ADJUVANT TREATMENT OF COLON CANCER

Name
Michel DUCREUX

Gustave Roussy Cancer Campus, Grand Paris, FRANCE
My wife is the Head of The Oncology Business Unit in Sandoz Company (French Affiliate)

**Participation to advisory boards:**
- ROCHE
- MERCK SERONO
- AMGEN
- NOVARTIS
- SANOFI
- BAYER
- SIRTEX
- LILLY
- SERVIER
- IPSEN

**Speaker in symposiums:**
- ROCHE
- MERCK SERONO
- NOVARTIS
- IPSEN
- LILLY
- AMGEN

**Research funding:**
- ROCHE
- MERCK SERONO
- PFIZER
Aims of the talk

- Adjuvant chemotherapy is indicated for stage III (N+)
  - FOLFOX / CapeOx; 3 months vs 6 months
  - Capecitabine or (inf.) FU/LV as an option for some patients
  - FOLFOX / CapeOx for patients < 70y, use with caution for pts > 70y
- Antibodies (EGFR, VEGF) are not indicated
- The decision for an adjuvant treatment should balance the risk of cancer mortality and that of comorbidities
- Specific problems
  - Stage II
  - The future.....😊😊😊
STAGE III (N+)…
First positive study: 5FU + levamisole...

Moertel et al NEJM 1990

Sargent D, J Clin Oncol 2009
X’Act trial (Capecitabine vs FuFol Mayo) Overall survival

Stage III colon (n= 1987)

Non infériority < 0.001
Superiority 0.05

Estimated Probability

5-year

Capecitabine (n=1004) 71.4%
S-FU/LV (n=983) 68.4%

HR=0.86 (95% CI: 0.74–1.01)
NI margin 1.14

Test of non-inferiority p=0.0001116
Test of superiority p=0.06
2004 combination chemotherapy!

FOLFOX new standard stage III
MOSAIC study

Main endpoint: Disease-Free Survival (3-years)
Secondary endpoint: tolerance, overall survival (6-years)

\[ n=2246 \]

Inclusion:
- Oct 1998–Jan 2001 (146 centres; 20 countries)
- Colon cancer, complete resection
- Stage II, 40%; Stage III, 60%
- Age 18–75 years
- KPS \( \geq 60 \)
- No previous CT

\[ \text{FOLFOX4} \]
\[ (LV5FU2 + \text{oxaliplatin } 85 \text{ mg/m}^2) \]
\[ (n=1123) \]

\[ \text{LV5FU2} \]
\[ (n=1123) \]

A. de Gramont et al., ASCO 2003 / T. André et al. NEJM 2004
MOSAIC: Long-term results
Overall survival ITT

Events
FOLFOX4 243/1123 (21.6%)
LV5FU2 279/1123 (24.8%)

HR [95% CI]: 0.84 [0.71–1.00]

Data cut-off: January 2007

A. de Gramont et al., ASCO 2007 / T. André et al. JCO 2009

ESMO PRECEPTORSHIP PROGRAM
Long-term Tolerance

Second cancer (% patients)

Peripheral Neuropathy

FOLFOX 5.5
LV5FU2 6.1

Evaluable patients
n=976 4-year
Grade 0 85.5%
Grade 1 12.0%
Grade 2 2.8%
Grade 3 0.7%

Data cut-off: January 2007
Overall survival Stage II / III

Data cut-off: January 2007

A. de Gramont et al., ASCO 2007 / T. André et al. JCO 2009

FOLFOX4 stage II
LV5FU2 stage II
FOLFOX4 stage III
LV5FU2 stage III

HR [95% CI]
Stade II 1.00 [0.70–1.41]
Stade III 0.80 [0.65–0.97]

p=0.986
p=0.023
XELOX
Stage III colon cancer
• No previous CT
• Resection ≤ 8 weeks
n=1886

Main endpoint
Better DFS

XELOX vs 5-FU/LV: NO16968 (XELOXANA) Phase III trial

Randomisation

n=944

XELOX (6 months)
Capecitabin 1000mg/m²
BID D1 to 14
(1 week rest)
+ oxaliplatin 130 mg/m² IV D1
every 3 weeks
8 cycles

Bolus 5-FU/LV (6 months)
Mayo Clinic [n=664]*oru
Roswell Park [n=278]**
Overall survival Xelox vs 5-FU/LV

HR = 0.87 (IC 95%: 0.72–1.05)  
*p = 0.1486

Mean follow-up: 59 months

Survival globale ITT population

Confirmed with longer follow-up: 73 vs 67%

78%

74%


ESMO PRECEPTORSHIP PROGRAM
## The last 15 years

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>3-y DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moertel 1990</td>
<td>Surveillance</td>
<td>52%</td>
</tr>
<tr>
<td>IMPACT 1993</td>
<td>Surveillance</td>
<td>44%</td>
</tr>
<tr>
<td>IMPACT 1994</td>
<td>FUFOL</td>
<td>62%</td>
</tr>
<tr>
<td>INT0089, 2005</td>
<td>FUFOL</td>
<td>63%</td>
</tr>
<tr>
<td>XELOXA, 2010</td>
<td>FUFOL ou RPMI</td>
<td>66%</td>
</tr>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>André, 2003</td>
<td>LV5FU2</td>
<td>61%</td>
</tr>
<tr>
<td>MOSAIC 2004</td>
<td>LV5FU2</td>
<td>65%</td>
</tr>
<tr>
<td>X-Act, 2005</td>
<td>Capecitabine</td>
<td>64%</td>
</tr>
<tr>
<td><strong>Poly CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOSAIC 2004</td>
<td>FOLFOX4</td>
<td>73%</td>
</tr>
<tr>
<td>XELOXA, 2010</td>
<td>XELOX</td>
<td>71%</td>
</tr>
</tbody>
</table>
A LITTLE BIT MORE COMPLICATED…
<table>
<thead>
<tr>
<th>Study</th>
<th>HR for DFS</th>
<th>P value</th>
<th>DFS Δ (%)</th>
<th>HR for OS</th>
<th>P value</th>
<th>OS Δ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIC (FOLFOX)</td>
<td>0.78</td>
<td>0.005</td>
<td>Δ 7.5%</td>
<td>0.80</td>
<td>0.023</td>
<td>Δ 4.2%</td>
</tr>
<tr>
<td></td>
<td>CI, 0.65-0.93 at 5 year</td>
<td></td>
<td>58.9% vs 66.4% at 5 year</td>
<td>CI, 0.65-0.97 at 6 year</td>
<td></td>
<td>68.7% vs 72.9% at 6 year</td>
</tr>
<tr>
<td>NSABP C-07 (FLOX)</td>
<td>0.78</td>
<td>0.0007</td>
<td>Δ 6.6%</td>
<td>0.85</td>
<td>0.052</td>
<td>Δ 2.7%</td>
</tr>
<tr>
<td></td>
<td>CI, 0.68-0.90 at 5 year</td>
<td></td>
<td>57.8% vs 64.4% at 5 year</td>
<td>CI, 0.72-1.00 at 5 year</td>
<td></td>
<td>73.8% vs 76.5% at 5 year</td>
</tr>
<tr>
<td>XELOXA (XELOX)</td>
<td>0.80</td>
<td>0.004</td>
<td>Δ 5%</td>
<td>0.83</td>
<td>0.04</td>
<td>Δ 3.0%</td>
</tr>
<tr>
<td></td>
<td>CI, 0.69-0.93 at 5 year</td>
<td></td>
<td>62% vs 67% at 3 year</td>
<td>CI, 0.70-0.99 at 5 year</td>
<td></td>
<td>74% vs 77% at 5y</td>
</tr>
<tr>
<td>X-ACT FU/FA bolus vs. Capecitabine</td>
<td>0.87</td>
<td>0.0528</td>
<td>Δ 3.6%</td>
<td>0.84</td>
<td>p=0.07</td>
<td>Δ 3.7%</td>
</tr>
<tr>
<td></td>
<td>CI, 0.75-1.00 at 3y</td>
<td></td>
<td>60.6% vs. 64.2% at 3y</td>
<td>CI: 0.69–1.01 @3y</td>
<td></td>
<td>77.6% vs. 81.3% @3y</td>
</tr>
</tbody>
</table>

1 André T, J Clin Oncol. 2009
2 Yothers G, J Clin Oncol 2011
3 Haller D, J Clin Oncol 2011
4 Schellekens IH, J Clin Oncol 2016
Overall survival stage III pT3-4 N+

For N 1-3:
- FOLFOX4: 440 patients, 117 events
- LV5FU2: 442 patients, 132 events

Log-rank $P = .248$
HR, 0.864; 95% CI, 0.673 to 1.108

For N > 3:
- FOLFOX4: 229 patients, 90 events
- LV5FU2: 231 patients, 117 events

Log-rank $P = .012$
HR, 0.705; 95% CI, 0.535 to 0.928
Recurrence risk over time ACCENT Database  N=12.233
A ROLE FOR TARGETED THERAPIES?
Bevacizumab

3 large negative studies (>6000 pts)
- NSABP- C08
- AVANT
- QUASAR 2
NSABP-C-08: bevacizumab, no effect

C. Allegra et al., ASCO 2011, A#3508

mFF6 1341 Pts, 224 deaths
mFF6+Bev 1337 Pts, 218 deaths
HR=0.96, 95% CI (0.79-1.15)
$p=0.64$

Allegra C et al 2013;31:359-64
Cetuximab

2 large negative studies (>6000 pts)
- N0147
- PETACC 8
PETACC8: PFS: Wt KRAS

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX4 + Cetuximab</th>
<th>FOLFOX4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No, events</td>
<td>190</td>
<td>179</td>
</tr>
<tr>
<td>S3-year PFS</td>
<td>75.1 [71.7; 78.1]</td>
<td>78.0 [74.8; 80.8]</td>
</tr>
<tr>
<td>HR pour SSR</td>
<td>1.047 [0.853; 1.286]</td>
<td>0.6562</td>
</tr>
<tr>
<td>p-value (log-rank)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meta-analysis: nothing....
3 MONTHS VERSUS 6 MONTHS... THE IDEA STORY...
# IDEA Trials Summary

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen(s)</th>
<th>Stage</th>
<th>Tumor Location</th>
<th>% CAPOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOSCA</td>
<td>CAPOX or FOLFOX4</td>
<td>II, III</td>
<td>Colon</td>
<td>35%</td>
</tr>
<tr>
<td>SCOT</td>
<td>CAPOX or mFOLFOX6</td>
<td>II, III</td>
<td>Colon/Rectum</td>
<td>67%</td>
</tr>
<tr>
<td>IDEA France</td>
<td>CAPOX or mFOLFOX6</td>
<td>III</td>
<td>Colon</td>
<td>10%</td>
</tr>
<tr>
<td>C80702</td>
<td>mFOLFOX6</td>
<td>III</td>
<td>Colon</td>
<td>0%</td>
</tr>
<tr>
<td>HORG</td>
<td>CAPOX or FOLFOX4</td>
<td>II, III</td>
<td>Colon</td>
<td>58%</td>
</tr>
<tr>
<td>ACHIEVE</td>
<td>CAPOX or mFOLFOX6</td>
<td>III</td>
<td>Colon</td>
<td>75%</td>
</tr>
</tbody>
</table>

Shi et al ASCO 2017
Global IDEA study: toxicity

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>FOLFOX</th>
<th></th>
<th>CAPOX</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G0 – 1</td>
<td>G2</td>
<td>G3 – 4</td>
<td>p-value</td>
</tr>
<tr>
<td>Global</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>3 months</td>
<td>30%</td>
<td>32%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>11%</td>
<td>32%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>3 months</td>
<td>83%</td>
<td>14%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>52%</td>
<td>32%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>3 months</td>
<td>84%</td>
<td>11%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>80%</td>
<td>13%</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

Less toxicity with 3 months of treatment..

Grothey A et al. NEJM 2018;378:1177-88
Disease-free survival: primary endpoint not met

Grothey A et al. NEJM 2018;378:1177-88
Primary DFS Analysis (mITT), cont.

Statistical Conclusions

3m TRT better

6m TRT better

Not proven

DFS HR = 1.07
95% CI, 1.00 to 1.15

Hazard Ratio

1.0

1.12

Non-Inferiority Margin

TRT: treatment

Presented by Qian Shi, PhD on behalf of IDEA collaborators

ESMO PRECEPTORSHIP PROGRAM

Presented By Qian Shi at 2017 ASCO Annual Meeting
DFS Forrest-plot....

