Bevacizumab with or without erlotinib as maintenance therapy, following induction first-line chemotherapy plus bevacizumab, in patients with metastatic colorectal cancer:

Efficacy and safety results of the international GERCOR DREAM phase III trial

Conflict of interest disclosure

- Advisory board member and lectures for:
  - Roche
  - Sanofi-Aventis
  - Merck
  - Amgen
  - Bayer
Rationale (1)

Evaluating maintenance therapy with targeted agents is the main objective of the DREAM trial

- VEGF inhibition (bevacizumab) increases survival in combination with oxaliplatin- or irinotecan-based chemotherapy in the first or second line\(^1\text{–}^3\)

- EGFR inhibition (panitumumab or cetuximab) increases survival in patients with Kras wt tumor\(^4\text{–}^7\)

- OPTIMOX1-2 studies validated oxaliplatin stop-and-go strategy\(^8\text{–}^9\)

Crosstalk between EGFR pathway and VEGF is involved in tumour growth and survival

Phase III studies in mCRC: combination of monoclonal antibodies targeting EGFR and VEGF provided no benefit\(^1,2\)

In colorectal cancer xenografts, combining TKIs targeting VEGFR and EGFR shows synergistic antitumor activity, even in KRAS mutant model\(^3\)

Combination of bevacizumab and erlotinib has been tested in preclinical models\(^4\)

Antitumor activity of bevacizumab and erlotinib against SW620 CRC xenografts (pooled data)

AK Larsen. Cancer Biology and Therapeutics, INSERM U938, Paris
**OPTIMOX3 – DREAM protocol**

**INDUCTION (N=700)**
- **mFOLFOX7 + bevacizumab**
- **XELOX2 + bevacizumab**
- **FOLFIRI + bevacizumab**

**MAINTENANCE (N=446)**
- Bevacizumab (7.5 mg/kg q3w) + erlotinib (150 mg/d) until PD

*No PD*

**Registration Date:**

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*a* Oxaliplatin 100 mg/m² d1 (6 cycles), 5-FU 2.4 g/m² d1–2, FA 400 mg/m² d1, bev 5 mg/kg d1, q2w, 6–12 cycles

*b* Oxaliplatin 100 mg/m² d1 (6 cycles), capecitabine 1.25–1.5 g/m² bid d1–d8, bev 5 mg/kg d1 q2w, 6–12 cycles

*c* Irinotecan 180 mg/m² d1, 5-FU 2.4 mg/m² d1–2, FA 400 mg/m² d1, bev 5 mg/kg d1, q2w, 12 cycles
Inclusion criteria

- Histologically proven colorectal adenocarcinoma
- Measurable or evaluable metastasis
- Not suitable for complete surgical resection
- No prior chemotherapy or targeted agent for metastatic disease
- Age 18–80 years
- WHO performance status 0–2
- Alkaline phosphatase <3–5 × ULN
- Bilirubin <1.5 × ULN
- Adjuvant chemotherapy >6 months before diagnosis of metastasis (2 years if oxaliplatin)
Endpoints

- **Primary endpoint**
  - Progression-free survival (PFS) on maintenance therapy

- **Secondary endpoints**
  - Overall survival
  - Overall survival from maintenance
  - Duration without chemotherapy
  - Response rate (RECIST)
  - Survival according to KRAS mutational status

- **Sample size**
  - Superiority study, power of 80%, 2-sided test $\alpha=0.05$
  - $\Delta$ median maintenance PFS: from 4.5 months (bevacizumab) to 6.5 months (bevacizumab + erlotinib)
  - Anticipated drop-out rate 40% (withdrawn consent, premature discontinuation, metastasis surgery or progression/death)
  - 700 patients to be enrolled
  - 418 evaluable patients
  - 231 events required

- **Endpoints**
CONSORT diagram

Declared (n=701)
- No consent form (n=1)

Included (n=700)
- Not treated (n=6)

Induction (n=694)
- Off-study during induction N=248
  - PD or death (n=108)
  - Toxicity (n=47)
  - Intercurrent disease (n=9)
  - Patient choice (n=9)
  - Other reason (n=75)

Randomized (n=446)

Bevacizumab (n=224)

Bevacizumab + erlotinib (n=222)

Efficacy analysis

Median follow-up: 31.0 months
## Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic, % patients</th>
<th>Bevacizumab (N=224)</th>
<th>Bevacizumab + erlotinib (N=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, &lt;70 / ≥70</td>
<td>73 / 27</td>
<td>74 / 26</td>
</tr>
<tr>
<td>Sex, male / female</td>
<td>56 / 44</td>
<td>66 / 34</td>
</tr>
<tr>
<td>Colon / rectum / both</td>
<td>73 / 25 / 2</td>
<td>74 / 23 / 3</td>
</tr>
<tr>
<td>Prior adjuvant chemotherapy</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Metachronous / synchronous disease</td>
<td>17 / 83</td>
<td>18 / 82</td>
</tr>
<tr>
<td>PS, 0 / 1 / 2</td>
<td>60 / 37 / 4</td>
<td>60 / 36 / 4</td>
</tr>
<tr>
<td><strong>Chemotherapy regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX-bev</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>XELOX-bev</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>FOLFIRI-bev</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Platelet count, &lt;400 / &gt;400</td>
<td>71 / 29</td>
<td>74 / 26</td>
</tr>
<tr>
<td>LDH, N / &gt;ULN</td>
<td>47 / 53</td>
<td>49 / 51</td>
</tr>
<tr>
<td>Alkaline phosphatase, N / &gt;ULN</td>
<td>48 / 52</td>
<td>50 / 50</td>
</tr>
<tr>
<td>CEA, N / &gt;ULN</td>
<td>15 / 81</td>
<td>15 / 83</td>
</tr>
</tbody>
</table>
Results
Maintenance PFS
(from randomization)

