Cediranib Plus FOLFOX/CAPOX Versus Placebo Plus FOLFOX/CAPOX in Patients With Previously Untreated Metastatic Colorectal Cancer: A Randomized, Double-Blind, Phase III Study (HORIZON II)

- **Journal:** Journal of Clinical Oncology
- **Publikationsjahr:** 2012
- **Autoren:** Paulo M. Hoff, Andreas Hochhaus, Bernhard C. Pestalozzi et al.
Welche Frage soll anhand der Studie beantwortet werden?

**Ist die Zugabe von** Cediranib zu bisherigen Therapieregimes mit Überlebensvorteilen verbunden?

- **P** - with histologic/cytologic confirmation of metastatic (stage IV) CRC
  - WHO performance status (PS) of 0 or 1
  - life expectancy of > 12 weeks
  - Patients must not have received prior systemic therapy for mCRC

- **I** - Cediranib

- **C** – Placebo

- **O** – PFS (progression free survival) und OS (overall survival)
Cediranib
- Tyrosin Kinase Inhibitor
- Wirkt über Hemmung von VEGF (vascular endothelial growth factor)

FOLFOX
- Flurouracil
- Folinsäure
- Oxaliplatin

CAPOX (XELOX)
- Capecitabin (Prodrug von 5FU)
- Oxaliplatin
Sind die Ergebnisse der Studie glaubwürdig?

- War die Zuordnung der Patienten zu den Gruppen randomisiert?
  - The chemotherapy regimen for each patient was selected by the individual investigator; the regimen options were FOLFOX4, mFOLFOX6, or CAPOX
  - Patients were initially randomly assigned 1:1:1 to receive once-per-day cediranib 30 mg, cediranib 20 mg, or placebo in combination with FOLFOX/CAPOX
    - Anschließend 2:1 Zuordnung
  - Recruitment to all three arms continued until a planned end-of-phase (EoP) II analysis, conducted by an independent data monitoring committee.
Erfolgte die Randomisierung verdeckt?

– Keine Information

– Patients randomly assigned to this double-blind, placebo-controlled study were stratified according to chemotherapy regimen, WHO PS, and baseline albumin and alkaline phosphatase values applied to centralized reference ranges.

– 860 patients randomly assigned to the cediranib 20 mg or placebo arms
  • 225 (26.2%) received FOLFOX4,
  • 147 (17.1%) received mFOLFOX6
  • 488 (56.7%) received CAPOX
Waren Patienten, Ärzte und Studienpersonal verblindet gegenüber der jeweiligen Behandlung?

- All study personnel other than the independent data monitoring committee remained blinded to the data until the trial ended.
### Waren die Gruppen zu Beginn der Studie vergleichbar?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cediranib (20 mg) (n = 502)</th>
<th>Placebo (n = 358)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>58.0</td>
<td>59.0</td>
</tr>
<tr>
<td>Range</td>
<td>2-83</td>
<td>22-82</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>299</td>
<td>212</td>
</tr>
<tr>
<td>Female</td>
<td>203</td>
<td>146</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>320</td>
<td>254</td>
</tr>
<tr>
<td>Black</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Asian</td>
<td>166</td>
<td>88</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td><strong>WHO performance status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>288</td>
<td>209</td>
</tr>
<tr>
<td>1</td>
<td>214</td>
<td>149</td>
</tr>
<tr>
<td><strong>Type of cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>288</td>
<td>232</td>
</tr>
<tr>
<td>Rectal</td>
<td>214</td>
<td>126</td>
</tr>
<tr>
<td><strong>Baseline liver covariate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP ≤ 320 U/L and albumin ≥ 3.5 g/dL</td>
<td>397</td>
<td>274</td>
</tr>
<tr>
<td>Other combinations of ALP and albumin</td>
<td>105</td>
<td>84</td>
</tr>
<tr>
<td><strong>Initial diagnosis to random assignment, months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>326</td>
<td>245</td>
</tr>
<tr>
<td>6 to &lt; 12</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>12 to &lt; 24</td>
<td>57</td>
<td>37</td>
</tr>
<tr>
<td>24 to &lt; 36</td>
<td>48</td>
<td>28</td>
</tr>
<tr>
<td>≥ 36</td>
<td>49</td>
<td>36</td>
</tr>
<tr>
<td><strong>Prior therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>69</td>
<td>40</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>104</td>
<td>80</td>
</tr>
</tbody>
</table>

Medizinische Universität Graz, Auenbruggerplatz 2, A-8036 Graz, www.medunigraz.at
1,076 patients
- Cediranib 30 mg (n=216)
  - Arm wurde aufgemacht
- Cediranib 20 mg (n=502)
- Placebo (n=358)

=> in combination with FOLFOX/CAPOX

- Data Cut off 21.3.2010
  - 720 Progression
  - 523 deaths
Wurden die Gruppen abgesehen von der Studienmaßnahme ähnlich behandelt?
– Keine Information

– Response Evaluation Criteria in Solid Tumors (RECIST)
  • Komplette Remission
  • Partielle Remission
  • Stabile Erkrankung
  • Progression

Wurden die Patienten in der Auswertung in den Gruppen berechnet, zu denen sie randomisiert waren?
– Efficacy analyses were performed on the intention-to-treat population for all patients randomly assigned to cediranib 20 mg or placebo.
Welche Endpunkte wurden gewählt?

**PFS** progression-free survival
- For PFS for a statistically significant improvement was observed for patients treated with cediranib 20 mg compared with placebo (HR, 0.84; 95% CI, 0.73 to 0.98; \( P = .0121 \)).
- The statistically significant improvement in PFS for patients treated with cediranib was confirmed by the independent central review (HR, 0.86; 95% CI, 0.73 to 1.02; \( P = .0307 \)).

**OS** overall survival
- For the coprimary end point of OS, there was no statistically significant difference between the cediranib 20 mg and placebo groups (HR, 0.94; 95% CI, 0.79 to 1.12; \( P = .5707 \)). The median OS was 19.7 and 18.9 months in the cediranib and placebo groups, respectively.
Sind diese Endpunkte klinisch bedeutsam?

- Ja

Wie groß war der Behandlungseffekt?

- OS (1-0,94) = 6%

- PFS (1-0,86) = 16%
  - 8,6 Monate gegen 8,3 Monate oder 9 Tage
<table>
<thead>
<tr>
<th>Response</th>
<th>Cediranib (20 mg) (n = 502)</th>
<th>Placebo (n = 358)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Responders</td>
<td>254</td>
<td>50.6</td>
</tr>
<tr>
<td>Complete response</td>
<td>10</td>
<td>2.0</td>
</tr>
<tr>
<td>Partial response</td>
<td>244</td>
<td>48.6</td>
</tr>
<tr>
<td>Stable disease</td>
<td>179</td>
<td>35.7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>43</td>
<td>8.6</td>
</tr>
<tr>
<td>Nonevaluable</td>
<td>26</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors.