Adjuvant Treatment Colon Cancer

Alberto Sobrero
IRCCS Policlinico San Martino Genova Italy

Disclosures: Roche Merck Sanofi Amgen Bayer Servier Astrazeneca, Lilly, Incyte
adjuvant

1. Size of benefit in stage II and III
2. Toll to pay
3. 3 vs 6
4. Why stage II is so complex
5. Algorithm for stage II
6. Refinement of decision making
Colon Cancer: adjuvant

STAGE

II
- HIGH RISK
  - Fluoropyrimidine
  - + 2-5%
- LOW RISK
  - No Rx

III
- Fluoropyrimidine
  - + 10-15%
- Folfox – FLOX-CAPOX
  - + 15-20%
Peripheral Sensory Neuropathy

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>During Tx</td>
<td>48.1</td>
<td>31.4</td>
<td>12.5</td>
</tr>
<tr>
<td>6 months</td>
<td>30.9</td>
<td>7.2</td>
<td>1.4</td>
</tr>
<tr>
<td>1 year</td>
<td>22.2</td>
<td>4.2</td>
<td>1.2</td>
</tr>
<tr>
<td>2 years</td>
<td>14.4</td>
<td>2.9</td>
<td>0.5</td>
</tr>
<tr>
<td>3 years</td>
<td>12</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>4 years</td>
<td>8.8</td>
<td>2.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

During Tx, 6 months, 1 year, 2 years, 3 years, 4 years
IDEA: ADVERSE EVENTS 3 vs 6 months

NEURO  2 to 6 times lower
DIARRHEA  20% to 30% lower
MUCOSITIS  2  times lower
H+F SYN  2 to 3 times lower
Primary Outcomes Analysis

Why making it difficult

Primary Outcomes Analysis

Presented by: Qian Shi, PhD on behalf of IDEA collaborators

Duration 3-yr DFS

<table>
<thead>
<tr>
<th>Duration</th>
<th>3-yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3m</td>
<td>74.6 %</td>
</tr>
<tr>
<td>6m</td>
<td>75.5 %</td>
</tr>
</tbody>
</table>

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

DFS HR = 1.07
95% CI, 1.00 to 1.15

N Patients At risk
6424 6410
5446 5530
4464 4477
3000 3065
1609 1679
826 873
321 334

Years from Randomization

Duration
3 Months
6 Months
Why making it difficult?

1. because small differences (1 to 4%) matter to pts
2. because IDEA showed that risk and regimen matter
3. because we will never have better data than these ones
Pts’ attitude: FIGHTERS vs FATALISTS

Considering the toxicities and inconveniences suffered, what % of cure rate would you be willing to sacrifice for a shorter treatment duration (3 mo)? N=45

<table>
<thead>
<tr>
<th>Potential reduction in cure rate</th>
<th>% responders</th>
<th>Definition of attitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2%</td>
<td>30%</td>
<td>fighter</td>
</tr>
<tr>
<td>2-4%</td>
<td>30%</td>
<td>fatalist</td>
</tr>
<tr>
<td>&gt;4 %</td>
<td>30%</td>
<td>fatalist</td>
</tr>
</tbody>
</table>

Percent of Patients Who Would Be Treated Again for Various Absolute Reductions in Relapse Rate. N 150

- Oxaliplatin
- No Oxaliplatin

Reduction in Risk of Recurrence

Love N. ASCO 2007
Why making it difficult?

1. *because small differences (1 to 4%) matter to pts*
2. *because IDEA showed that risk and regimen matter*
3. *because we will never have better data than these ones*
DFS by risk group and duration of therapy
DFS Comparison by Regimen

**FOLFOX**

- **3m** 73.6%
- **6m** 76.0%
- 3-yr DFS diff. = -2.4%
  95% CI, (-4.3 to -0.5%)

**CAPOX**

- **3m** 75.9%
- **6m** 74.8%
- 3-yr DFS diff. = 1.1%
  95% CI, (-1.3 to 3.5%)

Interaction p-value = 0.0051

Presented by: Qian Shi, PhD on behalf of IDEA collaborators
DFS Comparison by Risk Group and Regimen

**3-yr DFS % Diff. (95% CI)**
- T4 or N2
  - FOLFOX
    - 3m: 81.9 (80.2 – 83.6)
    - 6m: 83.5 (81.9 – 85.1)
  - XELOX
    - 3m: 85.0 (83.1 – 86.9)
    - 6m: 83.1 (81.1 – 85.2)

**3-yr DFS % Diff.**
- T1-3, N1
  - FOLFOX: -1.6 (-3.8 to 0.6)
  - XELOX: 1.9 (-0.8 to 4.6)

**HR 3m vs. 6m**
- FOLFOX: 1.10 (0.96 – 1.26)
- XELOX: 0.85 (0.71 – 1.01)
DFS Comparison by Risk Group and Regimen

3-yr DFS % Diff.  
-3.2 (-6.6 to 0.2)

HR  
1.20 (1.07 – 1.35)

3-yr DFS % Diff.  
0.1 (-3.9 to 4.1)