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab</th>
<th>Bevacizumab + erlotinib</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>224</td>
<td>222</td>
</tr>
<tr>
<td>Events</td>
<td>177 (79%)</td>
<td>150 (68%)</td>
</tr>
<tr>
<td>Censored</td>
<td>47 (21%)</td>
<td>72 (32%)</td>
</tr>
<tr>
<td>Median [95% CI]</td>
<td>4.57 [4.1–5.5]</td>
<td>5.75 [4.5–6.2]</td>
</tr>
<tr>
<td>HR [95% CI]</td>
<td>0.73 [0.59–0.91]</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0050</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk:
Bevacizumab
- 224
- 172
- 110
- 67
- 40
- 26
- 15
Bevacizumab + erlotinib
- 222
- 176
- 116
- 73
- 53
- 37
- 28
PFS from registration (randomised population)

<table>
<thead>
<tr>
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<th>Bevacizumab + erlotinib</th>
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<td>72 (32%)</td>
</tr>
<tr>
<td>Median [95% CI]</td>
<td>9.23 [8.5–10.1]</td>
<td>10.22 [9.6–11.1]</td>
</tr>
<tr>
<td>HR [95% CI]</td>
<td>0.73 [0.59–0.91]</td>
<td>0.0045</td>
</tr>
</tbody>
</table>

Maintenance PFS (%)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>224</td>
<td>224</td>
<td>216</td>
<td>185</td>
<td>123</td>
<td>76</td>
</tr>
<tr>
<td>Bevacizumab + erlotinib</td>
<td>222</td>
<td>222</td>
<td>218</td>
<td>193</td>
<td>136</td>
<td>90</td>
</tr>
</tbody>
</table>
Overall survival
(all patients, from registration)

Median overall survival 25.4 months [95% CI 22.96–28.19]
(n=700)

No. at risk:
700  660  580  469  384  313  231

Time (months)
## Survival summary

<table>
<thead>
<tr>
<th>Randomized patients</th>
<th>Bevacizumab (N=224)</th>
<th>Bevacizumab + erlotinib (N=222)</th>
<th>HR [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance PFS</td>
<td>4.57 [4.11–5.52]</td>
<td>5.75 [4.50–6.20]</td>
<td>0.73 [0.59--0.91]</td>
<td>0.0050</td>
</tr>
<tr>
<td>(from randomisation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>9.23 [8.54–10.05]</td>
<td>10.22 [9.63–11.10]</td>
<td>0.73 [0.59--0.91]</td>
<td>0.0045</td>
</tr>
<tr>
<td>(from registration)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall survival (all patients): **25.44 months** [95% CI 22.96–28.19]
Toxicity
# Toxicity (1)

<table>
<thead>
<tr>
<th>Selected grade 3/4 AEs$^a$, %</th>
<th>Bevacizumab (n=219)</th>
<th>Bevacizumab + erlotinib (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1.4</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.7</td>
<td>2.8</td>
</tr>
</tbody>
</table>

$^a$NCI-CTC version 3.0
# Toxicity (2)

<table>
<thead>
<tr>
<th>Grade, %</th>
<th>Bevacizumab (n=219)</th>
<th>Bevacizumab + erlotinib (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1  2  3  4</td>
<td>1  2  3  4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>11 1 1 0</td>
<td>29 20 9 0</td>
</tr>
<tr>
<td>Skin</td>
<td>8  0 0 0</td>
<td>28 37 19 1</td>
</tr>
</tbody>
</table>
# Treatment received

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab</th>
<th>Bevacizumab</th>
<th>Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of cycles</strong></td>
<td>1564</td>
<td>1763</td>
<td>1569</td>
</tr>
<tr>
<td><strong>Mean No. of cycles/patient</strong></td>
<td>7.1</td>
<td>8.1</td>
<td>7.2</td>
</tr>
<tr>
<td><strong>No. of cycles at full dose (%)</strong></td>
<td>1497</td>
<td>1716</td>
<td>1194</td>
</tr>
<tr>
<td></td>
<td>(95.7)</td>
<td>(97.3)</td>
<td>(76.1)</td>
</tr>
</tbody>
</table>
The addition of erlotinib to bevacizumab following induction therapy with bevacizumab-based chemotherapy significantly increases maintenance PFS.

The combination of bevacizumab and erlotinib is well tolerated, but with a substantial increase in diarrhoea and skin toxicity.

These results suggest that erlotinib may be active in patients with mCRC and provide a clinical rationale for double inhibition of VEGF and EGFR.

Overall survival and KRAS analyses are ongoing.
Acknowledgements

Patients and their families

Investigators from France, Austria and Canada:

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- LLEDÒ
- MABRO
- LOCHER
- RÉ
- LOUVET
- TUBIANA-MATHIEU
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- COLIN P
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- WENDEHENNE
- RAMEE
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- GARGOT
- MOULLET
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