How to Improve on the Adjuvant treatment in Stage III Colon Cancer

Aimery de Gramont
Barcelona 28th June 2014
Disclosure

Genomic Health
Roche, Sanofi: non related to this presentation
Colo-rectal Cancer

World Incidence: 1,361,000 (rank 3)
World Deaths: 694,000 (rank 4)

Colon/Colorectum: 75%

Colon Cancer Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>10%</td>
</tr>
<tr>
<td>Stage II</td>
<td>40%</td>
</tr>
<tr>
<td>Stage III</td>
<td>35%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>15%</td>
</tr>
</tbody>
</table>

Globocan 2012
AJCC 2010
Where we are:
• Standard Adjuvant Therapy Stage III

How to improve:
• Doing nothing
• Ongoing trials & idea(s)
• Biomarkers
• New Drugs
• New Trials
Were we are:
• Standard Adjuvant Therapy Stage III

How to improve:
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Library of Congress Catalog Card Number: 78–175463
Published in Great Britain by Henry Kimpton Publishers, London
Printed in the United States of America


<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dukes classification</td>
<td>Bussey et al.(^7)</td>
</tr>
<tr>
<td>(2037 cases)*</td>
<td>(1013 cases)*</td>
</tr>
<tr>
<td>Type A</td>
<td>81%</td>
</tr>
<tr>
<td>Type B</td>
<td>64%</td>
</tr>
<tr>
<td>Type C</td>
<td>27%</td>
</tr>
</tbody>
</table>

*Includes rectal carcinomas only.
†All large bowel carcinomas.
LEVAMISOLE AND FLUOROURACIL FOR ADJUVANT THERAPY OF RESECTED COLON CARCINOMA

Charles G. Moertel, M.D., Thomas R. Fleming, Ph.D., John S. Macdonald, M.D.,
Daniel G. Haller, M.D., John A. Laurie, M.D., Phyllis J. Goodman, M.S.,
James S. Ungerleider, M.D., William A. Emerson, M.D., Douglas C. Tormey, M.D.,
John H. Glick, M.D., Michael H. Veeder, M.D., and James A. Mailliard, M.D.*

Abstract Twelve hundred ninety-six patients with resected colon cancer that either was locally invasive (Stage B₂) or had regional nodal involvement (Stage C) were randomly assigned to observation or to treatment for one year with levamisole combined with fluorouracil. Patients with Stage C disease could also be randomly assigned to treatment with levamisole alone. The median follow-up time at this writing is 3 years (range, 2 to 5½).

Among the patients with Stage C disease, therapy with levamisole plus fluorouracil reduced the risk of cancer recurrence by 41 percent (P<0.0001). The overall death rate was reduced by 33 percent (P ≈ 0.006). Treatment with levamisole alone had no detectable effect. The results in the patients with Stage B₂ disease were equivocal and too preliminary to allow firm conclusions. Toxic effects of levamisole alone were infrequent, usually consisting of mild nausea with occasional dermatitis or leukopenia, and those of levamisole plus fluorouracil were essentially the same as those of fluorouracil alone — i.e., nausea, vomiting, stomatitis, diarrhea, dermatitis, and leukopenia. These reactions were usually not severe and did not greatly impede patients' compliance with their regimen.

We conclude that adjuvant therapy with levamisole and fluorouracil should be standard treatment for Stage C colon carcinoma. Since most patients in our study were treated by community oncologists, this approach should be readily adaptable to conventional medical practice. (N Engl J Med 1990; 322:352-8.)
Oxaliplatin plus 5FU is better than 5FU alone! The second step (2004)

Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer

Thierry André, M.D., Corrado Boni, M.D., Lamia Manedja-Boudaf, M.D., Nicolas Navarro, M.D., Josep Tabernero, M.D., Tamas Hickish, M.D., Clare Toppan, M.D., Marta Zannielli, M.D., Philip Chingan, M.D., John Bridgewater, M.D., Isabelle Tabah-Fisch, M.D., Aimery de Gramont, M.D., for the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators

ABSTRACT

Background The standard adjuvant treatment of colon cancer is fluorouracil plus leucovorin (FL). Oxaliplatin improves the efficacy of this combination in patients with metastatic colorectal cancer. We evaluated the efficacy of treatment with FL plus oxaliplatin in the postoperative adjuvant setting.

