Can we refine the selection for adjuvant treatment in colon cancer?

Aimery de Gramont
Franco-British Institute
Levallois-Perret
unpaid member of Roche and Sanofi advisory boards
<table>
<thead>
<tr>
<th>Stage</th>
<th>Bussey et al.⁷</th>
<th>McSherry et al.²⁶</th>
<th>Thomas et al.³⁰</th>
<th>Franklin &amp; McSwain¹⁶</th>
<th>Kuehner et al.²³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dukes classification</td>
<td>(2037 cases)*</td>
<td>(1013 cases)*</td>
<td>(356 cases)*</td>
<td>(314 cases)†</td>
<td>(277 cases)*</td>
</tr>
<tr>
<td>Type A</td>
<td>81%</td>
<td>61%</td>
<td>79%</td>
<td>72%</td>
<td>72%</td>
</tr>
<tr>
<td>Type B</td>
<td>64%</td>
<td>39%</td>
<td>25%</td>
<td>56%</td>
<td>45%</td>
</tr>
<tr>
<td>Type C</td>
<td>27%</td>
<td>28%</td>
<td>6%</td>
<td>16%</td>
<td>20%</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.)
There is an adjuvant therapy for colon cancer! The first step (1990)

5-year OS Stage III

1970: 25%
1990: 63%

Figure 3. Survival according to treatment arm. 5-FU = fluorouracil.

Fluorouracil plus Levamisole as Effective Adjuvant Therapy after Resection of Stage III Colon Carcinoma: A Final Report

Charles G. Moertel, MD; Thomas R. Fleming, PhD; John S. Macdonald, MD; Daniel G. Haller, MD; John A. Laurie, MD; Catherine M. Tangen, MS; James S. Ungerleider, MD; William A. Emerson, MD; Douglass C. Tormey, MD, PhD; John H. Glick, MD; Michael H. Veeder, MD; and James A. Mailliard, MD
Adjuvant Therapy (1990-2004)

DFS

6 months = 12 months
Low dose leucovorin
Elderly patients

Francini 1994
IMPACT 1995
NCCTG 1997
NCCTG-NCIC 1998
INT 0089 1998
NSABP C04 1999
QUASAR 2000

Moertel

5FU bolus + LV

5FU+lev
Small motion or stagnation (1990-2004)

« a decade of decadence »
by Norman Wolmark

New drugs and negative trials
Alpha-interferon
Raltirexed
Edrecolomab targeting cell surface glycoprotein 17-1A
DFS in MSI patients, pooled data

Stage II (N=102)

- Untreated: 87%
- Treated: 72%

5 yr DFS

Stage III (N=63)

- Untreated: 62%
- Treated: 67%

5 yr DFS

FP alone should not be given

Small benefit of FP alone

Sargent, JCO 2009
Adjuvant Therapy

DFS

better safety

5FU+lev

5FU bolus + LV

UFT+LV

LV5FU2/5FU protracted

Capecitabine

X-Act Twelves 2005
NSABPC06 Lambersky 2006

UK 2000-2004
INTERGROUP 0153 2000
GERCOR 2003
PETTACC 2
Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer

Thierry André, M.D., Corrado Boni, M.D., Lania Menudji-Boudaif, M.D., Matilde Navarro, M.D., Josep Tabernero, M.D., Tamas Hickish, M.D., Clare Topham, M.D., Marta Zanninelli, M.D., Philip Clingan, 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 2,246 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 1,123 patients were randomly assigned to each group. After a median follow-up of 37.9 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 78.2 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 second step (2004)

5 year OS Stage III

1970: 25%
1990: 63%
2004: 76%

Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study

Thierry André, Armand de Gramont, Dewi Vernerre, Benoist Chibaudel, Franck Bonnetain, Amélie Tijeras-Raballand, Aurelie Scrova, Tamas Hickish, Josep Tabernero, Jean Luc Van Laethem, Maria Banzzi, Eduard Maartense, Einai Shmueli, Goran U. Carlsson, Werner Scheithauer, Demeris Papamichael, Marcus Möehler, Stefania Landolfi, Pieter Demetter, Soudhir Colone, Christophe Tournigand, Christophe Louvet, Alex Duvat, Jean-François Fléjou, and Aimery de Gramont
Adjuvant Therapy (2004-2009)