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/Total No.</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>3263/12,834</td>
<td>1.07 (1.00–1.15)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX</td>
<td>1964/7763</td>
<td>1.16 (1.06–1.26)</td>
<td>0.006</td>
</tr>
<tr>
<td>CAPOX</td>
<td>1299/5071</td>
<td>0.95 (0.85–1.06)</td>
<td></td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1, T2, or T3</td>
<td>2175/10,090</td>
<td>1.04 (0.96–1.13)</td>
<td>0.14</td>
</tr>
<tr>
<td>T4</td>
<td>1075/2655</td>
<td>1.16 (1.03–1.31)</td>
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</tr>
<tr>
<td>Nodal stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>1866/9168</td>
<td>1.07 (0.97–1.17)</td>
<td>0.91</td>
</tr>
<tr>
<td>N2</td>
<td>1378/3567</td>
<td>1.07 (0.96–1.19)</td>
<td></td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1, T2, or T3 and N1</td>
<td>1313/7471</td>
<td>1.01 (0.90–1.12)</td>
<td>0.11</td>
</tr>
<tr>
<td>T4 or N2</td>
<td>1935/5256</td>
<td>1.12 (1.03–1.23)</td>
<td></td>
</tr>
<tr>
<td>T4 and N2</td>
<td>518/966</td>
<td>1.06 (0.89–1.25)</td>
<td></td>
</tr>
<tr>
<td>T4 and N1</td>
<td>553/1679</td>
<td>1.26 (1.06–1.49)</td>
<td></td>
</tr>
<tr>
<td>T1, T2, or T3 and N2</td>
<td>858/2597</td>
<td>1.09 (0.96–1.25)</td>
<td></td>
</tr>
</tbody>
</table>

Grothey A et al. NEJM 2018;378:1177-88
In conclusion, among patients with stage III colon cancer who were receiving adjuvant therapy with FOLFOX or CAPOX, the noninferiority of a 3-month duration of therapy, as compared with a 6-month duration, was not confirmed. However, the results were strongly affected by the selected treatment and risk group. In patients treated with CAPOX, 3 months of therapy was as effective as 6 months, particularly in the lower-risk subgroup. In patients treated with FOLFOX, 6 months of therapy resulted in a higher rate of disease-free survival, particularly in the high-risk subgroup. These data suggest that the choice of treatment regimen, duration of therapy, and characteristics of the patients may be balanced against the substantial risk of increased toxicity of longer oxaliplatin-based therapy, including persistent neurotoxicity.
<table>
<thead>
<tr>
<th>Subgroups</th>
<th>CT</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XELOX</td>
<td>FOLFOX</td>
<td>XELOX/FOLFOX combined</td>
</tr>
<tr>
<td></td>
<td>SSR 3-year, % (95% CI)</td>
<td>HR (95% CI)</td>
<td>SSR 3-year, % (95% CI)</td>
</tr>
<tr>
<td>Low risk (T1-3 N1) ~60%</td>
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<td></td>
<td>3 m</td>
<td>6 m</td>
<td>3 m</td>
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<tr>
<td>High risk (T4 and / or N2) ~40%</td>
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<tr>
<td></td>
<td>3 m</td>
<td>6 m</td>
<td>3 m</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>3 m</td>
<td>6 m</td>
<td>3 m</td>
</tr>
</tbody>
</table>

**Non-inferior** | **Uncertain** | **Inferior**
<table>
<thead>
<tr>
<th>Subgroups</th>
<th>3-year DFS (%)</th>
<th>HR / CT and subgroups</th>
<th>CT</th>
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<td>XELOX/FOLFOX combined</td>
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<tr>
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Grothey A et al. 2018;378:1177-88
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<td>~60%</td>
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<td>XELOX</td>
<td>SSR 3-year, % (95% CI) 3 m 6 m</td>
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<td>~40%</td>
<td></td>
<td>XELOX</td>
<td>64.1 (61.3-67.1) 64.0 (61.2-67.0) 1.02 (0.89-1.17)</td>
<td>61.5 (58.9-64.1) 64.7 (62.2-67.3) 1.20 (1.07-1.35)</td>
<td>62.7 (60.8-64.4) 64.4 (62.6-66.4) 1.12 (1.03-1.23)</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td>FOLFOX</td>
<td>SSR 3-year, % (95% CI) 3 m 6 m</td>
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**Non-inferior**

**Uncertain**

**Inferior**

Grothey A et al. 2018;378:1177-88
<table>
<thead>
<tr>
<th>Subgroups</th>
<th>XELOX</th>
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<th>XELOX/FOLFOX combined</th>
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<tr>
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<td>HR (95% CI)</td>
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<tr>
<td></td>
<td>64.0 (61.2-67.0)</td>
<td></td>
<td>64.7 (62.2-67.3)</td>
</tr>
<tr>
<td>Combined</td>
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</tbody>
</table>

