Advances in Chemotherapy of Colorectal Cancer

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Disease Settings

- **Adjuvant Therapy**
  - MOSAIC, FOLFOX  
    Andre et al

- **First Line**
  - Targeting VEGF  
    Hurwitz et al
  - Resection  
    Allgayer and  
    Bechstein et al

- **Second Line**

- **Beyond that**
Choices, Choices

5-FU/leucovorin
capcitabine
irinotecan
oxaliplatin
bevacizumab
PTK 787

Etc
cetuximab
gefitinib
erlotinib
panitumumab
Potential First Line Strategies

- 5-FU/LV
- Capecitabine
- FOLFOX
- FLOX
- FUFOX
- FOLFIRI
- CapeOX
- CapeIri
- IROX
- FOLFIRI NOX
- All + bevacizumab
- All + cetuximab
- All + panitumimab
- All + bev & cetux
- All + PTK 787
- Etc, Etc
What Seems to Matter When You Have Advanced CRC?

- **Quantity of life** (overall survival)
- A shot at a cure
  - Resection
  - CR
- Delayed progression
  - PR, CR, stable disease
- **Quality of life**
  - Convenience
  - Toxicity
# 5-FU Meta-analysis: 5-FU vs 5-FU/ LV

18 trials - 2751 pts

<table>
<thead>
<tr>
<th></th>
<th>5-FU</th>
<th>5-FU/ LV</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>12%</td>
<td>23%</td>
<td>.0001</td>
</tr>
<tr>
<td>1-yr Survival</td>
<td>43%</td>
<td>48%</td>
<td>.003</td>
</tr>
</tbody>
</table>

Piedbois P et al. JCO 2005
Should We Ever Use Single Agents in 2005?

- Doublets = 3.4 month increase in OS vs single agent  
  (Grothey, JCO 2004)

- Only ~70% of patients get 2nd line Rx  
  (Tournigand, Goldberg JCO 2004)
"All-3-Drugs" - Update 2005
11 Phase III Trials, 5768 Patients

Multivariate analysis:
Effect on OS $P$
First-line doublet 0.69
All 3 drugs 0.005

$\alpha = 0.85$
Is Combination Therapy the Standard of Care?

The FOCUS trial reopens the debate
FOCUS Schema

A: (700 pts) FU until it fails, then **change** to irinotecan

B(ir): (350) FU until it fails, then **add** irinotecan

B(ox): (350) FU until it fails, then **add** oxaliplatin

C(ir): (350) FU+ irinotecan **from the start** until it fails

C(ox): (350) FU+ oxaliplatin **from the start** until it fails

**3rd drug salvage** introduced Feb 03; prior to that “no crossover” salvage with Mitomycin/FU

2100 patients

time to failure of first 2 drugs.
## Response Rate

<table>
<thead>
<tr>
<th>Treatment regimen (n)</th>
<th>A, B(ir) &amp; B(ox)</th>
<th>C(ir)</th>
<th>C(ox)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified de Gramont 1157</td>
<td></td>
<td>Ir+ FU/LV 284</td>
<td>Ox+ FU/LV 299</td>
</tr>
<tr>
<td>CR+PR</td>
<td>28.5%</td>
<td>51.4%</td>
<td>56.2%</td>
</tr>
<tr>
<td>SD</td>
<td>47.9%</td>
<td>37.0%</td>
<td>30.1%</td>
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<tr>
<td>PD</td>
<td>23.6%</td>
<td>11.6%</td>
<td>13.7%</td>
</tr>
</tbody>
</table>
Time to Failure of the First 2 Drugs

<table>
<thead>
<tr>
<th>Plan</th>
<th>Patients at risk</th>
<th>Median FFS</th>
<th>p-value (versus A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>710</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>B(ir)</td>
<td>356</td>
<td>11.3</td>
<td>0.203</td>
</tr>
<tr>
<td>B(ox)</td>
<td>356</td>
<td>11.6</td>
<td>0.163</td>
</tr>
<tr>
<td>C(ir)</td>
<td>356</td>
<td>9.0</td>
<td>0.003</td>
</tr>
<tr>
<td>C(ox)</td>
<td>357</td>
<td>9.2</td>
<td>0.020</td>
</tr>
</tbody>
</table>

The graph below shows the proportion of patients at risk over months, with different lines representing each plan and the corresponding median FFS and p-values.
## Median Overall Survival

<table>
<thead>
<tr>
<th>Plan</th>
<th>First 2 drugs schedule</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>FU then Ir</td>
<td>13.9</td>
</tr>
<tr>
<td>B(ir) B(ox)</td>
<td>FU then FU/Ir, FU then FU/Ox</td>
<td>14.8, 15.2</td>
</tr>
<tr>
<td>C(ir) C(ox)</td>
<td>1(^{st})-line FU/Ir, 1(^{st})-line FU/Ox</td>
<td>16.3, 15.2</td>
</tr>
</tbody>
</table>
OS for 1st line Combinations

- 5-FU/LV (Saltz)
- 5-FU/LV (Douillard)
- 5-FU/LV (de Gramont)
- IFL (Goldberg)
- IFL (Saltz)
- FOLFIRI (Douillard)
- FOLFOX (de Gramont)
- FOLFOX (Goldberg)
- IFL + Avastin
- IFL + Avastin, Oxali

Median OS (months)

0 5 10 15 20 25
OS for 1\textsuperscript{st} line Combinations

1 drug 1\textsuperscript{st} line
- 5-FU/LV (Saltz)
- 5-FU/LV (Douillard)
- 5-FU/LV (de Gramont)
- IFL (Goldberg)
- IFL (Saltz)
- FOLFIRI (Douillard)
- FOLFOX (de Gramont)
- FOLFOX (Goldberg)
- IFL + Avastin
- IFL + Avastin, Oxali

2 drugs 1\textsuperscript{st} line
- Median OS (months)
  - 13.9
  - 14.8
  - 15.2
  - 15.8
  - 16.2
FOCUS Trial

- Large trial
- No significant difference by strategy
- Median survival across the study 13.9 (serial single agents) to 16.3 mos (FOLFIRI)
- About 40% of pts on combo got 2\textsuperscript{nd} line therapy, 25% on serial single agents
- Initially patients were discouraged from getting a 3\textsuperscript{rd} drug

- Does this change your mind about serial single agents?
If Combination Therapy Is the Standard of Care

Does the combination generalization apply to poor prognosis pts and the elderly?
FOLFOX is Active in Poor Prognosis Patients

- 67 pts in OPTIMOX trial with alk phos > 3x nl
- 75% PS = 1 or 2
- RR = 56%
- PFS = 29 wks
- OS = 50 wks

- FOLFOX in elderly pts: same RR, tox

Tournigand, ASCO 2004
PS 2 Analysis: ASCO 2006

- Study to estimate the toxicity, dose-intensity, and benefit of 5-FU based treatment by performance status in patients with advanced colon cancer
- 5707 patients, 488 PS 2
- Saltz, Douillard, Kohne, de Gramont, Tournigand, Grothey, N9741, FOCUS, OPTIMOX
- Analysis in progress
FOLFIRI in 85 Elderly Patients

- ≥ 72 years old
- PS 0 or 1
- CPT-11 180 mg/m² + 5-FU 3000 mg/m² over 48 hours q 2 wks
- Median TTP 8 mos, OS 15.3 mos
- G 3-4 tox: ANC 21%, diarrhea 17%, asthenia 13%
- 2 toxic deaths

Sastre, JCO 2005
FOLFOX in ≥ 70 Year Olds

- 3,700 patients in 4 trials
- 493 older than age 70
- No difference in overall survival
- No difference in toxicity
- No difference in 3rd and 6th cycle dose intensity

Sargent, Goldberg
World GI Congress, 2005
Phase III Studies: Comparing Doublets

- IFL
- FOLFOX
- FOLFIRI
- IROX
N9741 and Tournigand Trials

- **IFL:** Irinotecan + 5-FU/LV
- **FOLFOX:** Oxaliplatin + 5-FU/LV
- **IROX:** Irinotecan + oxaliplatin