DFS

better safety

FOLFOX4

FLOX

XELOX

LV5FU/iri

IFL

Capecitabine

5FU bolus + LV

LV5FU2

5FU+lev
Benefit improves over time

Stage III MOSAIC

Overall Survival (probability)

Time Since Enrollment (years)

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX4</th>
<th>LV5FU2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>672</td>
<td>675</td>
</tr>
<tr>
<td>Events</td>
<td>209</td>
<td>250</td>
</tr>
</tbody>
</table>

Log-rank $P = .015$

HR, 0.797; 95% CI, 0.663 to 0.958
The huge benefit of Oxaliplatin in stage IIIC

Stage III N2
15% absolute benefit

André T et al, JCO 2015
The benefit of Oxaliplatin is reduced in stage II

Low-risk

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX4</td>
<td>38</td>
</tr>
<tr>
<td>LV5FU2</td>
<td>32</td>
</tr>
</tbody>
</table>

High-risk

- T4 and/or bowel obstruction
- tumor perforation
- poorly differentiated tumor
- venous invasion
- <10 examined lymph nodes

A

Overall Survival (probability)

Time Since Enrollment (years)

B

Overall Survival (probability)

Time Since Enrollment (years)
Elderly patients seemed to experience reduced benefit from adding oxaliplatin to fluoropyrimidines in the adjuvant setting.

MOSAIC: women 70-75 did better than men 70-75

McCleary et al. JCO 2013
New drugs and negative trials
Bevacizumab: NSABP C08 - AVANT
Cetuximab: NO 147 - PETACC8

Subpopulations
Elderly
Stage II

No, because of better staging, new biomarkers and IDEA
For Patients with Dukes’ B (TNM Stage II) Colorectal Carcinoma, Examination of Six or Fewer Lymph Nodes Is Related to Poor Prognosis

Scott Caplin¹
Jean-Philippe Cerottini, M.D.¹
Fred T. Bosman, M.D.²
Michael T. Constanda³
Jean-Claude Givel, M.D.¹

¹ Department of Surgery, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.
² Department of Pathology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

BACKGROUND. Lymph node status is pivotal to the staging of colorectal carcinoma. The diagnosis of a lymph node negative tumor should imply a good prognosis; however, the outcomes for Dukes’ B (TNM Stage II) patients remain variable, possibly in part due to understaging. The aim of this study was to determine whether examining a specified minimum number of lymph nodes using conventional techniques would eliminate the risk of understaging and thus have an effect on prognosis.

METHODS. Data on patients who underwent surgery for colorectal carcinoma at a single institution between 1985 and 1990 were reviewed. Patients with Dukes’ B (TNM Stage II) or C (TNM Stage III) tumors and histologically confirmed disease-free resection margins who were treated with curative intent were included. Correlations among variables were assessed using the chi-square test, and survival comparisons were made using Kaplan–Meier curves and the log rank test. Multivariate analysis was performed using a Cox regression model.

RESULTS. Dukes’ B (TNM Stage II) patients with ≤6 lymph nodes examined had significantly poorer overall survival than those with ≥7 lymph nodes examined (P = 0.0014). Such a significant difference was not observed among Dukes’ C (TNM Stage III) patients (P = 0.7). Survival of Dukes’ C patients was significantly worse compared with that of Dukes’ B patients overall and Dukes’ B patients with ≥7 lymph nodes examined (P < 0.0001). There was no significant difference in survival between Dukes’ C and Dukes’ B patients with ≤6 lymph nodes examined (P = 0.02). The number of examined lymph nodes was the only significant parameter correlated with survival in the multivariate analysis (P = 0.002).

CONCLUSIONS. Because Dukes’ B patients with ≤6 examined lymph nodes have poorer outcomes than those with a higher number examined (probably due to understaging), the total number of examined lymph nodes should always be reported. Cancer 1998;83:666–72. © 1998 American Cancer Society.
3-Yr DFS in Stage III: Results over time

Survival %

LV/5FU
FP

Feb-82  Aug-87  Jan-93  Jul-98  Jan-04  Oct-06
3-Yr DFS in Stage III: Results over time

- Survival %
- LV/5FU
- FP
- Oxaliplatin

Time:
- Feb-82
- Aug-87
- Jan-93
- Jul-98
- Jan-04
- Oct-06
Will Rogers’ effect

Stage Migration

Recent trials vs. MOSAIC in Stage III

<table>
<thead>
<tr>
<th></th>
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</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>86.0%*</td>
<td>87.9%</td>
</tr>
<tr>
<td>3-yr DFS</td>
<td>73%</td>
<td>77%</td>
<td>56%</td>
<td>56%</td>
</tr>
<tr>
<td>5-yr OS</td>
<td>76%</td>
<td>85%</td>
<td>66%</td>
<td>66%</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>72%</td>
<td>56%</td>
</tr>
<tr>
<td>AVANT</td>
<td>77%</td>
<td>85%</td>
<td>85%</td>
<td>66%</td>
</tr>
</tbody>
</table>

+4%      +9%      +13%         +10%
Left and Right Colon

Weiss JM et al. JCO 2011

SEER database
The diagrams illustrate survival probability over time for Stage II and Stage III colon cancer patients in the MOSAIC study, focusing on the FOLFOX4 arm. The survival probability is measured in percentage, and the number at risk for each group is provided.

**Stage II**
- **Group: Right**
  - 0: 159, 1: 153, 2: 143, 3: 132, 4: 75, 5: 54, 6: 11, 7: 0
- **Group: Left**
  - 0: 242, 1: 230, 2: 214, 3: 185, 4: 105, 5: 75, 6: 12, 7: 0

**Stage III**
- **Group: Right**
- **Group: Left**

The diagrams show the survival probability over time for patients with Stage II and Stage III colon cancer who were treated with the FOLFOX4 regimen. The number at risk for each group is given at various time points, indicating the survival rate for Right and Left colon patients.
Left and Right Colon

Survival after relapse

LV5FU2

FOLFOX4

MOSAIC

André A et al. JCO 2015
ACCENT-Based Web Calculators to Predict Recurrence and Overall Survival in Stage III Colon Cancer" (L.A. Renfro et al., JNCI 106(10), 2014)
KRAS/BRAF and MS status

Figure 3. Effect of KRAS and BRAF Status on Disease-Free Survival (DFS) in Patients With Microsatellite-Stable and Microsatellite-Unstable Tumors

A. KRAS status in patients with microsatellite-stable tumors

- MSS KRAS
- MSI KRAS

B. BRAF status in patients with microsatellite-stable tumors

- MSS BRAF
- MSI BRAF

C. KRAS status in patients with microsatellite-unstable tumors

- MSS KRAS
- MSI KRAS

D. BRAF status in patients with microsatellite-unstable tumors

- MSS BRAF
- MSI BRAF

MSS poor pc of mutations

MSS good pc of mutations

Taieb J et al, JAMA Oncol 2016
Oxaliplatin is active in Stage III MSI

Fluoropyrimididine
Stage III (N=63)

FOLFOX4
Stage III (N=47)

5 yr DFS
Untreated 62%
Treated 67%

Sargent, JCO 2009

André, JCO 2015
Oxaliplatin is active in BRAF mut

RFS Stage III

MSS

MSI

André, JCO 2015
• We need predictive biomarkers to define:
  1. the stage II patients who should be treated
  2. the stage III patients who could not be treated
  3. the patients who could benefit from oxaliplatin
  4. the patients who could benefit from new therapies
Aspirin in mutant PIK3CA

A. Colorectal Cancer-Specific Mortality, Mutant PIK3CA
   - No aspirin use
   - Aspirin use
   - P < 0.001 by log-rank test

B. Colorectal Cancer-Specific Mortality, Wild-Type PIK3CA
   - Aspirin use
   - No aspirin use
   - P = 0.76 by log-rank test

C. Overall Mortality, Mutant PIK3CA
   - No aspirin use
   - Aspirin use
   - P = 0.01 by log-rank test

D. Overall Mortality, Wild-Type PIK3CA
   - Aspirin use
   - No aspirin use
   - P = 0.96 by log-rank test

Liao X. NEJM 2012
Prognostic Biomarkers

Recurrence score
Coloprint
GUCY2C expression in LN
Immunoscore
CDX2
CMS
...

