Can we Refine the Selection for Adjuvant Treatment in Stage III Colon Cancer?

Alberto Sobrero
Ospedale Policlinico San Martino
Genova Italy
Refine the selection: 4 levels

1. T and N sub-categories
2. Classical and newer pathological molecular factors
3. LB
4. Duration and regimen of adjuvant CT
5. So what.... in our practice
The problem

50% chances of cure by surgery only
70% chances of cure with surgery followed by doublet

not true for every stage III patient
Stage III, stem-like subtype has a poor prognosis and no oxaliplatin benefit: MOSAIC Results validate C-07

Stage III

○ Recurrence Free

- Others
  - Time (years)
  - Others: 362 288 266 243 212 156 36 0
  - Stem-like: 226 158 132 119 108 75 13 0

p < 0.001
HR = 1.562

- Others
- Stem-like

\[ p = 0.796 \]
\[ HR = 0.953 \]

Independence of oxaliplatin in Stage III colon cancer:

FL+oxaliplatin

FULV

katherine.pogue-geile@nsabp.org
Prognostic value of the Immunoscore in stage III patients

- 1062 patients with IS, 973 treated with mFOLFOX6 and 89 treated with CAPOX 178 patients with non conclusive results for IS

**DFS**

<table>
<thead>
<tr>
<th>DFS Free Survival Probability</th>
<th>N</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS High</td>
<td>100 (9.4%)</td>
<td>17</td>
</tr>
<tr>
<td>IS Int.</td>
<td>499 (47.0%)</td>
<td>133</td>
</tr>
<tr>
<td>IS Low</td>
<td>463 (43.6%)</td>
<td>167</td>
</tr>
</tbody>
</table>

**Logrank P < 0.0001**

HR = 1.67 (95%CI 1.02-2.80)  
HR = 2.42 (95%CI 1.47-3.99)
Stage III

Tumor deposits

Stem like

IS

Gunderson JCO 2010
Stage III RFS by ctDNA positivity

Post-Treatment ctDNA – All Patients

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events</th>
<th>2-yr RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ctDNA Negative</td>
<td>74</td>
<td>11</td>
<td>82%</td>
</tr>
<tr>
<td>ctDNA Positive</td>
<td>15</td>
<td>10</td>
<td>27%</td>
</tr>
</tbody>
</table>

HR: 7.1, p < 0.001

(Tie J et.al, ASCO 2018)
SU2C CRC Dream Team: Early treatment of occult metastatic disease following standard adjuvant therapy in stage III CRC

Aparna Parikh, M.D.

Surgery → SOC Adjuvant

- cDNA assessment for residual disease
- Exploratory cohorts:
  - Positive → All other patients → FOLFIRI x 6 months
  - Negative → SOC observation
- Exploratory cohorts:
  - MSI patients → Nivolumab
  - BRAF V600 patients → Enco/Bni/Cmab x 6 months
- Exploratory cohorts:
  - Exploratory cohorts:
  - Exploratory cohorts:
  - Exploratory cohorts:
  - Exploratory cohorts:
  - Exploratory cohorts:

Massachusetts General Hospital Teacher Cancer Center

Stand Up To Cancer
Proposed CIRCULATE IDEA Trial Design

Key Eligibility
- High-risk stage 2 or Low-risk stage 3 (T1-3 N1) colon cancer
- BRAF Wild-type
- MSS/pMMR
- Pre-Ope ctNDA Positive and Post-Ope ctDNA Negative

Primary Endpoints
- Rate of ctDNA Positive at 3 months
- DFS

Monitoring by ctDNA analysis for 2 years

Control arm CAPOX 4 cycles (3 months)

Analysis of ctDNA @ 3months

No Chemo

Chemo by Investigator's choice

Experimental arm No chemo

Analysis of ctDNA @ 3months

No Chemo

Monitoring by ctDNA analysis for 2 years

F/U for 7 years

Note: +ve, positive; -ve, negative
Refine the selection: 4 levels

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Primary Outcomes Analysis

- 3m: 74.6%
- 6m: 75.5%

3-yr DFS diff. = -0.9%,
95% CI, (-2.4 to 0.6%)