HR  
1.02 (0.89 – 1.17)
DFS Comparison by Risk Group

Percent Without Event

N2

T4
Clinical decision making in stage III colon cancer

1. FATALIST: always 3 months of CAPOX (11/11), even high risk

2. FIGHTERS:
   - low risk (T1-3 N1): always 3 months of CAPOX (11/11)
   - high risk N2: usually 3 months CAPOX (8/11); 6 months (3/11)
   - high risk T4: usually 6 months CAPOX (3/11) or FOLFOX (2/11)
Study Schema
• T4
• Poorly differentiated
• Invasion (vascular/lymphatic/perineural)
• Inadequate nodal harvest (<10 /<12)
• Obstruction
• Perforation

• HR ≥ 1.2  corresponding to 3.1% reduction in 5yr DFS (82.3% in 6mo to 79.2% in 3mo)
IDEA: ADVERSE EVENTS 3 vs 6 months

NEURO  2 to 6 times lower
MUCOSITIS  2 times lower
H+F SYN  2 to 3 times lower
DIARRHEA  20% to 30% lower

Neurotoxicity in IDEA stage II

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<tr>
<th></th>
<th>G2</th>
<th>G3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Mucos</td>
<td>26%</td>
<td>9%</td>
</tr>
<tr>
<td>H+F</td>
<td>&lt;0.0001</td>
<td>2%</td>
</tr>
<tr>
<td>Syn</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Diar</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>5-yr DFS</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>3m</td>
<td>80.7%</td>
<td></td>
</tr>
<tr>
<td>6m</td>
<td>83.9%</td>
<td></td>
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Events/Total
299/1639
254/1634
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients 3 month arm</th>
<th>Patients 6 month arm</th>
<th>HR (3m/6m)</th>
<th>Favors 3 months</th>
<th>Favors 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPOX</td>
<td>1006</td>
<td>979</td>
<td>1.018</td>
<td></td>
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</tr>
<tr>
<td>FOLFOX</td>
<td>615</td>
<td>622</td>
<td>1.408</td>
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<table>
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<tr>
<th>T stage</th>
<th>Patients 3 month arm</th>
<th>Patients 6 month arm</th>
<th>HR (3m/6m)</th>
<th>Favors 3 months</th>
<th>Favors 6 months</th>
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<tr>
<td>T1-3</td>
<td>1091</td>
<td>1094</td>
<td>1.217</td>
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</tr>
<tr>
<td>T4</td>
<td>544</td>
<td>538</td>
<td>1.094</td>
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</table>

<table>
<thead>
<tr>
<th>Inadequate Nodal Harvest</th>
<th>Patients 3 month arm</th>
<th>Patients 6 month arm</th>
<th>HR (3m/6m)</th>
<th>Favors 3 months</th>
<th>Favors 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>311</td>
<td>304</td>
<td>1.242</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1308</td>
<td>1307</td>
<td>1.162</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>5-yr DFS</td>
<td>Duration</td>
<td>5-yr DFS</td>
<td></td>
<td></td>
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<tr>
<td>----------</td>
<td>---------</td>
<td>----------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3m</td>
<td>81.7%</td>
<td>3m</td>
<td>79.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6m</td>
<td>82.0%</td>
<td>6m</td>
<td>86.5%</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Events/Total</th>
<th>171/1020</th>
<th>159/999</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Events/Total</th>
<th>128/619</th>
<th>95/635</th>
</tr>
</thead>
</table>
ADJUVANT THERAPY OF STAGE II IS VERY CONTROVERSIAL

1. What is high risk stage II?  ➔ > 20% risk of recurrence…

2. When is the risk > 20%?  ➔ N and or T4 and or G3 ….

3. Is DFS a surrogate of OS in stage II  ➔ no…

4. Is the benefit in DFS alone sufficient…?  ➔ may be…

5. Is the long term OS Benefit of FP 0,3, 5%  ➔ …

6. What is the size of Benefit of oxali for stage II  ➔ 0% OS 5-10% DFS…

7. If doublet is used, which regimen and duration  ➔ CAPOX/FOLFOX? 3/6?…
Algorithm for treatment decision in stage II colon cancer

Competing risks for non cancer death (age and co-morbidities)

- Low
  - Risk "high" (>20%...)
    - N<10-12
      - Consider 6 mo FP or 3 mo CAPOX
    - T4
      - Other risk factors G3, et al.
        - MMR testing
          - pMMR / MSS
          - dMMR / MSI-H
            - Consider 3 mo CAPOX only if T4
            - No adjuvant CT

- High
1. Size of benefit in stage II and III
2. Toll to pay
3. 3 vs 6
4. Why stage II is so complex
5. Algorithm for stage II
6. Refinement of decision making
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

Gunderson JCO 2010
STAGE III WITH AND WITHOUT TUMOR DEPOSITS

![Graph showing disease-free survival probability over time with and without tumor deposits.](image)

- **No tumor deposits**: 1758 events, 494 observed events
- **Tumor deposits**: 184 events, 67 observed events

