RIGHT VS LEFT SIDED COLON CANCER - SHOULD THE TREATMENT BE DIFFERENT?

Safiya Karim, MD, FRCPC
CAGPO Annual Meeting
October 1, 2017
Objectives

By the end of this presentation, you will be able to:

• Describe the biological, molecular and clinical differences between RCC and LCC

• Understand the prognostic value of primary tumour location in metastatic colon cancer

• Describe the predictive value of primary tumour location in the treatment of metastatic colon cancer

• Discuss the current guidelines that incorporate the primary tumour location in the treatment of metastatic colon cancer
Overview

- Case
- Background
- Individual Trial Data
- Meta-analyses
- Limitations
- Guidelines/Consensus Statements
Faculty/Presenter Disclosure

- Relationships with commercial interests:
  - Grants/Research Support: None
  - Speakers Bureau/Honoraria: None
  - Consulting Fees: None
  - Other: None
Disclosure of Commercial Support

• No Disclosures

• Potential for conflict(s) of interest: None
Mitigating Potential Bias

- Not applicable
Case – Mrs. K

- 63 yo F presented to the ER with a history of a 2 month change in bowel pattern and recent history of obstructive-like symptoms

- CT scan revealed a 5 cm obstructing ascending colon mass

- Numerous liver lesions were also visualized and were suspicious for metastatic disease

- Query peritoneal deposits
Case – Mrs. K

- Pre-op CEA = 52

- R hemicolecctiony:
  - Low-grade adenocarcinoma
  - Extension into the visceral peritoneum
  - 1/23 lymph nodes positive
  - Evidence of metastatic disease in omentum, appendix, mesentary and 1 peritoneal nodule
  - All RAS wild-type
Questions to Consider

- What is the estimated **prognosis** of this patient? Is it better or worse than a patient with left-sided metastatic colon cancer?

- What is the best **upfront treatment** for this patient
  a) Chemotherapy alone (FOLFIRI or FOLFOX)
  b) Chemotherapy + Bevacizumab
  c) Chemotherapy + Anti-**EGFR** (cetuximab or panitumumab)
Review: Prognostic vs. Predictive Factors

**Prognostic Marker**
Indicates the likelihood of an outcome regardless of the specific treatment

**Predictive Marker**
Indicates the likelihood of response to a given therapy
Colorectal cancer is the 2\textsuperscript{nd} most common cause of cancer death in the western world. Despite improvements in screening, 10-15\% of patients present with synchronous metastatic disease.

Several molecular and clinical characteristics have been identified that are prognostic or predictive of outcomes, i.e. MSI, KRAS, BRAF.
Sidedness as a Prognostic Marker

- Several studies in the 80s/90s studied sidedness as a prognostic factor in colon cancer
  - *Showed that RCC inferior OS compared to LCC*
  - *Limited by small sample sizes*

- Renewed interest in sidedness → ASCO 2016
ASCO 2016

GASTROINTESTINAL (COLORECTAL) CANCER

The relationship between primary tumor sidedness and prognosis in colorectal cancer.

Deborah Schrag, Shicheng Weng, Gabriel Brooks, Jeffrey A. Meyerhardt, Alan P. Venook
Left vs Right? What are the differences?

28% Range (19-38%)

72% Range (63-81%)

[Diagram showing brain functions]

Left vs Right? What are the differences?

1) Embryology
2) Blood supply
3) Molecular Characteristics
4) Clinical Characteristics

RCC associated with:
- Older age
- Female gender
- T3/T4
- Higher grade
- Mucinous
- Multiple vs single sites of metastatic disease

INDIVIDUAL TRIAL DATA
Studies with *EGFR* mAbs vs. chemo alone or BSC

1st line mCRC

- **CRYSTAL**
  - First line mCRC
  - Phase III
  - FOLFIRI
  - Cetux

- **PRIME**
  - First line mCRC
  - Phase III
  - FOLFOX
  - Pmab

2nd line mCRC

- **20050181**
  - Second line mCRC
  - Phase III
  - FOLFIRI + Pmab
  - FOLFIRI

3rd line + mCRC

- **NCIC CO.17**
  - Third line + mCRC
  - Phase III
  - Cetux
  - BSC
In both arms, LCCs had better OS compared to RCCs

<table>
<thead>
<tr>
<th>Parameter</th>
<th><strong>CRYSTAL</strong></th>
<th><strong>FOLFIRI + Cetuximab</strong></th>
<th><strong>FOLFIRI</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right-Sided Tumors (n = 33)</td>
<td>Left-Sided Tumors (n = 142)</td>
<td>Right-Sided Tumors (n = 51)</td>
</tr>
<tr>
<td>ORR Rate, %</td>
<td>42.4</td>
<td>72.5</td>
<td>33.3</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>3.55 (1.63-7.75)</td>
<td>1.39 (0.70-2.76)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td>PFS Median, mo</td>
<td>8.1</td>
<td>12.0</td>
<td>7.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.77 (1.08-2.91)</td>
<td>1.54 (0.96-2.46)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.02</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>OS Median, mo</td>
<td>18.5</td>
<td>28.7</td>
<td>15.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.93 (1.24-2.99)</td>
<td>1.35 (0.93-1.97)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.003</td>
<td>.11</td>
<td></td>
</tr>
</tbody>
</table>

CRYSTAL Trial – Predictive Impact

Only LCCs did better with the addition of Cetuximab

PRIME Trial – Predictive impact

Only LCC had improved OS with addition of Pmab

Median OS (95% CI), months

<table>
<thead>
<tr>
<th></th>
<th>Pmab + FOLFOX</th>
<th>FOLFOX</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>30.3 (25.8–36.1)</td>
<td>23.6 (18.2–26.9)</td>
<td>0.73 (0.57–0.93)</td>
</tr>
<tr>
<td>Right</td>
<td>11.1 (8.1–25.2)</td>
<td>15.4 (9.1–21.7)</td>
<td>0.87 (0.55–1.37)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; OS, overall survival; Pmab, panitumumab

PRIME – OS – 1st line

Douillard and Pignon. ESMO 2016.
2nd and 3rd line + Studies

■ 20050181 Study
  - No significant difference in OS or PFS between treatments for either LCC or RCC

■ NCIC CO.17 Study
  - Patients with LCC had a 6 months improvement in OS with cetuximab (10 mos vs 4.1 months, HR 0.49).
  - OS also improved in patients with RCC by 3 months but not statistically significant.
Studies comparing *EGFR* mAbs vs Bevacizumab

- **CALGB/SWOG 80405**
  - First line mCRC Phase III
  - FOLFIRI or FOLFOX (MD choice)
    - Chemo + Cetux
    - Chemo + Bev

- **FIRE-3**
  - First line mCRC Phase III
    - FOLFIRI + Cetux
    - FOLFIRI + Bev

- **PEAK**
  - First line mCRC Phase II
    - FOLFOX + Pmab
    - FOLFOX + Bev
CALGB/ SWOG 80405 – Prognostic Impact

80405: Overall Survival by Sidedness

<table>
<thead>
<tr>
<th>Side</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>732 (550)</td>
<td>33.3 (31.4-35.7)</td>
<td>1.55 (1.32-1.82)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Right</td>
<td>293 (242)</td>
<td>19.4 (16.7-23.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% Event Free vs Months From Study Entry

Graph shows a comparison of overall survival by sidedness, with longer survival times for left-sided patients compared to right-sided patients.
CALGB/ SWOG 80405 – Predictive Impact

80405: OS by Sidedness (Cetuximab)

<table>
<thead>
<tr>
<th>Side</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>376 (270)</td>
<td>36.0 (32.6-40.3)</td>
<td>1.87 (1.48-2.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right</td>
<td>143 (121)</td>
<td>16.7 (13.1-19.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% Event Free

Months From Study Entry

Presented at ASCO Annual Meeting '16
# FIRE-3 – Prognostic Impact

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FOLFIRI + Cetuximab (Right-Sided Tumors, n = 38)</th>
<th>FOLFIRI + Bevacizumab (Right-Sided Tumors, n = 50)</th>
<th>FOLFIRI + Cetuximab (Left-Sided Tumors, n = 157)</th>
<th>FOLFIRI + Bevacizumab (Left-Sided Tumors, n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR Rate, %</td>
<td>52.6</td>
<td>68.8</td>
<td>50.0</td>
<td>61.7</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.98 (0.97-4.08)</td>
<td>1.61 (0.85-3.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.09</td>
<td>.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS Median, mo</td>
<td>7.6</td>
<td>10.7</td>
<td>9.0</td>
<td>10.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>2.00 (1.36-2.93)</td>
<td>1.38 (0.99-1.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS Median, mo</td>
<td>18.3</td>
<td>38.3</td>
<td>23.0</td>
<td>28.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>2.84 (1.86-4.33)</td>
<td>1.48 (1.02-2.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>.04</td>
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<td></td>
</tr>
</tbody>
</table>

FIRE-3 - Predictive Impact

PEAK Study – Predictive Impact

Douillard and Pignon. ESMO 2016.
META-ANALYSES
Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials


Table 1. Source of patients for the analyses

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Trial characteristics</th>
<th>Phase of trial</th>
<th>Chemo-therapy backbone</th>
<th>Bevacizumab in control arm?</th>
<th>Anti-EGFR therapy</th>
<th>Treatment line</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRYSTAL [28, 45, 46]</td>
<td>III</td>
<td>FOLFIRI</td>
<td>No</td>
<td>Cetuximab</td>
<td>1st</td>
<td></td>
</tr>
<tr>
<td>FIRE-3 [28, 36]</td>
<td>III</td>
<td>FOLFIRI</td>
<td>Yes</td>
<td>Cetuximab</td>
<td>1st</td>
<td></td>
</tr>
<tr>
<td>PRIME [43, 44]</td>
<td>III</td>
<td>FOLFOX4</td>
<td>No</td>
<td>Panitumumab</td>
<td>1st</td>
<td></td>
</tr>
<tr>
<td>PEAK [35]</td>
<td>II</td>
<td>FOLFOX6</td>
<td>Yes</td>
<td>Panitumumab</td>
<td>1st</td>
<td></td>
</tr>
<tr>
<td>CALGB 80405 [27, 38]</td>
<td>III</td>
<td>FOLFIRI/ FOLFOX6</td>
<td>Yes</td>
<td>Cetuximab</td>
<td>1st</td>
<td></td>
</tr>
<tr>
<td>20050181 [48]</td>
<td>III</td>
<td>FOLFIRI</td>
<td>No</td>
<td>Panitumumab</td>
<td>2nd</td>
<td></td>
</tr>
</tbody>
</table>

# Prognostic Value – Pooled Analysis

## CT +/- Bev

<table>
<thead>
<tr>
<th>Category trial</th>
<th>No. deaths / No. entered</th>
<th>Hazard ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT + bevacizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIRE-3</td>
<td>38/50 106/149</td>
<td>1.48</td>
<td>[1.02–2.16]</td>
</tr>
<tr>
<td>CALGB80405</td>
<td>58/78 119/152</td>
<td>1.14</td>
<td>[0.80–1.61]</td>
</tr>
<tr>
<td>PEAK</td>
<td>12/14 33/54</td>
<td>2.86</td>
<td>[1.40–5.84]</td>
</tr>
<tr>
<td>Subtotal</td>
<td>108/142 258/355</td>
<td>1.41</td>
<td>[1.11–1.79]</td>
</tr>
<tr>
<td>CT alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRYSTAL</td>
<td>42/51 112/138</td>
<td>1.35</td>
<td>[0.93–1.97]</td>
</tr>
<tr>
<td>PRIME</td>
<td>44/49 136/159</td>
<td>1.27</td>
<td>[0.88–1.83]</td>
</tr>
<tr>
<td>20050181</td>
<td>36/39 123/148</td>
<td>1.51</td>
<td>[0.96–2.37]</td>
</tr>
<tr>
<td>Subtotal</td>
<td>122/139 371/445</td>
<td>1.36</td>
<td>[1.08–1.70]</td>
</tr>
</tbody>
</table>

### Test for heterogeneity:
- $P = 0.34$, $I^2 = 12\%$

## CT + EGFR inhibitor

<table>
<thead>
<tr>
<th>Category trial</th>
<th>No. deaths / No. entered</th>
<th>Hazard ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT + cetuximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIRE-3</td>
<td>31/38 86/157</td>
<td>2.84</td>
<td>[1.86–4.33]</td>
</tr>
<tr>
<td>CALGB80405</td>
<td>56/71 119/173</td>
<td>1.82</td>
<td>[1.27–2.56]</td>
</tr>
<tr>
<td>CRYSTAL</td>
<td>26/33 102/142</td>
<td>1.93</td>
<td>[1.24–2.99]</td>
</tr>
<tr>
<td>Subtotal</td>
<td>113/142 307/472</td>
<td>2.11</td>
<td>[1.68–2.66]</td>
</tr>
<tr>
<td>CT + panitumumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEAK</td>
<td>19/22 29/53</td>
<td>2.68</td>
<td>[1.31–5.46]</td>
</tr>
<tr>
<td>PRIME</td>
<td>34/39 126/169</td>
<td>1.58</td>
<td>[1.02–2.45]</td>
</tr>
<tr>
<td>20050181</td>
<td>28/31 129/150</td>
<td>2.01</td>
<td>[1.29–3.13]</td>
</tr>
<tr>
<td>Subtotal</td>
<td>81/92 284/372</td>
<td>1.90</td>
<td>[1.43–2.53]</td>
</tr>
</tbody>
</table>

### Test for heterogeneity:
- $P = 0.46$, $I^2 = 0\%$

**HR** = 1.38 (1.17-1.63), $p < 0.001$

**HR** = 2.03 (1.69-2.42), $p < 0.001$

### Predictive Value – Pooled

<table>
<thead>
<tr>
<th>Category</th>
<th>No. deaths / No. entered</th>
<th>Hazard ratio</th>
<th>HR interaction [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT + anti-EGFR CT ± bevacizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIRE3 - Left</td>
<td>86/157</td>
<td>106/149</td>
<td>2.08 [1.19–3.63]; P = 0.01</td>
</tr>
<tr>
<td>FIRE3 - Right</td>
<td>31/38</td>
<td>38/50</td>
<td></td>
</tr>
<tr>
<td>CALGB80405 - Left</td>
<td>119/173</td>
<td>119/152</td>
<td>1.77 [1.11–2.80]; P = 0.02</td>
</tr>
<tr>
<td>CALGB80405 - Right</td>
<td>56/71</td>
<td>58/78</td>
<td></td>
</tr>
<tr>
<td>PEAK - Left</td>
<td>29/53</td>
<td>33/54</td>
<td>0.86 [0.33–2.25]; P = 0.77</td>
</tr>
<tr>
<td>PEAK - Right</td>
<td>19/22</td>
<td>12/14</td>
<td></td>
</tr>
<tr>
<td>CRYSTAL - Left</td>
<td>102/142</td>
<td>112/138</td>
<td>1.66 [0.93–2.97]; P = 0.09</td>
</tr>
<tr>
<td>CRYSTAL - Right</td>
<td>26/33</td>
<td>42/51</td>
<td></td>
</tr>
<tr>
<td>PRIME - Left</td>
<td>126/169</td>
<td>136/159</td>
<td>1.19 [0.71–2.00]; P = 0.51</td>
</tr>
<tr>
<td>PRIME - Right</td>
<td>34/39</td>
<td>44/49</td>
<td></td>
</tr>
<tr>
<td>20050181 - Left</td>
<td>129/150</td>
<td>123/148</td>
<td>1.19 [0.67–2.10]; P = 0.55</td>
</tr>
<tr>
<td>20050181 - Right</td>
<td>28/31</td>
<td>36/39</td>
<td>1.50 [1.19–1.88]; P &lt; 0.001</td>
</tr>
<tr>
<td><strong>Total - Left</strong></td>
<td><strong>591/844</strong></td>
<td><strong>629/800</strong></td>
<td><strong>0.75 [0.67–0.84]; P &lt; 0.001</strong></td>
</tr>
<tr>
<td><strong>Total - Right</strong></td>
<td><strong>194/234</strong></td>
<td><strong>230/281</strong></td>
<td><strong>1.12 [0.87–1.45]; P = 0.381</strong></td>
</tr>
</tbody>
</table>

Between HR interaction heterogeneity: P = 0.47

CT + anti-EGFR better | CT ± bevacizumab better

The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials

Julian Walter Holch, Ingrid Ricard, Sebastian Stintzing, Dominik Paul Modest, Volker Heinemann

- 13 first-line RCTs and 1 prospective pharmacogenetic trial
- Prognostic and predictive impact of primary tumour location
- Predictive impact grouped into trials comparing anti-EGFR to chemo alone vs. anti-EGFR to Bevacizumab
Holch meta-analysis – Prognosis

<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>NO16966</td>
<td>1268</td>
<td>27</td>
<td>1.41</td>
<td>(1.22, 1.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FOCUS</td>
<td>1390</td>
<td>12.8</td>
<td>1.4</td>
<td>(1.2, 1.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>AGITG MAX</td>
<td>440</td>
<td>9.5</td>
<td>1.49</td>
<td>(1.18, 1.89)</td>
<td>0.001</td>
</tr>
<tr>
<td>AVF2107g</td>
<td>559</td>
<td>8.9</td>
<td>1.82</td>
<td>(1.43, 2.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CALGB80405</td>
<td>474</td>
<td>8.6</td>
<td>1.39</td>
<td>(1.09, 1.79)</td>
<td>0.009</td>
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<tr>
<td>FIRE-1</td>
<td>423</td>
<td>7.8</td>
<td>1.54</td>
<td>(1.19, 2)</td>
<td>0.001</td>
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<tr>
<td>FIRE-3</td>
<td>394</td>
<td>6.7</td>
<td>2.02</td>
<td>(1.53, 2.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRYSTAL</td>
<td>364</td>
<td>6.5</td>
<td>1.57</td>
<td>(1.18, 2.09)</td>
<td>0.002</td>
</tr>
<tr>
<td>FIRE-2</td>
<td>95</td>
<td>3.7</td>
<td>1.5</td>
<td>(1.09, 2.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRIME</td>
<td>416</td>
<td>2.8</td>
<td>1.6</td>
<td>(1, 2.4)</td>
<td></td>
</tr>
<tr>
<td>MAVERICC</td>
<td>376</td>
<td>2.3</td>
<td>1.25</td>
<td>(0.77, 2)</td>
<td>0.419</td>
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<td>PROVETTA</td>
<td>200</td>
<td>1.9</td>
<td>2.13</td>
<td>(1.25, 3.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>JACCRO-CC 05/06</td>
<td>110</td>
<td>1.4</td>
<td>3.57</td>
<td>(1.92, 6.67)</td>
<td>&lt;0.0001</td>
</tr>
<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): 1.54 (1.43, 1.65)  P-value = 0.162 (γ² test)

Summary (RE): 1.56 (1.43, 1.7)  P-value < 0.0001

Heterogeneity: I² = 16.3%, 95% CI = (0%, 83.9%)

### Overall Survival - Chemo+/-EGFR

#### Left-sided colorectal cancer

<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></td>
</tr>
<tr>
<td>CRYSTAL</td>
<td>280</td>
<td>44.9</td>
<td>0.65</td>
<td>(0.5, 0.86)</td>
<td></td>
</tr>
</tbody>
</table>

**Summary (FE)**
- Hazard ratio: 0.69
- 95% CI: (0.58, 0.83)
- P-value: <0.0001

**Summary (RE)**
- Hazard ratio: 0.69
- 95% CI: (0.58, 0.83)
- P-value: <0.0001

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

#### Right-sided colorectal cancer

<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)**
- Hazard ratio: 0.96
- 95% CI: (0.68, 1.35)
- P-value: 0.802

**Summary (RE)**
- Hazard ratio: 0.96
- 95% CI: (0.68, 1.35)
- P-value: 0.802

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

---

The figures illustrate the hazard ratios and 95% confidence intervals for overall survival in patients with left- and right-sided colorectal cancer, comparing chemotherapy with or without EGFR inhibitors. The summaries indicate a statistically significant survival benefit for chemotherapy plus EGFR inhibitors compared to chemotherapy alone for left-sided cancer, but not for right-sided cancer.
### Overall Survival - EGFR vs Bev

#### Left-sided colorectal cancer

<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>CALGB/SWOG 80405</td>
<td>325</td>
<td>53.8</td>
<td>0.77</td>
<td>(0.59, 0.99)</td>
<td>0.0003</td>
</tr>
<tr>
<td>FIRE-3</td>
<td>306</td>
<td>44.2</td>
<td>0.63</td>
<td>(0.48, 0.85)</td>
<td></td>
</tr>
<tr>
<td>PEAK</td>
<td>107</td>
<td>2</td>
<td>0.84</td>
<td>(0.22, 3.27)</td>
<td></td>
</tr>
</tbody>
</table>

Summary (FE) 0.71 (0.58, 0.85) 0.0003
Summary (RE) 0.71 (0.58, 0.85) 0.0003

Heterogeneity: $I^2 = 0\%$, 95% CI = (0%, 95.1%)
P-value = 0.575 ($\chi^2$ test)

#### Right-sided colorectal cancer

<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>CALGB/SWOG 80405</td>
<td>149</td>
<td>59.5</td>
<td>1.36</td>
<td>(0.93, 1.99)</td>
<td></td>
</tr>
<tr>
<td>FIRE-3</td>
<td>88</td>
<td>37.6</td>
<td>1.31</td>
<td>(0.81, 2.11)</td>
<td></td>
</tr>
<tr>
<td>PEAK</td>
<td>36</td>
<td>2.9</td>
<td>0.45</td>
<td>(0.08, 2.49)</td>
<td></td>
</tr>
</tbody>
</table>

Summary (FE) 1.3 (0.97, 1.74) 0.081
Summary (RE) 1.3 (0.97, 1.74) 0.081

Heterogeneity: $I^2 = 0\%$, 95% CI = (0%, 99.4%)
P-value = 0.468 ($\chi^2$ test)
Limitations

- Retrospective analyses
  - *Selection, systematic and random bias*
- Heterogeneity in line of treatment, comparator arm, *RAS/ BRAF* status
- Definition of RCC vs LCC
  - *Most studies have included transverse colon into RCC*
  - *Substantial heterogeneity within RCC and LCC?*
- No data on triplet therapy (i.e. FOLFOXIRI)
GUIDELINES/CONSENSUS STATEMENTS
Guidelines – NCCN

NCCN Guidelines Version 2.2017
Colon Cancer

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 1 of 10)

**Initial Therapy**
- FOLFOX ± bevacizumab
- CAPEOX ± bevacizumab
- FOLFOX + (cetuximab or panitumumab)³⁻⁵ (KRAS/NRAS WT and left-sided tumors only)
- FOLFIRI⁶ ± bevacizumab
- FOLFIRI⁶ + (cetuximab or panitumumab)³⁻⁵ (KRAS/NRAS WT and left-sided tumors only)
- FOLFOXIRI⁶ ± bevacizumab
- 5-FU/leucovorin (infusional preferred) ± bevacizumab⁷
- Capecitabine ± bevacizumab⁷

**Progression** → See COL-C 2 of 10

**Progression** → See COL-C 3 of 10

**Progression** → See COL-C 4 of 10

**Progression** → See COL-C 5 of 10

¹ Patient appropriate for intensive therapy²
Canadian Consensus Statement

The Predictive Impact of Primary Tumour Location in the Treatment of Metastatic Colorectal Cancer: A Canadian Consensus Statement

A.B.K. Abrahao¹*, S.Karim²,³*, B.Colwell⁴, S.Berry¹, J.Biagi²

*Co-first authors

Pending publication (October 2017)
Recommendations – 1st line

- Patients with RAS-wild-type LCC should receive chemotherapy with an \textit{EGFR} mAb (cetuximab or panitumumab)

- In patients with \textit{RAS} wild-type RCC, the combination of bevacizumab with standard chemotherapy remains the standard of care

- Extended RAS testing should be available in a timely manner to allow the appropriate selection of a biologic for first line treatment decisions.
Recommendations – 2\textsuperscript{nd} and 3\textsuperscript{rd} line

- At this time, there is no evidence to recommend the selective use of \textit{EGFR} mAbs in the second line setting based on tumour location.

- In the second line, patients who have not been treated with bevacizumab in the first line should be offered bevacizumab in combination with standard chemotherapy.

- In the third line or beyond, all \textit{RAS} wild type patients who have not previously been treated with an \textit{EGFR} mAb should be offered one.
Case Questions Revisited

- What is the estimated *prognosis* of this patient? Is it better or worse than a patient with left-sided metastatic colon cancer?
  - *OS is worse for patients with mRCC*
  - *mOS 15-23 months*

- What is the best *upfront treatment* for this patient:
  a) Chemotherapy alone (FOLFIRI or FOLFOX)
  b) Chemotherapy + Bevacizumab
  c) Chemotherapy + Anti-EGFR (cetuximab or panitumumab)
Summary and Conclusions

- RCC and LCC represent different entities and primary tumour location has a prognostic and predictive impact in mCRC

- Patients with metastatic RCC have inferior survival compared to LCC

- Having a LCC is predictive of response anti-EGFR mAb combined with chemotherapy in the 1st line setting
Summary and Conclusions

- Current treatment strategies should take into account the PTL to determine the best upfront targeted agent.
  - Application to pCODR for funding of panitumumab in combination with chemo for patients with LCC.

- Future clinical trials should stratify patients based on PTL.

- Further research should focus on understanding the patient and tumour related factors that underlie the differential benefits of biologics that have been observed based on PTL.
OMG, I have finally Discovered what’s wrong with my Brain:
on the left side, there is nothing right, and
on the right side, there is nothing left..