Cancer of the Large Intestines: the first 90 years

• SEER Database captures outcomes
• Staging standardized (Cuthbert Dukes -- 1932)
• Rectum distinguished from rest of large intestine
• Surgical techniques refined
• Fiberoptics
• Cross-sectional imaging
• Tumor mutational analysis
• Personalized Precision Medicine
Staging of Colorectal Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of tumor</th>
<th>A</th>
<th>B&lt;sub&gt;1&lt;/sub&gt;</th>
<th>B&lt;sub&gt;2&lt;/sub&gt;</th>
<th>C&lt;sub&gt;1&lt;/sub&gt;</th>
<th>C&lt;sub&gt;2&lt;/sub&gt;</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No deeper than</td>
<td></td>
<td>Not through</td>
<td>Through bowel</td>
<td>Not through</td>
<td>Through bowel</td>
<td>Distant</td>
</tr>
<tr>
<td></td>
<td>submucosa</td>
<td></td>
<td>bowel wall</td>
<td>bowel wall</td>
<td>bowel wall:</td>
<td>bowel wall:</td>
<td>metastases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lymph node</td>
<td>lymph node</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 90%</td>
<td>80–85%</td>
<td>70–75%</td>
<td>50–65%</td>
<td>25–45%</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

Adapted from Skarin. Slide Atlas of Diagnostic Oncology. Gower Medical Publishing; 1997:Fig 5.98.
COLON and RECTAL CANCER: SPLITTING, NOT LUMPING

RECTUM
Last 12 cm large intestine

Local recurrence risk:
Total Mesorectal Excision
Radiotherapy
RECTAL CANCER: SPLITTING

Total Mesorectal Excision
Radiation to circumferential margins

* Circumferential resection margin (CRM)
Metastatic Colorectal Cancer (mCRC)

- Stage III cecal cancer 3 months ago
- Stage II sigmoid cancer 8 yrs ago
- Rectal cancer w/ synchronous metastasis
ADVANCED COLORECTAL CANCER META-ANALYSIS PROJECT

Survival

Overall

Fig 2. Overall survival.

J Clin Oncol, 1992
Metastatic Colorectal Cancer:
Lumping By Decades

1970’s
5FU

1980’s
5FU
GITSG
RECTAL

1990’s
Oral Fluoro
Levamisole
Irinotecan

2000’s
LV/FU
FOLFOX/IRI
Bevacizumab
EGFR Ab’s

2010’s
CONTINUUM
OF CARE
BIOMARKERS
Colorectal Cancer: By Decades

1970’s
5FU

1980’s
5FU
GITSG
RECTAL

1990’s
ONCOGENES
Levamisole
Irinotecan

2000’s
LV/FU
FOLFOX/IRI
Bevacizumab
EGFR Ab’s

2010’s
CONTINUUM
OF CARE
BIOMARKERS

0% ADVANCED DISEASE CURE 10-15%

ADJUVANT

15th Annual West Coast Colorectal Cancer Symposium
Oct. 27, 2017
Colorectal Cancer: By Decades

- **1970’s**: 5FU
- **1980’s**: 5FU, GITSG, RECTAL
- **1990’s**: ONCOGENES, Levamisole, Irinotecan
- **2000’s**: LV/FU, FOLFOX/IRI, Bevacizumab, EGFR Ab’s
- **2010’s**: CONTINUUM OF CARE, BIOMARKERS

**ADJUVANT**
- **37% STAGE III SURVIVAL 70%**

**ADVANCED DISEASE SURVIVAL**: 6-8 months, 30-36 months

**ADVANCED DISEASE CURE**: 0%, 10-15%

**STAGE III SURVIVAL**
- 37%

**ADJUVANT**
- 37%
NCCN: Continuum of Care in Unresectable mCRC

**Oxaliplatin-Based First-Line**

- FOLFOX ± bev
- CapeOX ± bev

**Irinotecan-Based First-Line**

- FOLFIRI ± bev
- FOLFIRI ± cet or pan

**5-FU or Capecitabine ± Bevacizumab or FOLFOXIRI**

- 5-FU/LV or cape ± bev
- FOLFOXIRI ± bev

**Initial Therapy**

- Therapy after first progression
  - FOLFIRI or IRI ± aflib or bev
  - FOLFIRI or IRI ± cet or pan
  - FOLFIRI or CapeOX ± bev

- Therapy after second progression
  - Reg or Cet or pan or IRI
  - Reg or cet or pan or IRI
  - Reg or cet or pan or IRI

- Therapy after third progression
  - Clinical trial or BSC
  - Clinical trial or BSC
  - Clinical trial or BSC

**5-FU or Capecitabine ± Bevacizumab or FOLFOXIRI**

- 5-FU/LV or cape ± bev
- FOLFOXIRI ± bev

---

*a* RAS WT only. Aflib, aflibercept; Bev, bevacizumab; BSC, best supportive care; Cape, capecitabine; Cet, cetuximab; IRI, irinotecan; OX, oxaliplatin; Pan, panitumumab; Reg, regorafenib.

Pathologic Stages of Transformation of Colonic Epithelium

Pathway of Mutations in Colorectal Cancer

Prognostic Markers:
- Colonic Mucosa
- MLH 1
- MSH 2
- MSH 6
- MCC
- APC

Small Adenoma → Large Adenoma → Premalignant Changes → Colorectal Carcinoma

Colorectal Cancer, 2007
**Expanded RAS: Refining Patient Population**

Current actionable mutations:

- **KRAS** codons 12, 13, 61, 117, 146;
- **NRAS** codons 12, 13, 61, 117, 146;
- **BRAF** codon 600

- Use tumor tissue (FFPE) if available. Primary tumor ok.

- If tumor tissue not available, consider cfDNA (circulating free); wait 3 weeks after chemo or radiation to draw blood sample to avoid tumor necrosis/apoptosis effects [less evidence]

---

**BRAF V600E mutated Colorectal Cancer: Distinct Biology**

- Origin: serrated adenoma in proximal colon
- Microsatellite unstable
- Hyper-methylated
- RAS wild-type
- Patients: female, peritoneal, LN & brain metastases

---

Tran et al, *Cancer* 2011
**BRAF**$^{V600E}$ mCRC: Different Disease

Peritoneal implant

Extensive ascites

Courtesy Spencer Behr
Atreya et al, JNCCN, 2016
**BRAF** V600E mutations in mCRC: Poor Survival

Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial


Median OS = 9-10 mos

JCO, 2002
Sidedness: What is that?

Democritus 460 – 370 BC

The “laughing philosopher” because of his emphasis on the value of “cheerfulness”

Atomic Theory of the Universe
# Large Intestinal Cancer: Survival according to Primary Tumor Site

## Table 5. Survival According to Anatomical Segment Containing Primary Tumor

<table>
<thead>
<tr>
<th>Segment</th>
<th>No. of patients</th>
<th>5-yr survival ± SD</th>
<th>10-yr survival ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>669</td>
<td>0.222 ± 0.017</td>
<td>0.154 ± 0.016</td>
</tr>
<tr>
<td>Rectosigmoid</td>
<td>22</td>
<td>0.141 ± 0.087</td>
<td>0.071 ± 0.066</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>208</td>
<td>0.330 ± 0.034</td>
<td>0.196 ± 0.033</td>
</tr>
<tr>
<td>Descending</td>
<td>23</td>
<td>0.313 ± 0.102</td>
<td>—</td>
</tr>
<tr>
<td>Splenic flexure</td>
<td>15</td>
<td>0.467 ± 0.129</td>
<td>0.311 ± 0.153</td>
</tr>
<tr>
<td>Transverse</td>
<td>42</td>
<td>0.410 ± 0.082</td>
<td>0.358 ± 0.086</td>
</tr>
<tr>
<td>Hepatic flexure</td>
<td>18</td>
<td>0.286 ± 0.120</td>
<td>0.286 ± 0.120</td>
</tr>
<tr>
<td>Ascending</td>
<td>33</td>
<td>0.416 ± 0.087</td>
<td>0.360 ± 0.091</td>
</tr>
<tr>
<td>Cecum</td>
<td>98</td>
<td>0.232 ± 0.045</td>
<td>0.175 ± 0.050</td>
</tr>
<tr>
<td>Multiple segments</td>
<td>5</td>
<td>0.200 ± 0.179</td>
<td>0.200 ± 0.179</td>
</tr>
<tr>
<td>Indeterminable</td>
<td>4</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

Spratt JS, Spjut HJ. Cancer, 1976
Primary Tumor Site and Survival in NSABP studies

1021 patients from C-01 and R-01

### ECOG 2290 / CALGB 9092

#### Schema

<table>
<thead>
<tr>
<th>Arm A</th>
<th>5-FU Alone1</th>
<th>Arm B</th>
<th>PALA/5-FU1</th>
<th>Arm C</th>
<th>Oral Leucovorin/5-FU1</th>
<th>Arm D</th>
<th>IV Leucovorin/5-FU1</th>
<th>Arm E</th>
<th>5-FU/HFNa-2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>2600 mg (2.6 G) by continuous infusion over 24 hr</td>
<td>PALA</td>
<td>250 mg/m² IV over 10 minutes, day 1</td>
<td>Leucovorin</td>
<td>125 mg/m² PO hourly x 4 hours</td>
<td>Leucovorin</td>
<td>500 mg/m² IV over 2 hours</td>
<td>5-FU</td>
<td>750 mg/m²/day IV by continuous infusion for 5 days</td>
</tr>
<tr>
<td></td>
<td>Repeat weekly</td>
<td>5-FU</td>
<td>600 mg/m² bolus IV, 1 hour after last Leucovorin dose</td>
<td>Repeat weekly for a total of 6 weeks, then 2 weeks rest, then restart</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Repeat weekly for a total of 6 weeks, then 2 weeks rest, then restart</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>750 mg/m² 1 IV bolus weekly from day 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HFNa-2a 9 million units subcutaneously day 1, 3, 5 and 3 times weekly thereafter</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Stratification

- **Performance Status**
  - 0
  - 1, 2

- **Hepatic Metastases**
  - Yes
  - No

- **Measurable Disease**
  - Yes
  - No

- **Prior Chemotherapy**
  - Yes
  - No

N = 1120

Peter J. O'Dwyer et al. JCO 2001;19:2413-2421

©2001 by American Society of Clinical Oncology
ECOG 2290 / CALGB 9092

New standard: infusional 5FU

Peter J. O’Dwyer et al. JCO 2001;19:2413-2421
### ECOG 2290 / CALGB 9092

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>7.7</th>
<th>&lt; .001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left colon</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td>Right colon</td>
<td>10.9</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Yes</td>
<td>12.2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Measurable disease</td>
<td>15.8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>No</td>
<td>12.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Yes</td>
<td>12.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>20.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>No</td>
<td>12.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Yes</td>
<td>10.9</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Differentiation</td>
<td>10.9</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Well</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Treatment arms</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>5-FU alone</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>5-FU/S-5-FU</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>IV 5-FU</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>IFN-RI/5-FU</td>
<td>13.2</td>
<td>0.03</td>
</tr>
</tbody>
</table>

O'Dwyer et al, J Clin Oncol, 2001
ECOG 2290/CALGB 9092:
OS related to CpG Island Hypermethylation (CIMP)

ECOG 2290
5-FU based therapy
Frontline met CRC
N=188

HR 2.9, p<0.001
Median OS: 6 mo v 17 mo

Figure 1. Genetic pathways and associated clinicopathological characteristics in colorectal cancer. Modified from Soreide et al, Discovery Med, 2011.
CALGB/SWOG 80405

1\textsuperscript{st} LINE MET / ADVANCED COLORECTAL

\textbf{All RAS wt}

\begin{itemize}
  \item FOLFIRI or FOLFOX
  \item MD choice
\end{itemize}

\textbf{ESMO, SEP, 2014}

\begin{itemize}
  \item Chemo + Cetuximab
    \begin{itemize}
      \item OS = 32.0 mos
      \item PFS = 11.4 mos
    \end{itemize}
  \item Chemo + Bevacizumab
    \begin{itemize}
      \item OS = 31.2 mos
      \item PFS = 11.3 mos
    \end{itemize}
\end{itemize}

CONCLUSION: NO DIFFERENCE

\textbf{N = 526}

OS better than anticipated in both arms:
Treatment effect and/or Patient selection
CALGB 80405: Side of primary tumor

Methods

• Population
  – KRAS wt pts in main analysis
  – Pre-amendment KRAS mut pts
• Data extraction
  – Study chart, other supporting information if available
• Side of 1° determination
  – Definitive information:
    • Colonoscopy, surgical or imaging report
80405: Site of Primary Tumor

EXCLUDED:
- TRANSVERSE: N = 66
- NOT DETERMINED: N = 46

RIGHT
N = 293 (27%)

LEFT
N = 732 (68%)
<table>
<thead>
<tr>
<th></th>
<th>RIGHT-SIDED (N = 293)</th>
<th>LEFT-SIDED (N = 732)</th>
<th>TOTAL* (N = 1137)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>61.2</td>
<td>57.3</td>
<td>58.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Gender (M %)</td>
<td>54.9%</td>
<td>65.0 %</td>
<td>62.1%</td>
<td>0.002</td>
</tr>
<tr>
<td>Synchronous Stage IV</td>
<td>86.9%</td>
<td>76.0%</td>
<td>79.3%</td>
<td>0.0009</td>
</tr>
<tr>
<td>Prior Adjuvant</td>
<td>10.6%</td>
<td>15.7%</td>
<td>14.2%</td>
<td>0.03</td>
</tr>
<tr>
<td>FOLFOX / FOLFIRI</td>
<td>74.4 / 25.6</td>
<td>72.4 / 27.6</td>
<td>73.4 / 26.6</td>
<td>0.51</td>
</tr>
<tr>
<td>Primary in place</td>
<td>19.2%</td>
<td>29.6%</td>
<td>26.6%</td>
<td>0.0007</td>
</tr>
<tr>
<td>Pattern mets:</td>
<td></td>
<td></td>
<td></td>
<td>0.02**</td>
</tr>
<tr>
<td>liver only</td>
<td>27.5%</td>
<td>32.1%</td>
<td>30.9%</td>
<td></td>
</tr>
<tr>
<td>liver mets</td>
<td>40.5%</td>
<td>43.2%</td>
<td>42.8%</td>
<td></td>
</tr>
<tr>
<td>extra-hepatic</td>
<td>32.0%</td>
<td>24.7%</td>
<td>28.5%</td>
<td></td>
</tr>
</tbody>
</table>

*Transverse colon – 66 (excluded from analysis); unknown - 46

**Test of any liver metastases versus extrahepatic
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>
# Sidedness: Prognostic and Predictive

<table>
<thead>
<tr>
<th>KRAS wt N = 1025</th>
<th>R-sided Median OS (mo)</th>
<th>L-sided Median OS (mo)</th>
<th>HR 95% CI (adjusted*)</th>
<th>P (adjusted*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>19.4</td>
<td>33.3</td>
<td>1.55 (1.32, 1.82)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Cet</td>
<td>16.7</td>
<td>36.0</td>
<td>1.87 (1.48, 2.32)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Bev</td>
<td>24.2</td>
<td>31.4</td>
<td>1.32 (1.05, 1.65)</td>
<td>P = 0.01</td>
</tr>
</tbody>
</table>

### BIOLOGIC

<table>
<thead>
<tr>
<th>BIOLOGIC</th>
<th>SIDE OF PRIMARY</th>
<th>HR 95% CI</th>
<th>P (adjusted*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any biologic OS and PFS</td>
<td>Cetux v Bev; left</td>
<td>1.53 (1.13, 2.08)</td>
<td>P_{int} = 0.005</td>
</tr>
<tr>
<td></td>
<td>Cetux v Bev; right</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetux v Bev OS</td>
<td>Left</td>
<td>0.817 (0.69, 0.96)</td>
<td>p = 0.018</td>
</tr>
<tr>
<td>Cetux v Bev OS</td>
<td>Right</td>
<td>1.269 (0.98, 1.63)</td>
<td>p = 0.065</td>
</tr>
</tbody>
</table>
80405: Overall Survival by Sidedness and Biologic

- **Left/Bev**
  - Median (95%CI): 31.4 (28.3-33.6)

- **Left/Cet**
  - Median (95%CI): 36.0 (32.6-40.3)

- **Right/Bev**
  - Median (95%CI): 24.2 (17.9-30.3)

- **Right/Cet**
  - Median (95%CI): 16.7 (13.1-19.4)
CALGB/SWOG 80405: Limitations

- Only 1st-line therapy was specified by protocol. Analysis of subsequent lines underway.

- Not pre-planned so could not control for R and L imbalances, e.g. age, site(s) of metastases, primary in place or not.

- 80% stage IV at presentation.

- All of these patients had \textit{KRAS} wt tumors.
### PRIMARY TUMOR LOCATION AND SURVIVAL WITH EGF-R ANTIBODIES

#### Table 4. Prognostic results for RAS wild-type CRYSTAL, FIRE-3 and CALGB 80405 cetuximab trial patients, according to treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CRYS TAL</th>
<th>FIRE-3</th>
<th>CALGB 80405</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLIRI</td>
<td>FOLIRI + cetuximab</td>
<td>FOLIRI + bevacizumab</td>
</tr>
<tr>
<td>N</td>
<td>189</td>
<td>175</td>
<td>199</td>
</tr>
<tr>
<td>Right-sided tumors</td>
<td>n = 51</td>
<td>n = 138</td>
<td>n = 33</td>
</tr>
<tr>
<td>Left-sided tumors</td>
<td>n = 33</td>
<td>n = 142</td>
<td>n = 50</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>15.0</td>
<td>21.7</td>
<td>18.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.35 (0.93-1.97)</td>
<td>1.93 (1.24-2.99)</td>
<td>1.48 (1.02-2.16)</td>
</tr>
<tr>
<td>P value</td>
<td>0.12</td>
<td>0.003</td>
<td>0.04</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>7.1</td>
<td>8.9</td>
<td>8.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.54 (0.96-2.46)</td>
<td>1.77 (1.06-2.91)</td>
<td>1.38 (0.99-1.94)</td>
</tr>
<tr>
<td>P value</td>
<td>0.07</td>
<td>0.02</td>
<td>0.06</td>
</tr>
<tr>
<td>Rate, %</td>
<td>33.3</td>
<td>40.6</td>
<td>42.4</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>0.73 (0.39-1.38)</td>
<td>0.28 (0.13-0.61)</td>
<td>0.02 (0.36-1.07)</td>
</tr>
<tr>
<td>P value</td>
<td>0.33</td>
<td>0.001</td>
<td>0.09</td>
</tr>
</tbody>
</table>

^a Investigator choice.
^b Adjusted for treatment arm, protocol chemotherapy, prior adjuvant therapy, prior radiotherapy, age, sex, synchronous disease, in place primary, liver metastases.

CI, confidence interval; FOLIRI, fluorouracil, leucovorin and irinotecan; FOLFOX, fluorouracil, leucovorin and oxaplatin. HR, hazard ratio; OR, objective response rate; OS, overall survival; PFS, progression-free survival.

Arnold D et al, Ann Oncol, 2017
## Metastatic Colorectal Cancer: Does Side Matter?

<table>
<thead>
<tr>
<th>PUBLICATION (Study)</th>
<th>Patients N</th>
<th>Molecular Selection</th>
<th>Treatment</th>
<th>OUTCOME</th>
<th>RIGHT</th>
<th>LEFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Dwyer JCO, 2001 (E2290)</td>
<td>N = 1120</td>
<td>NONE</td>
<td>5FU VARIATIONS</td>
<td>OS (MOS)</td>
<td>10.9</td>
<td>15.8</td>
</tr>
<tr>
<td>Heinemann, ASCO, 2014 (FIRE-3 abs)</td>
<td>N =333</td>
<td>All RAS wt</td>
<td>FOLFIRI/BEV /CET</td>
<td>OS (MOS)</td>
<td>22.7</td>
<td>28.0</td>
</tr>
<tr>
<td>Von Einem, J Res Clin Oncol, 2014, AIO</td>
<td>N = 146 (AIO)</td>
<td>KRAS wt (95) KRAS mut (51)</td>
<td>CAPIRI/CAPOX/ CET</td>
<td>OS (MOS)</td>
<td>13.0</td>
<td>19.7</td>
</tr>
<tr>
<td>Loupakis, JNCI, 2015</td>
<td>N = 2053</td>
<td>NONE</td>
<td>FOLFIRI/BEV FUOX/BEV IFL/BEV</td>
<td>OS (MOS)</td>
<td>24.8</td>
<td>42.0</td>
</tr>
<tr>
<td>Brule, Eur J Canc, 2015 (CO-17)</td>
<td>N =399</td>
<td>KRAS wt</td>
<td>BSC v. BSC + CET</td>
<td>PFS (MOS)</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Moretto, The Oncologist, 2016</td>
<td>N = 75 (R=14; L=61)</td>
<td>RAS, BRAF wt</td>
<td>CET or Irino/CET</td>
<td>RR: PFS:</td>
<td>0%</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.3</td>
<td>6.6</td>
</tr>
</tbody>
</table>
CALGB/SWOG 80405:
Primary tumor location in KRAS wt mCRC

• Prognostic
  – Pts w/ L-sided primary have markedly better OS than pts w/ R-sided primary tumor regardless of treatment arm.

• Predictive
  – 1st-line Cetuximab and Bevacizumab have different treatment effects in subgroups defined by sidedness in this analysis.

SIDEDNESS CRITICAL IN PREDICTING EFFICACY OF EGF-R ANTIBODIES IN 1ST LINE MCRC
Sidedness Surrogate: Tumor Burden

• Right-sided colon cancer associated with greater tumor burden due to later diagnosis
  – Liquid stool, wider lumen in R colon
  – Colonic symptoms require greater mass and more infiltrating tumor
  – More time pre-diagnosis than Left-sided cancers
Possible Indicators of Tumor Burden

**DIRECT MEASURES**
- Laboratory parameters: LDH, CEA, WBC
- Volume / # sites of metastases

**INDIRECT EVIDENCE**
- SUGGESTS MORE TUMOR
  - Primary left in place
  - Goal palliation
- SUGGESTS LESS TUMOR
  - Recur post-adjuvant (under surveillance)
## CALGB/SWOG 80405: Sidedness and tumor burden

<table>
<thead>
<tr>
<th></th>
<th>RIGHT-SIDED (N = 167)</th>
<th>LEFT-SIDED (N = 330)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>195.5</td>
<td>196.5</td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>284.7 (225.2)</td>
<td>404 (528)</td>
<td></td>
</tr>
<tr>
<td># metastatic sites:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>53.9 %</td>
<td>55.9%</td>
<td>0.8168</td>
</tr>
<tr>
<td>2</td>
<td>33.9 %</td>
<td>30.1 %</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>11.5 %</td>
<td>13.1 %</td>
<td></td>
</tr>
<tr>
<td>Prior adjuvant therapy</td>
<td>12.0 %</td>
<td>18.8 %</td>
<td>0.0533</td>
</tr>
<tr>
<td>Primary in place at initiation of therapy</td>
<td>4.8 %</td>
<td>1.8 %</td>
<td>0.0937</td>
</tr>
<tr>
<td>Intent of treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative</td>
<td>86.4 %</td>
<td>83.1 %</td>
<td>0.3408</td>
</tr>
<tr>
<td>Curative</td>
<td>13.6 %</td>
<td>16.9 %</td>
<td></td>
</tr>
<tr>
<td>Pattern mets:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>liver only</td>
<td>30.3%</td>
<td>38.3%</td>
<td>0.0136*</td>
</tr>
<tr>
<td>liver mets plus</td>
<td>62.4%</td>
<td>73.3%</td>
<td></td>
</tr>
<tr>
<td>extra-hepatic only</td>
<td>37.0 %</td>
<td>25.8%</td>
<td></td>
</tr>
</tbody>
</table>

Venook et al, ASCO, 2017
Sidedness: Surrogate for Tumor Burden?

- Based on this data, there is no evidence in this population that patients with R-sided primary had greater tumor burden at the time of diagnosis.

- Differences in distribution of metastases and outcomes R v L appear to reflect differences in tumor biology.
Sidedness in mCRC: Biological surrogate

- Non-random distribution of mutations
  - *BRAF* R-sided, not enough to account for difference
- Transcriptional subtypes
- Hypermethylation
- Epiregulin, Amphiregulin
Correlative Studies
Tumor / Plasma / Serum > 44000 samples

• Comprehensive Molecular Analysis
  – Expanded RAS
  – Next-generation sequencing
    • Tumor DNA screen / Cell free, circulating tumor DNA
    • Tumor RNA (nanostring platform)
  – Genome-wide association study on germline DNA
  – Tumor transcriptome
  – Plasma proteomics
• Model CRC: Systems Biology approach

SWOG: HJ Lenz       ALLIANCE: F Innocenti
80405 Methods – Tumor Genetics

- DNA extracted from tumor specimens
- DNA mutations by PCR genotyping in 12 genes
  - AKT, APC, BRAF, CTNNB1, EGFR, FBXW7, HRAS, KRAS, MET, NRAS, PIK3CA, TP53
- MSI-H by mutation analysis of microsatellites
- Mutational Load by NGS (FoundationOne®) of 395 genes
  - Reported as N of mutations per Mb of target sequence
    - N mutations/Mb
Molecular Pathways to Colorectal Cancer

Serrated pathways
- Normal mucosa
- BRAF CIMP-H
- SSA
- MLH1 loss
- p16 loss
- MLST mutations e.g. TGFBR3 IGF1R
- SSAD
- MSS CRC

Conventional pathways
- Normal mucosa
- BRAF CIMP-H
- MSS CRC
- KRAS CIMP-L MSS CRC
- KRAS, CIMP-L MSS CRC
- Good prognosis
- Resistant to 5FU
- Sensitive to anti-EGFR therapy
- Standard prognosis
- Sensitive to 5FU
- Sensitive to anti-EGFR therapy
- Standard prognosis
- Sensitive to 5FU
- Resistant to anti-EGFR therapy

Familial pathways
- Lynch (germline mutation of a MMR gene)
- FAP (germline mutation of APC gene)
- Loss of remaining MMR allele, p53
- Hypomethylation
- Hundreds of TAs

Lynch
- Lynch
- APC
- TA
- Loss of remaining APC allele
- Hypomethylation

FAP
- FAP
- APC
- TA
- Loss of remaining APC allele
- Hypomethylation

**OS: BRAF V600E mutation**

N = 72 (14%)

### w/o sidedness adjust:

- **HR**$^{adj}$ 1.82
- (95% CI 1.37-2.44)
- p 0.0001

### w/ sidedness adjust:

- **HR** 1.67
- (95% CI 1.20-2.33)
- **P** = 0.0035
Overall survival: MSI-H

$N = 31$ (6.5%)

$\text{HR}_{\text{adj}}$ 0.84
(95% CI 0.51-1.39)
$p = 0.50$
**Consensus Molecular Subtypes of Colorectal Cancer**

<table>
<thead>
<tr>
<th>CMS1</th>
<th>CMS2</th>
<th>CMS3</th>
<th>CMS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI Immune</td>
<td>Canonical</td>
<td>Metabolic</td>
<td>Mesenchymal</td>
</tr>
<tr>
<td>14%</td>
<td>37%</td>
<td>13%</td>
<td>23%</td>
</tr>
</tbody>
</table>

- **CMS1**
  - MSI, CIMP high, hypermutation
  - SCNA high
  - **BRAF** mutations
  - Immune infiltration and activation
  - Worse survival after relapse

- **CMS2**
  - SCNA high
  - WNT and MYC activation

- **CMS3**
  - Mixed MSI status, SCNA low, CIMP low
  - Metabolic deregulation

- **CMS4**
  - SCNA high
  - Stromal infiltration, TGF-β activation, angiogenesis
  - Worse relapse-free and overall survival

**Figure 5** Proposed taxonomy of colorectal cancer, reflecting significant biological differences in the gene expression-based molecular subtypes. CIMP, CpG island methylator phenotype; MSI, microsatellite instability; SCNA, somatic copy number alterations.

OS – All Patients by CMS Subtype

Presented by: Heinz Josef Lenz      ASCO, 2017
Sidedness: independently Prognostic

- Age
- Race
- Gender
- Synchronous v metachronous
- Consensus Molecular Subtypes
- MSI, \textit{BRAF, NRAS, KRAS, HRAS}

\textit{Cox proportional hazard stratified: prior XRT, +/- adj chemotherapy}

\[ HR = 1.392 \ (1.032, \ 1.878), \ p = 0.031 \]

Venook, et al, ASCO, 2017
CALGB/SWOG 80405: Patience is a virtue

Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer
A Randomized Clinical Trial

Presented by:
80405: Sidedness Prognostic in KRAS mut patients

(KRAS mutant pts, pre-amendment cohort)

<table>
<thead>
<tr>
<th>KRAS mut** N = 213</th>
<th>Right 1° Median OS (mos)</th>
<th>Left 1° Median OS (mos)</th>
<th>Hazard Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>23.1</td>
<td>30.3</td>
<td>1.28 (0.95,1.73)</td>
</tr>
<tr>
<td>Cetuximab (N= 107)</td>
<td>23.3</td>
<td>27.9</td>
<td>1.31 (0.83, 1.46)</td>
</tr>
<tr>
<td>Bevacizumab (N=106)</td>
<td>23.0</td>
<td>31.1</td>
<td>1.26 (0.83, 1.92)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (mos)</th>
<th>Median PFS (mos)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>8.9</td>
<td>9.8</td>
<td>1.06 (0.78, 1.42)</td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>7.9</td>
<td>8.1</td>
<td>0.99 (0.65, 1.51)</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>10.2</td>
<td>12.6</td>
<td>1.12 (0.73, 1.71)</td>
<td></td>
</tr>
</tbody>
</table>
### 80405: Exploratory Analysis (wt v mut)

If true, we know less about RAS than we think we do

<table>
<thead>
<tr>
<th></th>
<th>Right 1° Median OS (mos)</th>
<th>Left 1° Median OS (mos)</th>
<th>Log Rank p (adjusted*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All pts</strong></td>
<td>19.4</td>
<td>33.3</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td><strong>KRAS wt</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cet</td>
<td>16.7</td>
<td>36.0</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Bev</td>
<td>24.2</td>
<td>31.4</td>
<td>P = 0.01</td>
</tr>
<tr>
<td><strong>KRAS mut</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cet</td>
<td>23.3</td>
<td>27.9</td>
<td></td>
</tr>
<tr>
<td>Bev</td>
<td>23.0</td>
<td>31.1</td>
<td></td>
</tr>
</tbody>
</table>

**KRAS wt N=1025**

**KRAS mut N=213**

* pre-amendment cohort

Presented by:
Selective Internal Radiation Therapy (SIRT)

- SIRT employs Yttrium-90 (Y-90) labelled resin microspheres as a liver-directed therapy (1)
  - Hepatic artery injection
  - Delivers a single large radiation dose to liver tumors
  - Radiation deposited over 3 weeks
  - FDA approved in 2002 for unresectable CRCLMs (2)

- Combining SIRT with first-line chemotherapy may improve control of CRC liver metastases and thereby improve overall survival (3, 4)

2. Colorectal cancer liver metastases.

SIRT + CHEMOTHERAPY v. CHEMOTHERAPY: COMBINED ANALYSIS

Wasan et al, Lancet Oncol, 2017
Overall Survival for mCRC Patients with Right-Sided Primary Tumours

Gibbs et al, World GI, 2017
Overall Survival for mCRC Patients with Left-Sided Primary Tumours

**Median Survival** (95% CI)
- **Chemo + SIRT**: 264 patients, 24.6 months (22.3–26.7)
- **Chemo**: 276 patients, 26.6 months (24.8–29.9)

**Hazard Ratio** 1.12 (0.92–1.36) p=0.279

Gibbs et al, World GI, 2017
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:

Initial Therapy

- FOLFOX ± bevacizumab
- CAPEOX ± bevacizumab
- FOLFOX + (Cetuximab or Panitumumab)³⁻⁵ (KRAS/NRAS WT and left-sided tumors only)

1st-line: R-sided ≠ EGFR Ab’s

If progression:
- See COL-C 2 of 10

Patient appropriate for intensive therapy²

- FOLFIRI⁶ + (Cetuximab or Panitumumab)³⁻⁵ (KRAS/NRAS WT and left-sided tumors only)
- FOLFOXIRI⁶ ± bevacizumab
- 5-FU/leucovorin (infusional preferred) ± bevacizumab⁷
- Capecitabine ± bevacizumab⁷

If progression:
- See COL-C 3 of 10
- See COL-C 4 of 10
- See COL-C 5 of 10

Patient not appropriate for intensive therapy²

- Infusional 5-FU + leucovorin ± bevacizumab
- Capecitabine ± bevacizumab
- (Cetuximab or Panitumumab)³⁻⁵ (category 2B) (KRAS/NRAS WT and left-sided tumors only or (Nivolumab or pembrolizumab) (dMMR/MSI-H only)³

If improvement in functional status:
- Consider initial therapy as above⁸

If no improvement in functional status:
- Best supportive care (See NCCN Guidelines, for Palliative Care)

See footnotes COL-C 6 of 10

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Location of Primary NCIC CO.17: Prognostic & Predictive for Cetuximab

unselected patients

Brule et al, Eur J Cancer, 2015
Location of Primary NCIC CO.17: Prognostic & Predictive for Cetuximab

KRAS wild-type

Brule et al, Eur J Cancer, 2015
NCCN Guidelines Version 2.2017
Colon Cancer

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:1 (PAGE 2 of 10)

Subsequent Therapy

FOLFIRI® ± (bevacizumab® [preferred] or ziv-afiblercept® or ramucirumab®)

or

Irinotecan® ± (bevacizumab® [preferred] or ziv-afiblercept® or ramucirumab®)

or

FOLFIRI® + (cetuximab or panitumumab) (KRAS/NRAS WT only)

or

Irinotecan® + (cetuximab or panitumumab) (KRAS/NRAS WT only)

or

(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)

See Subsequent therapy

Regorafenib®

or

Trifluridine + tipiracil®

or

Trifluridine + tipiracil®

See Subsequent therapy

Regorafenib®

or

Trifluridine + tipiracil®

or

(Nivolumab or pembrolizumab)*

(dMMR/MSI-H only)

See Subsequent therapy

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Sidedness in mCRC

What we think we know

• Predictive and prognostic
  – Validated in numerous other data sets
• RAS status not determinant w/ R-sided primary
• Prognostic independent of specific mutations so far
• Not clear if sidedness also impacts subsequent treatment
Sidedness in mCRC

What we know we do not know

• Sidedness is a surrogate for something – but for what?

• Possible explanations include:
  – Cell of origin (Embryologic)
  – Microbiome
  – Something else?
Embryology: The origin of the colon

- Rathke’s pouch
- Lung bud
- Liver
- Gallbladder
- Ventral pancreatic bud
- Yolk sac (vitelline duct)
- Cecal bud
- Allantois
- Cloaca

Pharyngeal pouches 1-4

Esophagus
Stomach
Celiac artery
Dorsal pancreatic bud

Superior mesenteric artery
Inferior mesenteric artery

Foregut
Midgut
Hindgut

Colon Cancer Sidedness

- Transverse colon
- Splenic flexure
- Right colon (ascending)
- Midgut (right-sided)
- Cecum
- Hindgut (left-sided)
- Left colon (descending)
- Rectum
- Sigmoid colon
MICROBIOME

slides courtesy P. Turnbaugh
Fusobacterium nucleatum in CRC tissue: Tumor location

Mima et al, Clin and Trans Gastroenterology, 2017
Dietary Patterns and Colorectal Cancer risk: Classified by *Fusobacterium nucleatum* in tissue

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P Value Trend</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prentice Dietary Pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall colorectal cancer</td>
<td>913,569</td>
<td>907,676</td>
<td>912,395</td>
<td>909,922</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>No. of cases (n = 1010), No. (%)</td>
<td>250 (24.5)</td>
<td>248 (24.3)</td>
<td>268 (26.3)</td>
<td>253 (24.8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age adjusted HR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>0.93 (0.77-1.11)</td>
<td>0.90 (0.75-1.08)</td>
<td>0.79 (0.61-0.95)</td>
<td>&lt;0.01</td>
<td>NA</td>
</tr>
<tr>
<td>Multivariable HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>0.95 (0.80-1.14)</td>
<td>0.95 (0.79-1.14)</td>
<td>0.85 (0.69-1.03)</td>
<td>&lt;0.01</td>
<td>NA</td>
</tr>
<tr>
<td>F. nucleatum-positive colorectal cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (n = 125), No. (%)</td>
<td>43 (34.4)</td>
<td>26 (20.8)</td>
<td>34 (27.2)</td>
<td>22 (17.6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age adjusted HR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>0.54 (0.33-0.88)</td>
<td>0.67 (0.42-1.05)</td>
<td>0.40 (0.24-0.67)</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Multivariable HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>0.56 (0.34-0.92)</td>
<td>0.70 (0.44-1.26)</td>
<td>0.43 (0.23-0.72)</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>F. nucleatum-negative colorectal cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (n = 884), No. (%)</td>
<td>237 (23.2)</td>
<td>232 (24.6)</td>
<td>234 (26.2)</td>
<td>231 (25.8)</td>
<td>NA</td>
<td>0.01</td>
</tr>
<tr>
<td>Age adjusted HR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>1.01 (0.83-1.22)</td>
<td>0.96 (0.79-1.16)</td>
<td>0.88 (0.73-1.08)</td>
<td>0.15</td>
<td>NA</td>
</tr>
<tr>
<td>Multivariable HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>1.04 (0.86-1.26)</td>
<td>1.00 (0.83-1.22)</td>
<td>0.95 (0.77-1.17)</td>
<td>0.47</td>
<td>NA</td>
</tr>
</tbody>
</table>

Western Dietary Pattern

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P Value Trend</th>
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<tbody>
<tr>
<td>Overall colorectal cancer</td>
<td>913,569</td>
<td>910,456</td>
<td>910,325</td>
<td>911,936</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>No. of cases (n = 1010), No. (%)</td>
<td>244 (23.8)</td>
<td>274 (27.0)</td>
<td>243 (23.8)</td>
<td>252 (25.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age adjusted HR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>1.24 (1.04-1.48)</td>
<td>1.21 (1.00-1.46)</td>
<td>1.46 (1.18-1.82)</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Multivariable HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>1.19 (1.00-1.43)</td>
<td>1.12 (0.92-1.36)</td>
<td>1.29 (1.01-1.62)</td>
<td>0.05</td>
<td>NA</td>
</tr>
<tr>
<td>F. nucleatum-positive colorectal cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (n = 125), No. (%)</td>
<td>75 (20.0)</td>
<td>33 (26.4)</td>
<td>33 (26.4)</td>
<td>34 (27.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age adjusted HR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>1.42 (0.84-2.40)</td>
<td>1.50 (0.64-2.85)</td>
<td>1.62 (1.12-2.39)</td>
<td>0.01</td>
<td>NA</td>
</tr>
<tr>
<td>Multivariable HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>1.37 (0.81-2.31)</td>
<td>1.40 (0.88-2.53)</td>
<td>1.65 (0.98-2.90)</td>
<td>0.05</td>
<td>NA</td>
</tr>
<tr>
<td>F. nucleatum-negative colorectal cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (n = 884), No. (%)</td>
<td>219 (24.5)</td>
<td>242 (27.3)</td>
<td>230 (25.3)</td>
<td>223 (25.9)</td>
<td>NA</td>
<td>0.23</td>
</tr>
<tr>
<td>Age adjusted HR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>1.75 (1.03-2.92)</td>
<td>1.16 (0.65-1.92)</td>
<td>1.42 (1.11-1.87)</td>
<td>0.006</td>
<td>NA</td>
</tr>
<tr>
<td>Multivariable HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (Reference)</td>
<td>1.20 (0.60-2.34)</td>
<td>1.08 (0.58-1.93)</td>
<td>1.25 (0.69-2.32)</td>
<td>0.12</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; NA, not applicable.

<a> According to prentice or western dietary score quartiles in the combined cohort of the health professionals follow-up study (1986-2012) and the nurses' health study (1980-2012).

<sup>a</sup> Stratified by age, calendar year, and sex and adjusted for total caloric intake (kilocalories per day).

<sup>b</sup> The model was further adjusted for body mass index, physical activity, smoking status, family history of colorectal cancer, endoscopy, alcohol consumption, dietary fiber intake, supplemental vitamin intake, and use of aspirin or nonsteroidal anti-inflammatory drugs ( NSAIDS ) or aspirin ( 32 tablets/week).
Fusobacterium nucleatum and colon cancer survival

Yu et al, Cell, 2017

Cohort 2

Survival Probability

RFS survival [months]

F. nucleatum abundance

Non-Recurrence

Recurrence

Para-tumor

Tumor

Para-tumor

Tumor

Univariable risk factor

F. nucleatum abundance

(high vs low)

AJCC stage

(III vs II)

Gender

(Male vs Female)

Pathological differentiation

(Poor vs Well & Moderate)

Penetration

(Serosa vs Muscular)

Tumor size

(>15cm² vs ≤ 15cm²)

Age

(≥60 vs <60)

HR (95% CI)  P

4.19(2.108-8.328) <0.001

2.369(1.291-4.445) 0.006

2.127(0.986-4.562) 0.054

1.213(0.65-2.266) 0.544

1.152(0.454-2.925) 0.766

0.977(0.528-1.807) 0.940

0.671(0.37-1.216) 0.189

HR = 4.3 (2.16 - 8.54)

logrank P = 6e-08

HR = 3.75 (2.4 - 5.9)

logrank P = 6e-10

Validation set

Survival Probability

RFS survival [months]
Fusobacterium nucleatum: promotes chemoresistance?

Yu et al, Cell, 2017
Targeting the Colorectal Cancer Stem Cell

Blocking of Signals from the Stromal Niche That Support the Survival of CSCs and Dedifferentiation of Colon-Cancer Cells

Differentiated cancer cells

Dedifferentiation

CSCs

Therapy targeted at blocking signals from the stromal-cell niche

Stromal signals

CSC niche is not maintained

Interaction Between Host, Bacteria, and Immune System in Oncogenesis
Statistical modeling of CALGB 80405 (Alliance) identifies influential factors in metastatic colorectal cancer (CRC) dependent on primary (1st) tumor side

Leon Furchtrott1*, David Gagge2*, Borna Hasani2, Ivan Khil1, Diane Wied1, Kelly Byrne1, Robert Milliner1, Andrew B. Nason2, Donna P. Venook4.

Background
CALGB/ALLiance is a recent Phase III clinical trial of FOLFOX4 and FOLFIRI in patients with metastatic CRC who progressed on FOLFOX4 (primary end point was overall survival).

Methods
We used clinical data from the full patient population (N = 477) to build a multivariable Cox proportional hazards model for OS and PFS. 18 variables were included in the model, which includes variables such as age, sex, primary tumor side, liver metastasis, and number of prior therapies. The model was then used to predict the probability of survival for each patient.

Results
The model was able to accurately predict survival for each patient with a c-index of 0.72 for OS and 0.67 for PFS. The model showed a significant improvement in survival for patients with right-sided primary tumors compared to left-sided tumors.

Conclusions
The model identified right-sided primary tumors as a significant predictor of better survival in patients with metastatic CRC. This finding is consistent with previous studies indicating that right-sided primary tumors have a better prognosis than left-sided tumors.

Presented by:
GNSHealth
TOWARDS PRECISION

*Identify curable patients early*
*Recognize unfavorable biology*
*Avoid useless therapies*

- Needs different therapy
- Will do well no matter treatment
- Locally curable disease only
- Potentially curable
TOWARDS PRECISION

Identify curable patients early
Recognize unfavorable biology
Avoid useless therapies