The left versus right colon cancer story

What is the truth?

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Ludwig-Maximilian-University of Munich, Germany

Three stages of truth \textit{(Schopenhauer)}
- Ridicule
- Violent opposition
- Acceptance for granted
Conflicts of Interest

- **Advisory Boards:**
  Merck, Amgen, Roche, Servier, Sanofi, Bayer, Novartis, Boehringer-Ingelheim, SIRTEX, MSD, BMS

- **Honorary fees:**
  Merck, Amgen, Roche, Servier, SIRTEX, MSD, BMS, Servier

- **Scientific grants:**
  Merck, Amgen, Roche, Servier, Boehringer-Ingelheim, SIRTEX, MSD, BMS, Pfizer, Shire
Sidedness affects treatment decisions

- **Molecular Profile**
  - **RAS wt**
    - CT doublet + moAb
    - Right-sided
  - **RAS mt**
    - Combination CT + bevacizumab
    - Left-sided
  - **BRAF mt**
    - CT triplet + bevacizumab

- **Most of the evidence**
- **20-40%**
- **60-80%**
### Prognostic Relevance of Primary Tumour Sidedness in Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Weight (%)</th>
<th>OS HR</th>
<th>95% CI</th>
<th>P-value</th>
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<td>AVF2107g</td>
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<td>CALGB80405</td>
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<td>1.39</td>
<td>(1.09, 1.79)</td>
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<td>FIRE-1</td>
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<td>1.54</td>
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<td>FIRE-3</td>
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<td>CRYSTAL</td>
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<td>(1.18, 2.09)</td>
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<td>FIRE-2</td>
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<td>1.5</td>
<td>(1.09, 2.33)</td>
<td>&lt;0.001</td>
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<tr>
<td>PRIME</td>
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<td>(1, 2.4)</td>
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<td>MAVERICC</td>
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<td>1.25</td>
<td>(0.77, 2)</td>
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<td>1.4</td>
<td>3.57</td>
<td>(1.92, 6.67)</td>
<td>&lt;0.0001</td>
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<tr>
<td>PEAK</td>
<td>143</td>
<td>0.2</td>
<td>1.9</td>
<td>(0.4, 9.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Summary (FE)**  
- **OS HR**: 1.54  
- **95% CI**: (1.43, 1.65)  
- **P-value**: <0.0001

**Summary (RE)**  
- **OS HR**: 1.56  
- **95% CI**: (1.43, 1.7)  
- **P-value**: <0.0001

**Heterogeneity**: $I^2 = 16.3\%$, 95% CI = (0%, 83.9%)  
- P-value = 0.162 (χ² test)

Clearly better outcome in LPT: **HR 1.5**
<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Right-sided location</th>
</tr>
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<tbody>
<tr>
<td>CRYSTAL</td>
<td>FOLFIRI + Cetuximab</td>
<td>19%</td>
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<td></td>
<td>FOLFIRI</td>
<td>27%</td>
</tr>
<tr>
<td>PRIME</td>
<td>FOLFOX + Panitumumab</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>FOLFOX</td>
<td>24%</td>
</tr>
<tr>
<td>FIRE-3</td>
<td>FOLFIRI + Cetuximab</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>FOLFIRI + Bev</td>
<td>25%</td>
</tr>
<tr>
<td>PEAK</td>
<td>FOLFOX + Panitumumab</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>FOLFOX + Bev</td>
<td>21%</td>
</tr>
<tr>
<td>CALGB</td>
<td>Chemo + Cetuximab</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Chemo + Bev</td>
<td>34%</td>
</tr>
</tbody>
</table>

Range: 19-34%
Bevacizumab
Effect of sidedness on survival
Pooled Analysis: NO16966 and AVF2107