**Randomisation**

- **795 pts**
- **220 pts**

**Comparisons:**

- **FOLFOX6** vs. **FOLFIRI**
- **FOLFIRI** vs. **FOLFOX6**
## N9741/Tournigand Trial: Results

<table>
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<tr>
<th></th>
<th>IFL</th>
<th>FOLF</th>
<th>P-value</th>
<th>IROX</th>
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<td>45</td>
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<td>.26</td>
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<tr>
<td>TTP mos</td>
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<td>OS mos</td>
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<td>19.5</td>
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## N9741 and Tournigand Trials

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Overall Survival

- IFL
- FOLFOX
- IROX

IFL vs. FOLFOX: P=0.0001
IFL vs. IROX: P=0.04
FOLFOX vs. IROX: P=0.09

19.5 mo
17.4 mo
15.0 mo

Goldberg: JCO 2004
## N9741 and Tournigand Trials

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Sequential Strategy
Overall survival

Tournigand et al. (2004)
What Seems to Matter When You Have Advanced CRC?

- Quantity of life (overall survival)
- A shot at a cure
  - Resection
  - CR
- Delayed progression
  - PR, CR, stable disease
- Quality of life
  - Convenience
  - Toxicity
Resections in N9741

- 795 pts randomized to IFL, IROX, or FOLFOX
- No formal resection/RFA policy in the protocol
- 24 (3.3%) resected (22 liver, 2 lung)
- 92% on an oxaliplatin regimen
- Median OS in resected pts 42 months
- 29% disease free, (0/6 after RFA)

Delanoit, Ann Oncol 2005
Resections in Tournigand

- 9% FOLFI RI
- 22% FOLFOX ($p = .02$)
- Median OS > 47 mos

Tournigand, J CO, 2004
Profile of N9741
Complete Responders

- 62/1508 (4%) CRs (Not including surgical CRs)
- IFL 2%, IROX 3%, FOLFOX 6%
- Factors correlated with CR
  - Non measurable
  - Initial Dx
  - Single site, not liver or lung
- Median time to CR: 6 mos
- Median TTP after CR: 10 mos
- Median OS: 42 mos (for all 1500 pts 17 mos)
N9741 Follow-up

- 11% of patients treated with FOLFOX first line are alive at 4 years
- Project 9% at 5 years
- Fewer than half of these underwent surgical resection
What Seems to Matter When You Have Advanced CRC?

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  - CR
- Delayed progression
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  - Convenience
  - Toxicity
PR, CR, or Stable Disease

Concept: Disease Control
**Response Rates in FOCUS Trial**

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<td>23.6%</td>
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<td>13.7%</td>
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(Measurable patients with ≥1 follow-up assessment)
Later Disease Strategies
“BOND 1” Trial: Schema

- Refractory to 5-FU/CPT-11
- Primary Endpt: RR; Secondary Endpt: OS, TTP

2:1 Randomize

CPT-11 + cetuximab

cetuximab

CPT-11 + cetuximab

Cunningham D, et al. NEJM 2004
## Cetuximab/I vs. Cetuximab

Cunningham et al. NEJM 2004

<table>
<thead>
<tr>
<th></th>
<th>Combination</th>
<th>Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>218</td>
<td>111</td>
</tr>
<tr>
<td><strong>Resp. rate</strong></td>
<td>22.9%</td>
<td>10.8%</td>
</tr>
<tr>
<td><strong>CR+PR+SD</strong></td>
<td>55.5%</td>
<td>32.4%</td>
</tr>
<tr>
<td><strong>Med. TTP</strong></td>
<td>4.1 mo.</td>
<td>1.5 mo.</td>
</tr>
<tr>
<td><strong>Med. Surv.</strong></td>
<td>8.6 mo.</td>
<td>6.9 mo.</td>
</tr>
</tbody>
</table>
BOND 2
Treatment Plan

- **Arm A (CBI)**
  - Cetuximab, 400 mg/m² load then 250 mg/m²/wk
  - Bevacizumab 5 mg/kg every other week
  - Irinotecan at same dose and schedule as *last* given prior to study entry

