 67.1</td>
</tr>
<tr>
<td></td>
<td>0.63-1.99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RAS mutant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N= 178)</td>
<td>38.0</td>
<td>28.1 – 48.8</td>
<td>51.2</td>
<td>40.1 – 62.1</td>
</tr>
<tr>
<td></td>
<td>0.32-1.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BRAF mutant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N= 48)</td>
<td>52.2</td>
<td>30.6 – 73.2</td>
<td>40.0</td>
<td>21.1 – 61.3</td>
</tr>
<tr>
<td></td>
<td>0.52-5.14</td>
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</tr>
</tbody>
</table>

*p = *one-sided Fisher's exact test; **two-sided Fisher's exact test*
Progression free survival
BRAF mutant population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events n/N (%)</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI + Cetuximab</td>
<td>22/23 (95.7%)</td>
<td>4.9</td>
<td>2.4 – 8.8</td>
</tr>
<tr>
<td>FOLFIRI + Bevacizumab</td>
<td>25/25 (100%)</td>
<td>6.0</td>
<td>4.3 – 7.8</td>
</tr>
</tbody>
</table>

HR 0.87 (95% CI: 0.49 – 1.57)
p (log-rank) = 0.65
Overall survival
BRAF mutant population

- FOLFIRI + Cetuximab
  Events n/N (%): 18/23 (78.3%)
  Median (months): 12.3
  95% CI: 5.5 – 21.7

- FOLFIRI + Bevacizumab
  Events n/N (%): 24/25 (96.0%)
  Median (months): 13.7
  95% CI: 7.8 – 19.5

HR 0.87 (95% CI: 0.47 – 1.61)

p (log-rank) = 0.65

No. at risk:
23 11 4 1 1
25 12 3 1 1

Probability of survival
months since start of treatment
## PiK3CA mutant population

<table>
<thead>
<tr>
<th>ORR</th>
<th>FOLFIRI + Cetuximab</th>
<th>FOLFIRI + Bevacizumab</th>
<th>Odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS exon 2 WT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT population (N= 592)</td>
<td>62.0</td>
<td>58.0</td>
<td>1.18</td>
<td>0.183*</td>
</tr>
<tr>
<td></td>
<td>56.2 – 67.5</td>
<td>52.1 – 63.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RAS WT</strong> (N= 342)</td>
<td><strong>65.5</strong></td>
<td><strong>59.6</strong></td>
<td><strong>1.28</strong></td>
<td><strong>0.32</strong>**</td>
</tr>
<tr>
<td></td>
<td>57.9 – 72.6</td>
<td>51.9 – 67.1</td>
<td><strong>0.83-1.99</strong></td>
<td><strong>0.32</strong>**</td>
</tr>
<tr>
<td><strong>RAS mutant</strong> (N= 178)</td>
<td>38.0</td>
<td>51.2</td>
<td>0.59</td>
<td>0.097**</td>
</tr>
<tr>
<td></td>
<td>28.1 – 48.8</td>
<td>40.1 – 62.1</td>
<td><strong>0.32-1.06</strong></td>
<td><strong>0.097</strong>**</td>
</tr>
<tr>
<td><strong>PiK3CA mutant</strong> (N= 38)</td>
<td>47.4</td>
<td>57.9</td>
<td><strong>0.85</strong></td>
<td><strong>0.84</strong>**</td>
</tr>
<tr>
<td></td>
<td>24.4 – 71.1</td>
<td>33.5 – 79.7</td>
<td><strong>0.18-2.36</strong></td>
<td><strong>0.84</strong>**</td>
</tr>
</tbody>
</table>

*p = *one-sided Fisher’s exact test; **two-sided Fisher’s exact test
Progression free survival
PIK3CA mutant population

<table>
<thead>
<tr>
<th>Events n/N (%)</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI + Cetuximab</td>
<td>18/19 (94.7%)</td>
<td>7.8</td>
</tr>
<tr>
<td>FOLFIRI + Bevacizumab</td>
<td>15/19 (78.9%)</td>
<td>13.3</td>
</tr>
</tbody>
</table>

HR 1.61 (95% CI: 0.80 – 3.25)
p (log-rank)= 0.18

No. at risk
19 9 3 1 0
19 5 1 1 1
Overall survival
PIK3CA mutant population

<table>
<thead>
<tr>
<th></th>
<th>Events n/N (%)</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI + Cetuximab</td>
<td>13/19 (68.4%)</td>
<td>26.5</td>
<td>14.2 – 30.6</td>
</tr>
<tr>
<td>FOLFIRI + Bevacizumab</td>
<td>11/19 (57.9%)</td>
<td>25.9</td>
<td>21.0 – 33.2</td>
</tr>
</tbody>
</table>

HR 1.08 (95% CI: 0.48 – 2.43)
p (log-rank)= 0.86

No. at risk
19 14 7 1 1
19 14 7 3 1 1
Summary
BRAF and PIK3CA mutations

• In BRAF mutant tumors comparable results could be observed in ORR, PFS and OS between FOLFIRI plus cetuximab when compared to FOLFIRI plus bevacizumab.

• In PIK3CA mutant tumors comparable results could be observed in ORR and OS between FOLFIRI plus cetuximab when compared to FOLFIRI plus bevacizumab.

• In PIK3CA mutant tumors PFS was longer in the FOLFIRI plus bevacizumab arm, but did not reach the level of significance.
Conclusions mutations

- Upfront determination of RAS (KRAS and NRAS) mutation status appears highly recommendable in patients with metastatic colorectal cancer.

- Patients with all-RAS wild-type tumors have a clinically relevant survival benefit when first-line treatment with FOLFIRI plus cetuximab is offered.

- Comparable effects on overall survival are observed when cetuximab and bevacizumab are compared in small subsets of patients with BRAF- or PIK3CA mutated tumors.