Sidedness was determined in 1590 (72%) of 2214 pts
- 27% right
- 73% left

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT</td>
<td>bev + CT</td>
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<tr>
<td>Right side</td>
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<td></td>
</tr>
<tr>
<td>NO16966</td>
<td>N</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>7.6 (5.9, 9.9)</td>
</tr>
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<td></td>
<td>117</td>
<td>17.7 (14.7, 21.0)</td>
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<td>AVF2107</td>
<td>N</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>Median (95% CI)</td>
<td>8.7 (8.1, 10.6)</td>
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<tr>
<td></td>
<td>210</td>
<td>210</td>
</tr>
<tr>
<td>Pooled</td>
<td>N</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>Median (95% CI)</td>
<td>17.7 (14.7, 21.0)</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>107</td>
</tr>
</tbody>
</table>

HR (95% CI) p value
- 0.75 (0.61, 0.93) 0.008
- 0.82 (0.65, 1.03) 0.085

Left side

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT</td>
<td>bev + CT</td>
</tr>
<tr>
<td>NO16966</td>
<td>N</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td></td>
<td>386</td>
<td>8.5 (8.0, 9.0)</td>
</tr>
<tr>
<td></td>
<td>380</td>
<td>22.4 (20.5, 24.6)</td>
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<tr>
<td>AVF2107</td>
<td>N</td>
<td>199</td>
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<tr>
<td></td>
<td>Median (95% CI)</td>
<td>11.0 (10.2, 13.0)</td>
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<td></td>
<td>585</td>
<td>585</td>
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<tr>
<td>Pooled</td>
<td>N</td>
<td>386</td>
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<tr>
<td></td>
<td>Median (95% CI)</td>
<td>22.4 (20.5, 24.6)</td>
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<td></td>
<td>380</td>
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</table>

HR (95% CI) p value
- 0.76 (0.67, 0.86) <0.001
- 0.85 (0.74, 0.98) 0.028

Conclusions:
- Incomplete analysis
- Bevacizumab comparably improves OS in LSP and RSP
- Effect not significant in RSP

Loupakis BJC 2018
**TRIBE: Impact of Sidedness on OS**

Unselected pts

**LSP: HR 0.99**

**RSP: HR 0.56**

<table>
<thead>
<tr>
<th>Unselected pts</th>
<th>Right-sided</th>
<th>Left-sided</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFOXIRI + Bev</td>
<td>FOLFIRI + Bev</td>
</tr>
<tr>
<td>ORR</td>
<td>63.9%</td>
<td>54.6%</td>
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</tbody>
</table>

TRIBE: Impact of Sidedness on OS

RSP: FOLFOXIRI plus bevacizumab may be regarded as a preferred option in pts fit for combination and independent of their molecular status

LSP: Doublet plus bevacizumab remains the preferred option

Anti-EGFR agents

Effect of sidedness on survival

- Meta-analysis: chemo doublet +/- EGFR-i (PRIME, CRYSTAL)
- Meta-analysis: head-to-head comparisons: EGFR-i versus bevacizumab (CALGB, FIRE-3, PEAK)
PRIME (FOLFOX +/- Panitumumab): Effect of Sidedness


- **Clear benefit from Pmab**
- **No benefit from Pmab**

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmab + FOLFOX</td>
<td>30.3 (25.8, 36.1)</td>
<td>11.1 (8.1, 25.2)</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>23.6 (18.2, 26.9)</td>
<td>15.4 (9.1, 21.7)</td>
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<tr>
<td>HR</td>
<td>0.73 (0.57, 0.93)</td>
<td>0.87 (0.55, 1.37)</td>
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</table>
Meta-analysis: addition of an anti-EGFR agent to chemo

Overall Survival

**Left-sided mCRC**

<table>
<thead>
<tr>
<th>study</th>
<th>n</th>
<th>Weight (%)</th>
<th>OS HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIME</td>
<td>328</td>
<td>55.1</td>
<td>0.73</td>
<td>(0.57, 0.93)</td>
<td>&lt;0.0001</td>
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<tr>
<td>CRYSTAL</td>
<td>256</td>
<td>44.9</td>
<td>0.65</td>
<td>(0.5, 0.86)</td>
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</table>

Summary (FE) | 0.69 (0.58, 0.83) | <0.0001
Summary (RE) | 0.69 (0.58, 0.83) | <0.0001