- **Arm A (CB)**
  - Cetuximab, 400 mg/m² load then 250 mg/m²/wk
  - Bevacizumab 5 mg/kg every other week

Saltz ASCO, 2005
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>PR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB</td>
<td>35</td>
<td>23%</td>
<td>6.9 mos</td>
</tr>
<tr>
<td>CBI</td>
<td>39</td>
<td>38%</td>
<td>8.5 mos</td>
</tr>
</tbody>
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- Quantity of life (overall survival)
- A shot at a cure
  - Resection
  - CR
- Delayed progression
  - PR, CR, stable disease
- Quality of life
  - Convenience
  - Toxicity
Attributes of a Convenient Regimen

- No or minimal IVs: Capecitabine based
- Small molecules (pills)
- Few clinic visits: IROX or capecitabine regimens q 3 week
Arkenau, ASCO 2005

476 pts randomized

242 CAPOX

Median # cycles 6
3-week cycles

234 FUFOX

Median # cycles 4
5-week cycles
# Response Rates

<table>
<thead>
<tr>
<th></th>
<th>CAPOX n=238 (%)</th>
<th>FUFOX n=230 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>p=0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI, 41–54</td>
<td></td>
<td>95% CI, 43–56</td>
</tr>
<tr>
<td>Complete response</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Partial response</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>Stable disease</td>
<td>27</td>
<td>24</td>
</tr>
</tbody>
</table>
Progression-Free Survival

Estimated probability

- CAPOX (n=238) Median 7.0 months
- FUFOX (n=230) Median 8.0 months

p=0.11
Overall Survival

Estimated probability

- CAPOX (n=238): 16.3 months
- FUFOX (n=230): 17.2 months

p=0.72
What Seems to Matter When You Have Advanced CRC?

- Quantity of life (overall survival)
- A shot at a cure
  - Resection
  - CR
- Delayed progression
  - PR, CR, stable disease
- Quality of life
  - Convenience
  - Toxicity
Things That Matter

- Treatment related deaths
- Nausea and vomiting
- Diarrhea
- Febrile neutropenia
- Alopecia
- Hospitalization
- Etc
N9741
Toxicity grade ≥3

P > 0.002 for all comparisons of IFL vs FOLFOX and IFL vs IROX

IFL
FOLFOX
IROX

F. neutropenia
Diarrhea
Nausea
Vomiting
Paresthesia

0 10 20 30 40 %

15% 11% 12% 16% 14% 18%
4% 6% 3% 3% 7%

12%
16%
19%
22%
28%
24%

28% 16% 19% 22% 18% 15%
11% 12% 6% 3% 7% 4%

24% 19% 22% 7%
60 Day Mortality

- IFL: 4.5% (95% CI: 2.4% - 7.8%)
- FOLFOX: 2.6% (95% CI: 1.1% - 5.3%)
- IROX: 2.7% (95% CI: 1.1% - 5.4%)
Choices, Choices

- Combinations $\Rightarrow$ singlets
- Phase III data supports
  - FOLFOX, FOLFIRI
  - + Bevacizumab
  - ? capecitabine
- CR surgically or via chemotherapy indicates predicts survival
- Chemotherapy cures may be possible
- Toxicity issues are increasingly important
- We must learn to quantify QOL better
? in Need of Answers

- ? Is bevacizumab + chemo the new standard
- ? How to integrate stop and go strategies
  - FOLFOX, any chemotherapy
- ? Is there an optimal sequence
  - ? What is the best strategy after adjuvant FOLFOX
- ? Should we be doubling antibodies
? in Need of Answers

- ? What’s the long-term cure rate
- ? How will small molecules fit into our armamentarium
- ? When will pharmacogenomics permit individualized treatment choices
- ? When and whom do we operate on
Intergroup C80405 Schema

Stratify
- Prior adj
- Cape v. FU
- Prior XRT

RANDOMIZATION

N= 2500

FOLFOX or FOLFIRI
- + C-225

FOLFOX or FOLFIRI + C-225 + Bevacizumab

FOLFOX or FOLFIRI + Bevacizumab
Thank you

Any Questions?