DFS HR = 1.07
95% CI, 1.00 to 1.15
DFS by risk group and duration of therapy

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Duration</th>
<th>Event</th>
<th>3 Year Est (95% CI)</th>
<th>HR (95% CI)</th>
<th>Sup p</th>
<th>NI p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-3 N1</td>
<td>3 Months</td>
<td>657</td>
<td>83.1 (81.8-84.4%)</td>
<td>1.01 (0.90-1.12)</td>
<td>0.9193</td>
<td>0.0256</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>656</td>
<td>83.3 (82.1-84.6%)</td>
<td>Reference</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>T4 or N2</td>
<td>3 Months</td>
<td>1016</td>
<td>62.7 (60.8-64.6%)</td>
<td>1.12 (1.03-1.23)</td>
<td>0.0108</td>
<td>0.5233</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>919</td>
<td>64.4 (62.6-66.4%)</td>
<td>Reference</td>
<td>--</td>
<td>--</td>
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</table>

<table>
<thead>
<tr>
<th>Years from Randomization</th>
<th>T1-3 N1</th>
<th>T3 N1</th>
<th>T4 or N2</th>
<th>T5 or N2</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>3744</td>
<td>3313</td>
<td>2634</td>
<td>2622</td>
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<tr>
<td>1</td>
<td>3727</td>
<td>3336</td>
<td>2099</td>
<td>2151</td>
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<tr>
<td>2</td>
<td>2796</td>
<td>1934</td>
<td>1640</td>
<td>1655</td>
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<tr>
<td>3</td>
<td>1064</td>
<td>527</td>
<td>531</td>
<td>586</td>
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<td></td>
<td>292</td>
<td>301</td>
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<tr>
<td>5</td>
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<td>107</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
DFS Comparison by Regimen

**FOLFOX**

- **3-month Duration**: 73.6%
- **6-month Duration**: 76.0%

3-yr DFS diff. = -2.4%
95% CI, (-4.3 to -0.5%)

**CAPOX**

- **3-month Duration**: 75.9%
- **6-month Duration**: 74.8%

3-yr DFS diff. = 1.1%
95% CI, (-1.3 to 3.5%)

Interaction p-value = 0.0051
Refine the selection: 4 levels

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The classical questions by the informed stage III pt

1. What are my chances of cure after surgery only?
2. How much can I add with 6 mo FP alone?
3. How much can I add with 6 mo OX based CT?
4. How much do I loose if I get only 3 mo OX based CT?
A new approach to refining pt selection now

- Cannot use control data from initial trials

- Worked backward starting from most recent IDEA data

- Some groups have few events → metaregression model to predict 3 yr DFS

- Projected from 3 to 5 yr (0-3 75%; 3-5 15%; >5 10%) × HR 1.2

- Subtracted the effects of OXALI: average 3 trials HR 0.78 → estimate of FP alone

- Subtracted the effects of FP: 6 trials average HR 0.7 → estimated 5 surgery alone

- Subtracted the effects of 3 months vs 6 months oxali as per IDEA HR 1/1.07

Sobrero, Puccini, Shi, Grothey, Andre, Shields, and Bruzzi. Submitted to JCO, 2019
Predicted long term DFS according to different Rx

- T1N1a: 83.1%
- T2N1b: 64.4%
- T3N1a: 59.0%
- T3N1b: 50.4%
- T4N1a: 37.6%
- T4N1b: 28.4%
- T3N2b: 13.2%
- T4N2b: 2.9%

Various treatments: Solo chirurgia, Fluoropirimidina, FOLFOX/CAPOX 3 mesi, FOLFOX/CAPOX 6 mesi

Sobrero, Puccini, Shi, Grothey, Andre, Shields, and Bruzzi. Submitted to JCO, 2019
Can we Refine the Selection for Adjuvant Treatment in Stage III Colon Cancer?

1. Yes, $\rightarrow$ T+N based px within stage III
2. Further refining by classical and new path and molec factors
3. Further individualizing risk by LB
4. Then, use clinical judgment and SDM to decide for
   • No treatment (few cases)
   • FP only
   • Doublets for 3 months
   • Doublets for 6 months
   • More intense treatment regimens