Heterogeneity: I^2 = 0%, 95% CI = (0%, 99.7%)  
P-value = 0.533 (χ² test)

**Left-sided primary**  
Clear benefit from anti-EGFR therapy

**Right-sided mCRC**

<table>
<thead>
<tr>
<th>study</th>
<th>n</th>
<th>Weight (%)</th>
<th>OS HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIME</td>
<td>88</td>
<td>55.7</td>
<td>0.87</td>
<td>(0.55, 1.37)</td>
<td></td>
</tr>
<tr>
<td>CRYSTAL</td>
<td>84</td>
<td>44.3</td>
<td>1.08</td>
<td>(0.65, 1.81)</td>
<td></td>
</tr>
</tbody>
</table>

Summary (FE) | 0.96 (0.68, 1.35) | 0.802
Summary (RE) | 0.96 (0.68, 1.35) | 0.802

Heterogeneity: I^2 = 0%, 95% CI = (0%, 99.7%)  
P-value = 0.537 (χ² test)

**Right-sided primary**  
No benefit from anti-EGFR therapy

Holch J, Eur J Cancer
Head to head comparisons
anti-EGFR agents versus bevacizumab
FIRE-3
(FOLFIRI + Cetuximab versus FOLFIRI + Bevacizumab)
Effect of Sidedness

Meta-Analysis of Head to Head Comparisons

**Overall survival**

**Left-sided primary**
Clear benefit from anti-EGFR agents compared to bevacizumab

**Right-sided primary**
Strong trend in favor of bevacizumab

*Holch J, Eur J Cancer. 2017*
Meta-Analysis of Head to Head Comparisons
Progression-free survival

Comment
Comparable effects of sidedness on PFS and OS
H-to-H Comparisons: FIRE-3, PEAK, CALGB
Overall Survival according to sidedness

<table>
<thead>
<tr>
<th>Study</th>
<th>Right-Sided Primary Tumours</th>
<th>Left-Sided Primary Tumours</th>
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<tbody>
<tr>
<td></td>
<td>Chemo + anti-EGFR</td>
<td>Chemo + Bevacizumab</td>
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<tr>
<td>FIRE-3 (n=394)</td>
<td>18.3 mo</td>
<td>23.0 mo</td>
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<tr>
<td>CALGB (n=474)</td>
<td>13.7 mo</td>
<td>29.2 mo</td>
</tr>
<tr>
<td>PEAK (n=234)</td>
<td>17.5 mo</td>
<td>21.0 mo</td>
</tr>
</tbody>
</table>

Very poor survival in EGFR-i treated RPT
EGFR-i work even better in LSP
Bevacizumab works in LSP
Anti-EGFR agents

Effect of sidedness on ORR
Meta-analysis: addition of an anti-EGFR agent to chemo

**ORR: Left- and right-sided mCRC**

### Left-sided mCRC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Weight (%)</th>
<th>ORR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIME</td>
<td>328</td>
<td>65.7</td>
<td>1.9</td>
<td>(1.3, 2.7)</td>
<td>&lt;0.00001</td>
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<tr>
<td>CRYSTAL</td>
<td>280</td>
<td>34.3</td>
<td>3.99</td>
<td>(2.4, 6.6)</td>
<td>0.007</td>
</tr>
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</table>

Summary (FE): 2.45 (1.82, 3.3) <0.00001
Summary (RE): 2.69 (1.3, 5.57) 0.007

Heterogeneity: $I^2 = 81.6\%$, 95% CI = (7.5%, 99.9%)
P-value = 0.02 ($\chi^2$ test)

**Left-sided primary**
Clearly favors anti-EGFR treatment

### Right-sided mCRC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Weight (%)</th>
<th>ORR</th>
<th>95% CI</th>
<th>P-value</th>
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<tbody>
<tr>
<td>PRIME</td>
<td>88</td>
<td>54.2</td>
<td>1.4</td>
<td>(0.6, 3.1)</td>
<td>0.253</td>
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<tr>
<td>CRYSTAL</td>
<td>84</td>
<td>45.8</td>
<td>1.45</td>
<td>(0.58, 3.46)</td>
<td>0.253</td>
</tr>
</tbody>
</table>

