Correlation of Capecitabine-Induced Skin Toxicity with Treatment Efficacy in Patients with Metastatic Colorectal Cancer (mCRC): AIO KRK-0104 Trial


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FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (mCRC): Analysis of patients with KRAS mutated tumors in the randomized German AIO study KRK-0306

**Purpose**
The AIO KRK-0104 randomized phase II trial investigated the efficacy and safety of two capecitabine-based regimens: CAPIRI plus cetuximab (CAPIRI-C) and CAPOX plus cetuximab (CAPOX-C) in the first-line treatment of metastatic colorectal cancer (mCRC). Treatment related skin toxicity was evaluated separately for capecitabine and cetuximab. The present analysis investigates the correlation of capecitabine- attributed skin toxicity (Cape-ST) and parameters of treatment efficacy.

**Patients and Methods**
mCRC patients were randomized to cetuximab (400mg/m² day 1, followed by 250mg/m² weekly) plus CAPIRI (irinotecan 200mg/m², day 1; capecitabine 800mg/m² twice daily days 1-14, every 3 weeks) or cetuximab plus CAPOX (oxaliplatin 130mg/m² day 1; capecitabine 1000mg/m² twice daily days 1-14, every 3 weeks).

**Results**
Of 185 recruited patients, 149 patients (CAPIRI-C, n=78; CAPOX-C, n=71) received study treatment beyond the first tumor assessment and were evaluable for efficacy. While cetuximab-specific skin toxicity such as acneiform rash, dry skin and others occurred in >90% of patients, Cape-ST, predominantly hand-foot syndrome, was observed in only 33.2% of patients. No Cape-ST grade 4 was documented. Cape-ST grade 1-3 was associated with a significantly higher CR rate (13.9% vs 2.1%, p=0.038) and disease control rate (DCR) (97.9% vs 86.1%, p=0.038) compared to grade 0 toxicity. Moreover, Cape-ST grade 1-3 related to a markedly longer PFS (9.9 vs 5.6 months, p<0.001) and OS (32.8 vs 22.4 months, p=0.008). Separate analyses of treatment arms indicated that the effect of Cape-ST on PFS remained significant for the CAPIRI-C arm (8.5 vs 5.2 months, p=0.011) and the CAPOX-C arm (9.9 vs 6.5 months, p=0.004), while the effect on OS remained apparent as a strong trend for the CAPIRI-C arm (32.0 vs 19.7 months, p=0.125) and the CAPOX-C arm (37.5 vs 24.0 months, p=0.056).

**Conclusion**
This analysis supports the hypothesis that for the evaluated regimens a correlation exists between capecitabine-specific skin toxicity and treatment efficacy regarding DCR, PFS and OS.
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Study Design

Randomized, multicenter, phase II study in previously untreated mCRC patients.

Cetuximab
Capecitabine
Irinotecan

versus

Cetuximab
Capecitabine
Oxaliplatin

Recruiting centers: 35
## Treatment Regimens

<table>
<thead>
<tr>
<th>Day</th>
<th>XELIRI + Cet: (*)</th>
<th>XELOX + Cet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Irinotecan 200mg/m², 30min i.v.</td>
<td>Oxaliplatin 130mg/m², 120min i.v.</td>
</tr>
<tr>
<td>8</td>
<td>Cetuximab 250mg/m², 60min i.v.</td>
<td>Cetuximab 250mg/m², 60min i.v.</td>
</tr>
<tr>
<td>15</td>
<td>Capecitabine 800mg/m² p.o., twice daily</td>
<td>Capecitabine 1000mg/m² p.o. twice daily</td>
</tr>
<tr>
<td>21</td>
<td>(*) 20% dose reduction for patients &gt; 65 years, arm A</td>
<td>q 3 weeks</td>
</tr>
</tbody>
</table>

(*) Cetuximab initial dose: 400mg/m², 120min
FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (mCRC): Analysis of patients with KRAS mutated tumors in the randomized German AIO study KRK-0306

CONSORT Diagram

185 patients randomly assigned

93 patients arm A (XELIRI+cetuximab)
- 4 patients not treated
- 89 patients
  - treated
  - evaluable regarding toxicity
  - intent to treat population

Early dropout patients (before first tumor assessment):
- 1 patient early death
- 1 patient withdrew consent
- 3 patients allergic reactions to cetuximab
- 2 patients unacceptable toxicities related to treatment
- 4 patients severe adverse events unrelated to treatment

78 patients
- evaluable regarding response

92 patients arm B (XELOX+cetuximab)
- 4 patients not treated
- 88 patients
  - treated
  - evaluable regarding toxicity
  - intent to treat population

