Advances in our understanding of the role of EGFR- and VEGF-inhibitors in metastatic colorectal cancer

8th Annual Clinical Cancer Update
1.24.09

Emily Bergsland
UCSF
Helen Diller Family Comprehensive Cancer Center

Chemotherapy for Metastatic CRC
- Bolus 5-fluorouracil/leucovorin (5-FU/LV) was standard of care in US until 2000
- Additional combination chemotherapy regimens
  - IFL: irinotecan, 5-FU, and leucovorin
  - FOLFOX: oxaliplatin, leucovorin, and 5-FU
  - FOLFIRI: irinotecan, leucovorin, and 5-FU
  - FOLFOXIRI: FOLFOX + irinotecan
  - IROX: irinotecan and oxaliplatin
  - CapeOX: capecitabine and oxaliplatin
  - CapeIRI: capecitabine and irinotecan


Inhibition of VEGF
- Inhibits metastasis
  - Blocks VEGF-induced peritumor lymph drainage\(^1\)
  - Blocks VEGF(A)-induced dysfunctional angiogenesis\(^2\)
  - Inhibits invasion of circulation by the tumor\(^3\)
  - Decreases vascular density of tumor
- Increases killing of established tumors
  - Improves chemotherapy delivery to tumor


Bevacizumab
- Recombinant humanized monoclonal antibody to VEGF-A
- Selectively targets, binds to, and inhibits the activity of VEGF
- In combination with 5-FU-based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic CRC

Avastin (bevacizumab) Prescribing Information. Available at: http://www.rxlist.com/cgi/generic/avastin.htm

Mean Overall Survival Correlates with Availability of Effective Drugs
- Patients with three drugs (%)

3 drugs: 5-FU/LV, irinotecan, oxaliplatin.
**Survival Benefit When Bevacizumab Added to IFL**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bevacizumab + IFL (n=402)</th>
<th>IFL (n=411)</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (mo)</td>
<td>20.3</td>
<td>16.6</td>
<td>0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>10.6</td>
<td>6.2</td>
<td>0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>44.8</td>
<td>34.8</td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Median duration response (mo)</td>
<td>10.4</td>
<td>7.1</td>
<td>0.62</td>
<td>0.001</td>
</tr>
</tbody>
</table>


---

**Benefit of Adding Bevacizumab to FOLFOX4: E3200**

- 829 mCRC patients randomized to FOLFOX4, FOLFOX4 + bevacizumab, or bevacizumab alone
- Hypertension, bleeding, vomiting more common with bevacizumab + FOLFOX4
- Bowel perforation occurred at rate of 1% with bevacizumab

Response | FOLFOX4 | FOLFOX4 + bevacizumab | P-value*
----------|---------|-----------------------|---------|
Median OS, mos | 10.8 | 12.9 | 10.2 | 0.0011 |
Median PFS, mos | 4.7 | 7.3 | 2.7 | <0.0001 |
ORR, % | 8.6 | 22.7 | 3.3 | <0.0001 |

*For FOLFOX4 vs FOLFOX4 + bevacizumab


---

**NO16966: Bevacizumab improves PFS (modest) but not ORR when added to 1st-line oxaliplatin-based chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX or XELOX + Bevacizumab (n=699)</th>
<th>FOLFOX or XELOX + Placebo (n=701)</th>
<th>HR (97.5% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, (mo)</td>
<td>9.4</td>
<td>8.0</td>
<td>0.83</td>
<td>0.002</td>
</tr>
<tr>
<td>Median TTP, (mo)</td>
<td>6.9</td>
<td>6.0</td>
<td>0.84</td>
<td>0.003</td>
</tr>
<tr>
<td>Median OS, (mo)</td>
<td>21.3</td>
<td>19.9</td>
<td>0.89</td>
<td>0.0769</td>
</tr>
<tr>
<td>ORR*, %</td>
<td>38%</td>
<td>38%</td>
<td>0.76-1.03</td>
<td></td>
</tr>
</tbody>
</table>

PFS, progression-free survival; TTP, time to progression; OS, overall survival; ORR, overall response rate; HR, hazard ratio; CI, confidence interval.