Summary (FE): 1.42 (0.78, 2.6) 0.253
Summary (RE): 1.42 (0.78, 2.6) 0.253

Heterogeneity: $I^2 = 0\%$, 95% CI = (0%, 69.4%)
P-value = 0.955 ($\chi^2$ test)

**Right-sided primary**
Trend in favor of anti-EGFR treatment

**Meta-analysis: Head to head comparisons**

**ORR: Left- and right-sided mCRC**

**Left-sided mCRC**

<table>
<thead>
<tr>
<th>study</th>
<th>n</th>
<th>Weight (%)</th>
<th>ORR</th>
<th>95% CI</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>CALGB/SWOG 80405</td>
<td>325</td>
<td>57.7</td>
<td>1.6</td>
<td>(1.2, 2.3)</td>
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<tr>
<td>FIRE-3</td>
<td>306</td>
<td>27.3</td>
<td>1.37</td>
<td>(0.85, 2.19)</td>
<td></td>
</tr>
<tr>
<td>PEAK</td>
<td>107</td>
<td>15.1</td>
<td>1.3</td>
<td>(0.7, 2.5)</td>
<td></td>
</tr>
</tbody>
</table>

Summary (FE) 1.49 (1.16, 1.9) 0.002
Summary (RE) 1.49 (1.16, 1.9) 0.002

Heterogeneity: $I^2 = 9\%$, 95% CI = (0%, 88%)
P-value = 0.786 ($\chi^2$ test)

**Left-sided primary**

Clearly favors anti-EGFR treatment

**Right-sided mCRC**

<table>
<thead>
<tr>
<th>study</th>
<th>n</th>
<th>Weight (%)</th>
<th>ORR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB/SWOG 80405</td>
<td>149</td>
<td>55.2</td>
<td>1.1</td>
<td>(0.6, 2)</td>
<td></td>
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<tr>
<td>FIRE-3</td>
<td>88</td>
<td>28.2</td>
<td>1.11</td>
<td>(0.48, 2.59)</td>
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</tr>
<tr>
<td>PEAK</td>
<td>36</td>
<td>16.6</td>
<td>1.8</td>
<td>(0.6, 5.4)</td>
<td></td>
</tr>
</tbody>
</table>

Summary (FE) 1.2 (0.77, 1.87) 0.432
Summary (RE) 1.2 (0.77, 1.87) 0.432

Heterogeneity: $I^2 = 0\%$, 95% CI = (0%, 94.2%)
P-value = 0.728 ($\chi^2$ test)

**Right-sided primary**

Trend in favor of anti-EGFR treatment

# VOLFI

(FOLFOXIRI + Panitumumab versus FOLFOXIRI)

## Effect of intensified treatment in RPT vs LPT

<table>
<thead>
<tr>
<th></th>
<th>ORR (primary objective)</th>
<th>FOLFOXIRI + Pmab</th>
<th>FOLFOXIRI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full analysis set</strong></td>
<td>96</td>
<td>87.3%</td>
<td>60.6%</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Left</strong></td>
<td>78</td>
<td>90.6%</td>
<td>68.0%</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Right</strong></td>
<td>18</td>
<td>70.0%</td>
<td>37.5%</td>
<td>0.34</td>
</tr>
</tbody>
</table>

## Conclusion

In RPT there is a **discordant effect** of Pmab on ORR and PFS

Geissler M, et al. ASCO #3509, 2018
Later treatment lines

Effect of sidedness on OS
**Conclusions**

- Highly selected patient population
- BRAF V600 mutation
  - RC 4.7%
  - LC 0.8%
- Cetuximab is effective compared to BSC
- Effects smaller in right-sided than left-sided mCRC

*Patients who had previously been treated with a fluoropyrimidine, irinotecan, and oxaliplatin or had contraindications to treatment with these drugs*
What is the truth?
Continuum of DNA Alterations