Early dropout patients (before first tumor assessment):
- 3 patients early death
- 3 patients withdrew consent
- 8 patients allergic reactions to cetuximab
- 2 patients unacceptable toxicities related to treatment
- 1 patient severe adverse events unrelated to treatment

88 patients
- evaluable regarding response
### Dose Reductions / Treatment Delay

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cape-ST Grade 0</th>
<th>Cape-ST Grade 1-3</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Evaluable treatment cycles</td>
<td>539</td>
<td>100</td>
<td>381</td>
<td>100</td>
</tr>
<tr>
<td>Cycles with dose reduction*</td>
<td>158</td>
<td>29.31</td>
<td>172</td>
<td>45.14</td>
</tr>
<tr>
<td>Cycles with treatment delay†</td>
<td>113</td>
<td>20.96</td>
<td>59</td>
<td>15.49</td>
</tr>
</tbody>
</table>

** Fisher test (two-sided)
### Skin Toxicity: Frequency of Occurrence

<table>
<thead>
<tr>
<th>Grade</th>
<th>CAPOX + cetuximab (n=71)</th>
<th>CAPIRI + cetuximab (n=78)</th>
<th>both arms (n=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Grade 0*</td>
<td>43</td>
<td>60.6</td>
<td>43</td>
</tr>
<tr>
<td>Grade 1*</td>
<td>7</td>
<td>9.9</td>
<td>9</td>
</tr>
<tr>
<td>Grade 2*</td>
<td>13</td>
<td>18.3</td>
<td>9</td>
</tr>
<tr>
<td>Grade 3*</td>
<td>8</td>
<td>11.3</td>
<td>2</td>
</tr>
</tbody>
</table>

* according to NCI CTC-AE 3.0
** Fisher test (two-sided)
Correlation with Response

<table>
<thead>
<tr>
<th></th>
<th>Grade 0**</th>
<th>Grade 1-3**</th>
<th>p-value Fisher exact (two sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>101 (67.8%)</td>
<td>48 (32.2%)</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Complete remission (CR)*</td>
<td>5 (5.0%)</td>
<td>3 (6.3%)</td>
<td>0.713</td>
</tr>
<tr>
<td>Partial remission (PR)*</td>
<td>50 (49.5%)</td>
<td>25 (52.1%)</td>
<td>0.861</td>
</tr>
<tr>
<td>Stable disease (SD)*</td>
<td>32 (31.7%)</td>
<td>19 (39.6%)</td>
<td>0.361</td>
</tr>
<tr>
<td>Progressive disease (PD)*</td>
<td>14 (13.9%)</td>
<td>1 (2.1%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Overall response rate (ORR)*</td>
<td>55 (54.5%)</td>
<td>28 (58.3%)</td>
<td>0.725</td>
</tr>
<tr>
<td>Disease control rate (DCR)*</td>
<td>87 (86.1%)</td>
<td>47 (97.9%)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

*according to RECIST, ** according to NCI CTC-AE 3.0
FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (mCRC): Analysis of patients with KRAS mutated tumors in the randomized German AIO study KRK-0306

### Survival According to Skin Toxicity

<table>
<thead>
<tr>
<th>Capecitabine related skin toxicities</th>
<th>Grade 0 n=101 (78.5%)</th>
<th>Grade 1 n=16 (10.7%)</th>
<th>Grade 2 n=22 (14.8%)</th>
<th>Grade 3 n=10 (6.7%)</th>
<th>p-value logrank **</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months) 95%CI</td>
<td>5.6 (4.8 – 6.3)</td>
<td>8.5 (5.0 – 11.9)</td>
<td>8.9 (7.1 – 10.6)</td>
<td>13.6 (10.4 – 16.9)</td>
<td>0.002</td>
<td>0.72 (0.60 – 0.86)</td>
</tr>
<tr>
<td>OS (months) 95%CI</td>
<td>22.4 (17.6 – 27.2)</td>
<td>30.5 (27.0 – 33.9)</td>
<td>33.1 (20.8 – 45.5)</td>
<td>37.5 (24.4 – 46.0)*</td>
<td>0.053</td>
<td>0.74 (0.60 - 0.92)</td>
</tr>
</tbody>
</table>