*Independent review


---

**BICCC-C: Period 2 Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FOLFIRI + Bevacizumab (n=144)</th>
<th>mIFL + Bevacizumab (n=141)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (mo)</td>
<td>28.0</td>
<td>19.2</td>
<td>.037*</td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>87</td>
<td>60.5</td>
<td>-</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>9.0</td>
<td>8.3</td>
<td>0.66</td>
</tr>
<tr>
<td>Overall RR (%)</td>
<td>63.2</td>
<td>53.3</td>
<td>0.37</td>
</tr>
</tbody>
</table>

*Celecoxib did not impact safety or efficacy


---

**Bevacizumab + IFL: Selected Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Bevacizumab + IFL (n=393)</th>
<th>IFL (n=397)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3/4 event (%)</td>
<td>84.9</td>
<td>74.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Any hypertension (%)</td>
<td>22.4</td>
<td>8.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Grade 3/4 hypertension (%)</td>
<td>11.0</td>
<td>2.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Grade 3/4 diarrhea (%)</td>
<td>32.4</td>
<td>24.7</td>
<td>NS</td>
</tr>
<tr>
<td>Grade 3/4 leukopenia (%)</td>
<td>37.0</td>
<td>31.1</td>
<td>NS</td>
</tr>
<tr>
<td>Any thrombotic event (%)</td>
<td>19.4</td>
<td>16.2</td>
<td>NS</td>
</tr>
<tr>
<td>Any proteinuria (%)</td>
<td>26.5</td>
<td>21.7</td>
<td>NS</td>
</tr>
<tr>
<td>GI perforation (%)</td>
<td>1.5</td>
<td>0.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Summary: Bevacizumab and chemotherapy for mCRC

- First-line setting:
  - BEV enhances activity of IFL, 5 mo increase OS vs 5-FU
  - Incremental benefit of BEV added to XELOX or FOLFOX is modest (1 mo TTP, no diff OS or RR)
  - Utility of BEV + FOLFIRI has not been established

- BEV enhances activity of FOLFOX in 2nd line setting (2x RR, 2.5 mo increase in PFS, 2 mo increase OS)
- Utility of continued treatment past progression is unknown
- Additional studies ongoing

Cetuximab

- IgG1 chimerized anti-EGFR mAb
- Binds to EGFR domain with high affinity, prevents ligand binding and activation
- Mean t1/2=114 hours at recommended dosage – (400 mg/m² initial dose, then 250 mg/m² weekly)
- Approved as a single agent or in combination with irinotecan for patients with metastatic CRC who are refractory to irinotecan-based chemotherapy

BOND 1: Randomized Pivotal Trial in Metastatic Colorectal Cancer

- N=329
- Patients with mCRC who progressed during or within 3 mo after irinotecan
- EGFR+ CRC

Cetuximab + irinotecan
- Cetuximab (initial dose, 400 mg/m² then weekly infusion 250 mg/m²) + irinotecan (same as pre-study therapy) (n=218)
- Histamine receptor antagonist premedication given before at least the first cetuximab infusion.

Cetuximab
- Cetuximab (initial dose, 400 mg/m² then weekly infusion 250 mg/m²) (n=111)

Cetuximab with irinotecan (n=218)
- Objective Response Rate
  - 22.8% vs 10.8% (P=0.007)
- Median Duration of Response
  - 5.7 mo vs 4.2 mo (P=0.007)

Cetuximab as a single agent (n=111)
- Median TTP, mo
  - 4.1 vs 1.5 (Hazard ratio 0.54, 95% CI (0.42-0.71), P<0.001)

Cetuximab Randomized Pivotal Trial: Response Rates

Safety of Cetuximab + Irinotecan

- Adverse Event
  - Cetuximab + Irinotecan (n=212)
  - Single-agent Cetuximab (n=115)
  - P-value
  - 65.7 vs 43.5, <0.001
  - 0.4 vs 0, <0.001
  - 21.2 vs 1.7, <0.001
  - 13.7 vs 10.4, 0.49
  - 9.4 vs 5.2, 0.20
  - 7.1 vs 4.3, 0.47
  - 1.4 vs 13.0, <0.001
  - 0 vs 3.5, 0.01

Cetuximab
- IgG1 chimerized anti-EGFR mAb
- Binds to EGFR domain with high affinity, prevents ligand binding and activation
- Mean t1/2=114 hours at recommended dosage – (400 mg/m² initial dose, then 250 mg/m² weekly)
- Approved as a single agent or in combination with irinotecan for patients with metastatic CRC who are refractory to irinotecan-based chemotherapy