According to Yamauchi M. et al., Gut 2012;61:847-54

CIMP: CPG-island methylation phenotype; MSI, microsatellite instability

*CIMP-high

MSI-high

BRAF Mutation

Anteil positive Fälle (%)

right-sided

left-sided

Caecum (n = 243) Colon ascendens (n = 295) Hepatic flexur (n = 46) Colon transversum (n = 91) Splenic flexur (n = 33) Colon descendens (n = 83) Colon sigmoideum (n = 314) Recto-sigmoid (n = 106) Rectum (n = 232)

According to Yamauchi M. et al., Gut 2012;61:847-54

*CIMP: CPG-island methylation phenotype; MSI, microsatellite instability
Prevalence of CMS According to Sidedness

608 patients with stage I-IV CRC

FIRE-3

<table>
<thead>
<tr>
<th>CMS</th>
<th>n/N</th>
<th>Median OS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS1</td>
<td>40/46</td>
<td>14.8</td>
<td>(8.5-21.1)</td>
</tr>
<tr>
<td>CMS2</td>
<td>69/127</td>
<td>31.9</td>
<td>(25.2-38.7)</td>
</tr>
<tr>
<td>CMS3</td>
<td>22/36</td>
<td>18.7</td>
<td>(na-37.4)</td>
</tr>
<tr>
<td>CMS4</td>
<td>62/104</td>
<td>24.8</td>
<td>(21.3-28.2)</td>
</tr>
</tbody>
</table>

Log-rank test, p<0.0001

CMS 2 in right and left-sided mCRC

Right-sided N=71

Left-sided N=244

35% CMS1: Immune
27% CMS2: Canonical
28% CMS3: Metabolic
12% CMS4: Mesenchymal

11% CMS2
45% CMS4
HR for OS According to Primary Tumor Location

Multivariate model

Model included primary tumor location (HR shown in graphic) and non-location based variables (HR in table below). Other variables considered for inclusion in the model but with $P > 0.1$ during model creation are shown in Supplementary Table 3.

<table>
<thead>
<tr>
<th>Non-Location Based Variables</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic at Diagnosis</td>
<td>1.52 (1.30–1.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mucinous/Signet Histology</td>
<td>1.49 (1.24–1.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BRAFV600 Mutation</td>
<td>1.83 (1.36–2.46)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>KRAS</td>
<td>1.32 (1.13–1.54)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HR for overall survival relative to rectum

1.0  2.0

Loree JM,.... Kopetz S; Clin Cancer Res 2018
FIRE-3:
Greater DpR correlates with longer OS


Depth of response correlated significantly with OS (two-sided Bravais Pearson test)

Δ = 8.1 months
Sidedness differentially affects the relation between EGFR-i induced ORR and OS

Discordance of ORR and OS in **right-sided** mCRC

DpR is predictor of OS in **left-sided** mCRC
Left versus right colon cancer story: My Take

RAS wt

Right-sided
- **T + EGFR-i**
  - if **ORR** is a primary goal

- **D/T + Bev**
  - if **OS** is a primary goal (default recommendation)

Left-sided
- **D + EGFR-i**
  - if **OS** is a primary goal (default recommendation)

- **D + Bev**
  - if EGFR-i are not accepted/tolerated

D: chemo doublet
T: chemo triplet
Clinical Practice Recommendation:

LPT RAS-wt mCRC:

- Define RAS- and BRAF mutation status upfront

- Prefer an anti-EGFR agent in 1st-line treatment if prolongation of OS is a primary goal (most patients)

- If anti-EGFR agents are not accepted or tolerated switch to a doublet plus bevacizumab
Clinical Practice Recommendation:

**RPT RAS-wt mCRC:**

- Focus on exploration of family history
- Define BRAF mutation and MSI status upfront

- **Preferred 1st-line treatment option:** triplet plus bevacizumab

- **Alternative option:** triplet plus anti-EGFR agent
  - if tumor reduction or conversion therapy is a primary goal
  - if you are willing to evaluate early tumor response (e.g. after 6-8 weeks)
  - in case of insufficient response: immediately switch to bev-based therapy