*= 95% CI of mean as 50% of pts. are censored for SD of median

**= logrank for differences of all grades
**Survival According to Skin Toxicity Grade 0 vs Grades 1-3**

<table>
<thead>
<tr>
<th>Capecitabine related skin toxicities</th>
<th>Grade 0**</th>
<th>Grade 1-3**</th>
<th>p-value</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months) 95%CI</td>
<td>5.6 (4.8 – 6.3)</td>
<td>9.9 (8.2 – 11.6)</td>
<td>&lt;0.001</td>
<td>0.51 (0.36 – 0.72)</td>
</tr>
<tr>
<td>OS (months) 95%CI</td>
<td>22.4 (17.6 – 27.2)</td>
<td>32.8 (22.9 – 42.3)</td>
<td>0.008</td>
<td>0.56 (0.36 – 0.86)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Capecitabine related skin toxicities</th>
<th>Grade 0**</th>
<th>Grade 1-3**</th>
<th>p-value</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A (CAIPIRI) n=78</td>
<td>5.2 (4.5 – 5.9)</td>
<td>8.5 (5.3 – 11.7)</td>
<td>0.011</td>
<td>0.52 (0.31 – 0.87)</td>
</tr>
<tr>
<td>PFS (months) 95%CI</td>
<td>19.7 (11.9 – 27.5)</td>
<td>32.0 (25.5 – 38.5)</td>
<td>0.125</td>
<td>0.63 (0.35 – 1.14)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Capecitabine related skin toxicities</th>
<th>Grade 0**</th>
<th>Grade 1-3**</th>
<th>p-value</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm B (CAPOX) n=71</td>
<td>6.5 (4.7 – 8.4)</td>
<td>9.9 (8.3 – 11.5)</td>
<td>0.004</td>
<td>0.48 (0.29 – 0.80)</td>
</tr>
<tr>
<td>PFS (months) 95%CI</td>
<td>24.0 (11.9 – 36.1)</td>
<td>37.5 (30.8 – 46.4)*</td>
<td>0.056</td>
<td>0.54 (0.29 – 1.03)</td>
</tr>
</tbody>
</table>

*= 95% CI of mean as 50% of pts. are censored for SD of median,
** according to NCI CTCAE 3.0
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Percentage of PD, ORR and DCR

<table>
<thead>
<tr>
<th>Grade</th>
<th>PD</th>
<th>ORR</th>
<th>DCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14%</td>
<td>86%</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>0%</td>
<td>100%</td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td>5%</td>
<td>54%</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>0%</td>
<td>0%</td>
<td>70%</td>
</tr>
</tbody>
</table>
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Hand-Foot-Syndrome:
Time of Occurrence by Cycle

Graph showing the percentage of first occurrence of Hand-Foot-Syndrome (HFS) and the time of maximal HFS by cycle.
FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (mCRC): Analysis of patients with KRAS mutated tumors in the randomized German AIO study KRK-0306

**Progression-Free Survival (Grade 0 vs Grades 1-3)**

- median PFS
  - grade 1-3 (n=48): 9.9mo
  - grade 0 (n=101): 5.6mo
  - p <0.001 (log-rank)
FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (mCRC): Analysis of patients with KRAS mutated tumors in the randomized German AIO study KRK-0306

Overall Survival
(Grade 0 vs Grades 1-3)

median OS
grade 1-3 (n=48): 32.8mo
grade 0 (n=101): 22.4mo
p = 0.008 (log-rank)
CAPIRI + Cetuximab (Arm A)
Progression-Free Survival
(Grade 0 vs Grades 1-3)

median PFS
- grade 1-3 (n=20): 8.4mo
- grade 0 (n=58): 5.2mo
p = 0.011 (log-rank)

Munich, 01/06/11
Prof. Dr. med. V. Heinemann | University of Munich – Klinikum Grosshadern
FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (mCRC): Analysis of patients with KRAS mutated tumors in the randomized German AIO study KRK-0306

CAPIRI + Cetuximab (Arm A) Overall Survival (Grade 0 vs Grades 1-3)

median OS
grade 1-3 (n=20): 32.0mo
grade 0 (n=58): 19.7mo
p = 0.125 (log-rank)
FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (mCRC): Analysis of patients with KRAS mutated tumors in the randomized German AIO study KRK-0306

CAPOX + Cetuximab (Arm B)
Progression-Free Survival
(Grade 0 vs Grades 1-3)

- median PFS
  - grade 1-3 (n=28): 9.9mo
  - grade 0 (n=43): 6.5mo
  - p = 0.004 (log-rank)
CAPOX + Cetuximab (Arm B)
Overall Survival
(Grade 0 vs Grades 1-3)

median OS
- grade 1-3 (n=28): 37.5mo
- grade 0 (n=43): 24.0mo
p = 0.056 (log-rank)
Conclusions

This analysis supports the hypothesis that for the evaluated regimens a correlation exists between capecitabine-specific skin toxicity and treatment efficacy regarding DCR, PFS and OS.