Opportunities and Challenges for Neoadjuvant Trials in GI Cancers

Alan Venook, MD
UC San Francisco
What is a biomarker?

• “Any measurable diagnostic indicator that is used to assess the risk or presence of disease”

• AKA “*in vitro* diagnostic”
  [www.fda.gov](http://www.fda.gov)

• Includes tests for:
  – Future risk
  – Screening
  – Diagnosis
  – Prognosis
  – Staging
  – Monitoring response
  – Optimizing treatment outcomes
GI “Neoadjuvant” Trials

Accruing

• N1048
  – Selective XRT in rectal cancer

• C80303
  – PET-directed combined modality in esophageal

Completed / successor planned

• A021101
  – Borderline resectable pancreas pilot
GI “Neoadjuvant” Trials

Completed

• C80405
  – Chemo /biologic metastatic CRC

Pending

• A021302
  – PET-directed chemotherapy in gastric cancer
Opportunities: GI Neoadjuvant Setting

• Standard approach
  – Esophageal
  – Gastric
  – Rectal
• Large volume disease
• Access to tissue
  – Liver commonly site of metastases
Opportunities: CRC Neoadjuvant Setting

• CRC Liver metastases amenable to curative approach
• 30% of patients with synchronous disease
• Ready access to tissue
CALGB/SWOG 80405: FINAL DESIGN

1° Endpoint: Overall Survival

N = 1140

mCRC 1st-line

KRAS wild type (codons 12,13)

STRATA: FOLFOX/FOLFIRI
Prior adjuvant
Prior XRT

FOLFIRI or FOLFOX
MD choice

Chemo + Cetuximab

Chemo + Bevacizumab
## CALGB/SWOG 80405: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ARM A CHEMO + BEV N=559 (%)</th>
<th>ARM B CHEMO + CETUX N=578 (%)</th>
<th>TOTAL N=1137 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (range)</td>
<td>59 (21-85)</td>
<td>59 (20-89)</td>
<td>59 (20-89)</td>
</tr>
<tr>
<td>Male</td>
<td>348 (62.3)</td>
<td>349 (60.4)</td>
<td>697 (61.3)</td>
</tr>
<tr>
<td>Primary in place</td>
<td>157 (28)</td>
<td>154 (27)</td>
<td>311 (28)</td>
</tr>
<tr>
<td>Palliative Intent</td>
<td>465 (86.4)</td>
<td>458 (82.5)</td>
<td>923 (84.4)</td>
</tr>
<tr>
<td>FOLFOX / FOLFIRI (%)</td>
<td>73 / 27</td>
<td>74 / 26</td>
<td>73 / 27</td>
</tr>
</tbody>
</table>
### CALGB/SWOG 80405: Baseline Characteristics
**Resected Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Kras WT codons 12/13</th>
<th></th>
<th>Resected Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=1137</td>
<td></td>
<td>n=180</td>
</tr>
<tr>
<td></td>
<td>Chemo + Bev</td>
<td></td>
<td>Chemo + Bev</td>
</tr>
<tr>
<td></td>
<td>n=559</td>
<td></td>
<td>n=75</td>
</tr>
<tr>
<td></td>
<td>Chemo + Cetux</td>
<td></td>
<td>Chemo + Cetux</td>
</tr>
<tr>
<td></td>
<td>n=578</td>
<td></td>
<td>n=105</td>
</tr>
<tr>
<td>Age, years</td>
<td>59 (21–85)</td>
<td></td>
<td>55 (24–82)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>59 (20–89)</td>
<td></td>
<td>55 (21–79)</td>
</tr>
<tr>
<td>Male, %</td>
<td>62.3</td>
<td></td>
<td>64.0</td>
</tr>
<tr>
<td>Non-Caucasian, %</td>
<td>14.6</td>
<td></td>
<td>9.3</td>
</tr>
<tr>
<td>FOLFOX, %*</td>
<td>73</td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>Prior Radiation, %*</td>
<td>14.5</td>
<td></td>
<td>8.0</td>
</tr>
<tr>
<td>Prior Adjuvant Chemotherapy, %*</td>
<td>8.9</td>
<td></td>
<td>6.7</td>
</tr>
<tr>
<td>Palliative intent, %</td>
<td>86.4</td>
<td></td>
<td>62.7</td>
</tr>
<tr>
<td>Primary in place, %</td>
<td>28</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Liver metastases only, %</td>
<td>29.3</td>
<td></td>
<td>53.3</td>
</tr>
<tr>
<td>Achieve NED:</td>
<td>132 /180</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Stratification Factor
### CALGB/SWOG 80405: OS from Randomization

*(NED Post-Surgery)*

<table>
<thead>
<tr>
<th>RAS</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>65 (17)</td>
<td>78.8 (63 – NR)</td>
<td>0.52 (0.2-1.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mut</td>
<td>11 (5)</td>
<td>47.9 (13.4 - NR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Number of Patients at Risk**

| RAS Mut | 11 | 9  | 5  | 2  | 0  | 0  |
| RAS WT  | 65 | 63 | 34 | 19 | 2  | 1  |

**Survival Probability**

![Survival Probability Graph](image-url)
Challenges: GI Neoadjuvant Setting

- Coordination
- Cost
- Invasive
- Heterogeneity of tumor
- Delay treatment
BEV beyond PD

FOLFOX ± bevacizumab
or CapeOX ± bevacizumab
or FOLFOX ± panitumumab
(KRAS/NRAS wild-type [WT] gene only)

FOLFOX + cetux

FOLFIRI ± bevacizumab
or FOLFIRI ± ziv-afibercept
or Irinotecan ± bevacizumab
or Irinotecan ± ziv-afibercept
or FOLFIRI + (cetuximab or panitumumab)
(KRAS WT gene only)

(Cetuximab or panitumumab) (KRAS/NRAS WT gene only) + irinotecan;
for patients not able to tolerate combination, consider single
agent (cetuximab or panitumumab) (KRAS/NRAS WT gene only)
or Regorafenib

Regorafenib (if not given previously)
or Clinical trial or Best supportive care

MAINTENANCE
HOLIDAYS
REPEAT LINE

OTHER
Challenges: GI Neoadjuvant Setting

- Coordination
- Cost
- Invasive
- Heterogeneity of tumor
- Delay treatment
- Risk
General Schema: *Matched Patient PDX-Directed Clinical Trial*

**Stage 1**
“Umbrella” protocol enrolls patients for tumor tissue to develop PDX

**Stage 2**
Each patient PDX is tested for multiple drug/drug combinations

**Stage 3**
Based on drug responses in PDX, patients are enrolled in human clinical trials

- **Stage 4**
  - Molecular analyses – responders/non-responders
  - Tumor Bank resource for future hypothesis testing

- **Stage 5**
  - Definitive clinical trial - path to registration

**Participating Medical Centers**