...
ACCENT Study in stage II patients

Model and score established with Age, BMI, CEA, Perforation, sex and site (right, left) from MOSAIC
IDEA – Meta-Analysis

mFOLFOX6/XELOX
12/8 cycles

mFOLFOX6/XELOX
6/4 cycles

stage III

Non inferiority trial (HR<1.12 – N 10500)
N=10500  N=12626

SCOT
N=3983

TOSCA
N=2402

GERCOR
N=2010

CALGB/SWOG 80702
N=2440

ACHIEVE
N=1291

HORG
N=708
IDEA Clinical Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer

Risk group

- T1-3 N1
  - (~60% of stage III)
- T4 and/or N2
  - (Or other high-risk factors)

Recommended duration of adjuvant therapy

- 3 months
- 6 months

Duration of therapy determined by
- tolerability of therapy
- patient preference
- assessment of risk of recurrence
- Regimen (CAPOX vs FOLFOX)
IDEA Clinical Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer

**Risk group**

- **T1-3 N1**
  - Recommended duration of adjuvant therapy: 3 months
  - (~60% of stage III)

- **T4 and/or N2**
  - Recommended duration of adjuvant therapy: 6 months
  - (Or other high-risk factors)

**Duration of therapy determined by**
- efficacy of FOLFOX in this setting
- superiority of FOLFOX 12 vs 6 cycles
- non inferiority non demonstrated for CAPOX

**Per protocol results**
Reassessment when overall survival will be mature

ASCO 2017 Presented by: Qian Shi, PhD on behalf of IDEA collaborators
> 2017 What is ongoing?

« adjuvant colon cancer » N=334

- Adjuvant colon, unpublished or ongoing N=30
  - Drugs N=15
    - IDEA/IDEA like n=5
    - Aspirin n=6
    - Regorafenib n=1
    - Tegafur n=1
    - Atezolizumab n=1
    - Irinotecan+oxaliplatin=1
  - Route N=3
    - HIPEC n=1
    - Intraportal n=2
  - Other N=8
  - Immunology N=2
    - Cytokine-induced killer cells n=2
    - Support N=2
    - Neurotoxicity n=1
    - Physical training n=1
    - Elderly n=2
    - Timing to chemo n=4
    - Traditional Chinese n=2

Results posted N=33
Published, completed<6/2015 N=100
No accrual N=5
Observational studies N=28
Phases I or II N=44
Non Colon/ non Cancer N=16
MCRC N=15
Rectal cancer N=1
Others N=5

Biomarkers/Surgery/Behavioral N=18

11
3
3
2
2

>1000 n=10
(5 IDEA)
Industry sponsored 0

Clinical trials June 2017
Conclusions

The selection for adjuvant treatment in colon cancer can be refined for staging, using multiparameters beyond T and N: BMI, side (Mayo Clinic calculator*), MS status (stage II) and including new prognostic biomarkers, if available, to define the risk of recurrence.

Low-risk patients (risk 3-10%), such as stage II with or without MSI should go on surveillance.

Intermediate-risk patients (risk 10-25%), such as stage II MSS or stage III T1-3N1 can receive fluoropyrimidines alone (risk < 15%) or CAPOX 3 months or FOLFOX 3 to 6 months.

High-risk patients (risk > 25%), such as stage II T4b, stage III T4 and/or N2 can be offered FOLFOX 6 months or CAPOX
Conclusions

In case of toxicity after 3 months, oxaliplatin can be stopped based on IDEA.

Elderly patients can receive fluoropyrimidines alone, especially male patients.

We urgently need new drugs, new predictive biomarkers and clever new trials.