Methods We randomly assigned 2246 patients who had undergone curative resection for stage II or III colon cancer to receive FL alone or with oxaliplatin for six months. The primary end point was disease-free survival.

Results A total of 1123 patients were randomly assigned to each group. After a median follow-up of 27.9 months, 237 patients in the group given FL plus oxaliplatin had had a cancer-related event, as compared with 293 patients in the FL group (21.1 percent vs. 26.1 percent; hazard ratio for recurrence, 0.77; P=0.002). The rate of disease-free survival at three years was 79.2 percent (95 percent confidence interval, 75.6 to 80.7) in the group given FL plus oxaliplatin and 72.9 percent (95 percent confidence interval, 70.2 to 75.7) in the FL group (P=0.002 by the stratified log-rank test). In the group given FL plus oxaliplatin, the incidence of febrile neutropenia was 1.8 percent; the incidence of gastrointestinal adverse effects was low, and the incidence of grade 3 sensory neuropathy was 12.4 percent during treatment, decreasing to 1.1 percent at one year of follow-up. Six patients in each group died during treatment (death rate, 0.5 percent).

Conclusions Adding oxaliplatin to a regimen of fluorouracil and leucovorin improves the adjuvant treatment of colon cancer.
The disillusion of targeted therapies in adjuvant colon cancer therapy

Bevacizumab
NSABP C08 Allegra JCO 2010
AVANT Lancet Oncol 2012

Cetuximab
N0 147 Alberts JAMA 2012
PETACC8 Taieb WGIC 2012
Were we are:
• Standard Adjuvant Therapy Stage III

How to improve:
• Doing nothing
• Ongoing trials & idea(s)
• Biomarkers
• New Drugs
• New Trials
3-Year DFS in Stage III: Results over time

Survival %

Feb-82  Aug-87  Jan-93  Jul-98  Jan-04  Oct-06

LV/5FU  FP  Oxaliplatin
Stage Migration

“When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.”

Will Rogers
## Will Rogers’ effect

### Recent trials vs. MOSAIC in Stage III

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>LV5FU2</td>
<td>FOLFOX4</td>
<td>XELOX</td>
<td>mFOLFOX6</td>
</tr>
<tr>
<td>3yr OS</td>
<td>81.3%</td>
<td>84.3%</td>
<td>86%*</td>
<td>87.9%</td>
</tr>
</tbody>
</table>

* from curves

### FOLFOX4 MOSAIC vs. FOLFOX4 AVANT

<table>
<thead>
<tr>
<th></th>
<th>3-yr DFS</th>
<th>5-yr OS</th>
<th>3-yr DFS &lt;4LN</th>
<th>3-yr DFS ≥4LN</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIC</td>
<td>73%</td>
<td>76%</td>
<td>71.8%</td>
<td>56.2%</td>
</tr>
<tr>
<td>AVANT</td>
<td>77%</td>
<td>85%*</td>
<td>85%</td>
<td>66%</td>
</tr>
</tbody>
</table>

* preliminary results

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MOSAIC data
Haller, et al. JCO 2011
Alberts, et al. JAMA 2012
Lancet Oncol 2012
Were we are:
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• New Trials
Incidence of Neurosensory Symptoms during Treatment and Follow-up after FOLFOX

Evaluable patients n=811 at 4 years

<table>
<thead>
<tr>
<th>Grade</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84.3%</td>
</tr>
<tr>
<td>1</td>
<td>12.0%</td>
</tr>
<tr>
<td>2</td>
<td>2.8%</td>
</tr>
<tr>
<td>3</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Relapse-free Survival by Adjuvant Treatment Arms
6 Months of bolus 5FU/LV vs. 3 months of Continuous Infusion 5FU

IDEA – Meta-Analysis

mFOLFOX6/XELOX

12/8 cycles

mFOLFOX6/XELOX

6/4 cycles

stage II-III

Non inferiority trial (HR<1.1 – N 10500)
N= 14500 (June 2014)

TOSCA
N= 3759

SCOT
N= 5836

CALGB  HORG  JAPAN  GERCOR
N= 1364  N= 745  N=731  N= 2023
Data from Observational Studies for Stage I-III Disease

- Decrease risk of recurrence
  - Physical activity
  - Avoidance of Western pattern diet
  - Avoidance of class II/III obesity (BMI > 35 kg/m²)
  - Aspirin or COX-2 inhibitor
  - Higher vitamin D levels

- No association with recurrence to date
  - Weight change (gain or loss)
  - Obesity < 35 kg/m²
  - Smoking status or history
  - Multivitamin

Credits:
Charles Fuchs
Jeffrey Meyerhardt
Brian Wolpin
Kimmie Ng
Andrew Chan
Nadine McCleary
Donna Niedzwiecki
Donna Hollis
CALGB
Ongoing Trials (June 2014)

CALGB 80702: Phase III Trial of 6 vs. 12 Treatments of Adjuvant Folfox Plus Celecoxib or Placebo for Patients with Resected Stage III Colon Cancer N=2500

ASCOLT: Aspirin vs Placebo
Stage II-III Colon & Rectum N=2660 Asia

CHALLENGE: Colon Health + Life-Long Exercise Change trial

Japan: UFT +/- PSK stage IIIAB n=300
UK: CAPOX vs no therapy locally advanced rectal cancer N=800
France: follow-up vs laparotomy+HIPEC High-risk peritoneal N=130
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• New Trials
# The need of Biomarkers

Different biology between stage II and III.

<table>
<thead>
<tr>
<th>Markers</th>
<th>Stage II</th>
<th></th>
<th>Stage III</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR§</td>
<td>p value*</td>
<td>HR§</td>
<td>p value*</td>
</tr>
<tr>
<td>T Stage (T4 vs T3)</td>
<td>2.8</td>
<td>0.0001</td>
<td>1.6</td>
<td>0.0006</td>
</tr>
<tr>
<td>N Stage (N2 vs N1)</td>
<td>N/A</td>
<td>N/A</td>
<td>2.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Histologic Grade (3-4 vs 1-2)</td>
<td>0.6</td>
<td>0.55</td>
<td>1.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Age (&gt;60 vs ≤60)</td>
<td>1.8</td>
<td>0.026</td>
<td>1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>MSI (High vs Stable)</td>
<td>0.3</td>
<td>0.027</td>
<td>0.7</td>
<td>0.12</td>
</tr>
<tr>
<td>p53 (High)</td>
<td>0.7</td>
<td>0.27</td>
<td>1.3</td>
<td>0.015</td>
</tr>
<tr>
<td>SMAD4 (any loss)</td>
<td>1.0</td>
<td>0.9</td>
<td>1.6</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Treatment, Sex, Site, KRAS, BRAF, TS, 18qLOH (Stage II: HR 1.4, p=0.33), hTERT: not significant

* p values from the Wald test in a multivariate Cox regression

§ HR = hazard ratio

Roth A et al. ASCO 2009
Biomarker-driven Decision Algorithm in Stage III

CALGB 8903

DFS in dMMR patients, pooled data

Stage II (N=102)

- Untreated: 87%
- Treated: 72%

Stage III (N=63)

- Untreated: 62%
- Treated: 67%

HR: 2.80 (0.98 - 8.97), p=0.05
HR: 1.08 (0.44 - 2.68), p=0.86

Sargent, JCO 2009
Oxaliplatin is active in Stage III dMMR

Fluoropyrimidine Stage III (N=63)

FOLFOX4 Stage III (N=47)

5 yr DFS
Untreated 62%
Treated 67%

Sargent, JCO 2009
Fléjou, ASCO 2013
Oxaliplatin is active in Stage III BRAF mut

FOLFOX4 vs LV5FU
Stage III (N=74)

FOLFOX4 vs LV5FU
Stage III (N=20)

MOSAIC data
New Biomarkers

Detection of guanylyl cyclase C mRNA in lymph nodes of resected stage II colorectal cancer is highly correlated with the risk of tumor recurrence. Hyslop CCR 2011

Molecular signatures: Oncotype Dx Colon 12

<table>
<thead>
<tr>
<th></th>
<th>5 year Recurrence Risk based on Recurrence Score Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Stage IIIA/B</td>
<td>21%</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>40%</td>
</tr>
</tbody>
</table>

NSABP C07 – O’Connell et al ASCO 2012 Abstract 3512
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Were we are:
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Aspirin in mutant PIK3CA

Figure 1. Mortality among Patients with Colorectal Cancer, According to Regular Use or Nonuse of Aspirin after Diagnosis and PIK3CA Mutation Status.

Panels A and B show colorectal cancer–specific mortality among patients with mutant-PIK3CA tumors and those with wild-type PIK3CA tumors, respectively, and Panels C and D show overall mortality in the respective subgroups of patients.

Liao X. NEJM 2012
ASPIK

Aspirin in PIK3CA-mutation Selected

Patients after Resection of Colorectal Cancer

Eligible patient

Aspirin 200mg
1 tablet daily
3 years

Placebo
1 tablet daily
3 years

D Kerr
Tumor Cell Dormancy

- Arrested angiogenesis is a component of cell dormancy (Almog, Cancer Letters 2010)

DFS: Cumulative Hazard Ratio (ITT Stage III)

Bev effect on undetectable metastases
Dormancy induction

Recovery from Dormancy

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>FOLFOX4 + Bev</th>
<th>XELOX + Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00 1.02</td>
<td>1.12 1.15</td>
</tr>
<tr>
<td>1.5</td>
<td>0.63 0.61</td>
<td>1.11 1.13</td>
</tr>
<tr>
<td>2</td>
<td>1.11 1.13</td>
<td>1.08</td>
</tr>
<tr>
<td>2.5</td>
<td>1.11 1.13</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.13 1.08</td>
<td></td>
</tr>
</tbody>
</table>

Time from randomization (years)
COLADJ 2014

Antiangiogenic Agent X

Control

ASCO 2018
Cost of an adjuvant trial

>100 000 000 €

Doing better trials
What is the signal to launch an adjuvant trial?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Preclinical model</th>
<th>Metastatic trial</th>
<th>Adjuvant study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levamisole</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td>LV5FU</td>
<td>Yes</td>
<td>Phase III</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Yes</td>
<td>Phase III</td>
<td>No</td>
<td>Negative</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Yes</td>
<td>Phase III (PFS)</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td>Interferon α</td>
<td>Yes</td>
<td>Phase II</td>
<td>No</td>
<td>Negative</td>
</tr>
<tr>
<td>Edrecolomab</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Negative</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Yes</td>
<td>Phase II</td>
<td>No</td>
<td>Negative</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Yes</td>
<td>Phase III</td>
<td>No</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Results of the adjuvant pivotal trials in colon cancer triggered by the previous clinical studies in metastatic and adjuvant setting

<table>
<thead>
<tr>
<th>Clinical signal</th>
<th>Phase III</th>
<th>Phase II</th>
<th>Phase I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced colorectal cancer</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Small adjuvant trial</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No experience</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Adjuvant trial result:
- Positive
- Equivalency
- Negative

de Gramont A, Current Colorectal Cancer Reports 2013
Comparison of expected and observed results in the control arm of colon cancer adjuvant trials

de Gramont A, Current Colorectal Cancer Reports 2014
Comparison of expected and observed results in the control arm of colon cancer adjuvant trials when 3-year DFS was the primary endpoint

![Graph showing correlation between observed and expected control arm results with r = 0.63](image)

de Gramont A, Current Colorectal Cancer Reports 2014
Comparison of expected and observed results in the investigational arms of colon cancer adjuvant trials
Conclusions

New drug
\[\rightarrow\]
Registration in advanced disease
\[\rightarrow\]
Good sales
\[\rightarrow\]
Adjuvant trial

Rationale for adjuvant
\[\rightarrow\]
Academic groups
Public & private fundings
\[\rightarrow\]
New Adjuvant trial designs

Registration in advanced disease