Logrank p-value: 0.0079

N at risk:
<table>
<thead>
<tr>
<th>Time since random assignment (years)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>No tumor deposits</td>
<td>1758</td>
<td>1565</td>
<td>1357</td>
<td>1079</td>
<td>705</td>
<td>373</td>
<td>129</td>
</tr>
<tr>
<td>Tumor deposits</td>
<td>184</td>
<td>157</td>
<td>125</td>
<td>93</td>
<td>59</td>
<td>31</td>
<td>13</td>
</tr>
</tbody>
</table>

Delattre, Andre Svrcek et al. ASCO 2019
Stage III, stem-like subtype has a poor prognosis and no oxaliplatin benefit: MOSAIC Results validate C-07

Stage III

\[
p < 0.001 \\
\text{HR} = 1.562
\]

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Others</th>
<th>Stem-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>156</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>212</td>
<td>108</td>
</tr>
<tr>
<td>9</td>
<td>243</td>
<td>119</td>
</tr>
<tr>
<td>8</td>
<td>266</td>
<td>132</td>
</tr>
<tr>
<td>7</td>
<td>288</td>
<td>158</td>
</tr>
<tr>
<td>6</td>
<td>362</td>
<td>226</td>
</tr>
</tbody>
</table>

Stem-Like

\[
p = 0.796 \\
\text{HR} = 0.953
\]

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>FL+oxaliplatin</th>
<th>FULV</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>56</td>
<td>31</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>116</td>
<td>77</td>
</tr>
</tbody>
</table>

Presented by: Kay Pogue-Geile katherine.pogue-geile@nsabp.org
Stage III

Tumor deposits

Stem like

IS

Gunderson JCO 2010
Post-Treatment ctDNA – All Patients

Recurrence Free Survival

Follow-up time from surgery (months)

HR: 7.1, p < 0.001

<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>
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

- cfDNA assessment for residual disease

- Positive:
  - All other patients: FOLFIRI x 6 months, SOC observation
- Exploratory cohorts:
  - MSI patients: Nivolumab
  - BRAF V600 patients: Enco/Bini/Cmab x 6 months

- Negative:
  - SOC observation
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 ctDNA 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
- Yes +ve
- Yes -ve
- No Chemo
- Chemo by Investigator’s choice
- No Chemo

Experimental arm
- No Chemo
- Analysis of ctDNA @ 3months
- Yes +ve
- No Chemo
- F/U for 7 years

Note: +ve, positive; -ve, negative
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

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STAGE III WITH AND WITHOUT TUMOR DEPOSITS

![Graph showing disease-free survival probability over time with and without tumor deposits.](image)

- **N** and **Event** counts:
  - No tumor deposits: 1758 events, 494 events
  - Tumor deposits: 184 events, 67 events

- **Logrank p = 0.0079**

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<td>1</td>
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<td>6</td>
<td>373</td>
</tr>
<tr>
<td>7</td>
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**Legend:**
- 1: no tumor deposits
- 2: tumor deposits
Stage III, stem-like subtype has a poor prognosis and no oxaliplatin benefit: MOSAIC Results validate C-07

- **Stage III**
  - % Recurrence Free
  - Time (years): 0, 2, 4, 6, 8, 10, 12, 14
  - Stem-like: 100, 80, 60, 40, 20, 0
  - Others: 100, 80, 60, 40, 20, 0
  - p < 0.001
  - HR = 1.562

- **Stem-Like**
  - % Recurrence Free
  - Time (years): 0, 2, 4, 6, 8, 10, 12, 14
  - FL+oxaliplatin: 100, 80, 60, 40, 20, 0
  - FULV: 100, 80, 60, 40, 20, 0
  - p = 0.796
  - HR = 0.953

**Others**
- Time: 0, 2, 4, 6, 8, 10, 12, 14
- Events: 362, 288, 266, 243, 212, 156, 36, 0

**Stem-like**
- Time: 0, 2, 4, 6, 8, 10, 12, 14
- Events: 226, 158, 132, 119, 108, 75, 13, 0

**FL+oxaliplatin**
- Events: 116, 81, 71, 61, 56, 44, 5, 0

**FULV**
- Events: 110, 77, 61, 58, 52, 31, 8, 0

**PRESENTED BY:** Kay Pogue-Geile  katherine.pogue-geile@nsabp.org
Disease Free Survival Probability

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
</tr>
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<tbody>
<tr>
<td>IS High</td>
<td>100</td>
<td>17</td>
</tr>
<tr>
<td>IS Int.</td>
<td>499</td>
<td>133</td>
</tr>
<tr>
<td>IS Low</td>
<td>463</td>
<td>167</td>
</tr>
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HR = 1.67 (95%CI 1.02-2.80)
HR = 2.42 (95%CI 1.47-3.99)

Logrank P < 0.0001

Courtesy by T. Andre
Stage III

Tumor deposits
Stem like
IS

Observed 5-Year Survival (%)

TN Category

Gunderson JCO 2010
RFS by ctDNA positivity

Post-Treatment ctDNA – All Patients

HR: 7.1, p < 0.001

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Note: +ve, positive; -ve, negative