**3-year DFS (%) HR / CT and subgroups**

**CT**

**XELOX**

**FOLFOX**

**XELOX/FOLFOX combined**

**SSR 3-year, % (95% CI)**

**HR (95% CI)**

**SSR 3-year, % (95% CI)**

**HR (95% CI)**

**SSR 3-year, % (95% CI)**

**HR (95% CI)**

**Subgroups**

- **Low risk (T1-3 N1) ~60%**
- **High risk (T4 and / or N2) ~40%**
- **Combined**

**Non-inferior**

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Grothey A et al. 2018;378:1177-88
## 3-year DFS (%)

### HR / CT and subgroups

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<td>3 m</td>
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<td><strong>XELOX</strong></td>
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</tr>
<tr>
<td>85.0 (83.1-86.9)</td>
<td>83.1 (81.1-85.2)</td>
<td><strong>0.85</strong> (0.71-1.01)</td>
<td>81.9 (80.2-83.6)</td>
<td>83.5 (81.9-85.1)</td>
</tr>
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<td><strong>FOLFOX</strong></td>
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<td>1.10 (0.96-1.26)</td>
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<td>1.20 (1.07-1.35)</td>
</tr>
<tr>
<td>Combined</td>
<td>75.9 (74.2-77.6)</td>
<td>0.95 (0.85-1.06)</td>
<td>73.6 (71.2-75.1)</td>
<td>1.16 (1.06-1.26)</td>
</tr>
</tbody>
</table>

P-value interaction test: CT: 0.0061
Risk-groups : 0.11
# IDEA: Recommandations

<table>
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<tr>
<th>Risk groups</th>
<th>CT</th>
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<tr>
<td>Low-risk (T1-3 N1)</td>
<td>XELOX</td>
<td>3 months</td>
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<tr>
<td>~60%</td>
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<td></td>
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<tr>
<td>High-risk (T4 et/ou N2)</td>
<td>FOLFOX</td>
<td>6 months</td>
</tr>
<tr>
<td>~40%</td>
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Non-inferior | Uncertain | Inferior

Grothey A et al. 2018;378:1177-88
### IDEA : Recommandations

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- **Non-inferior**
- **Uncertain**
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Grothey A et al. 2018;378:1177-88
STAGE II DISEASE.... !!!!!
Stage II

Small benefit (3%) with 5FU

No clear improvement with FOLFOX

Is-t possible to define a subgroup that could benefit from FOLFOX?
Some Stage II tumours with poor prognosis

![Graph showing 5-year real overall survival (OS) for Stage II and Stage III tumours.](image-url)
QUASAR – old study, small benefit

Survival – Dukes stage B

% Survival

Chemotherapy
Observation

Deaths O-E Var
Chemotherapy 224 -22.1 121.5
Observation 262

p=0.04

Years from randomisation

ESMO PRECEPTORSHIP PROGRAM
MOSAIC : FOLFOX vs LV5FU2, all stage II patients: no difference

![Graph showing overall survival comparison between FOLFOX4 and LV5FU2](image)

- Log-rank $P = .981$
- HR, 1.004; 95% CI, 0.744 to 1.354

ESMO PRECEPTORSHIP PROGRAM

MOSAIC late follow-up and Stage II disease

A

Low risk

B

High risk

Overall Survival (probability)

Time Since Enrollment (years)

FOLFOX4

LVFU2

Events

No. at risk

Time Since Enrollment (years)

Events

No. at risk

FOLFOX4

LVFU2

Events

Log-rank P = .515

HR, 1.168; 95% CI, 0.730 to 1.870

Log-rank P = .578

HR, 0.895; 95% CI, 0.606 to 1.323
Do we even know how to select high risk patients?

Overall 5-year survival

- 1950 colon cancer
  - Groupe 1, occlusion without perforation, n=120 33%
  - Groupe 2, occlusion + perforation tumour, n=35 50%
  - Groupe 3, occlusion + proximal perforation, n=13 33%
  - Groupe 4, no occlusion, no perforation, n=1682 51%

Fig 2. Five-year cancer-free survival.

Chen et al, 2000
Low number of lymph nodes remains not good…

- 134 567 pT3N0
- < 12 LN analysed
  - 23.3% of the patients
  - 46.8% in 2003 – 12.5% en 2012
  - 5-year overall survival: 66.8%
    - 69.8% > 12 LN versus 58.7% p< 0.001
  - 16.7% of adjuvant CT if less than 12 LN:
    - OS with CT 78.4% versus 54.7% without, p< 0.001
Role of perineural invasion

- US National Database: 21,488 patients:
  - 55.2% T3, 23.1% T2, 14.4% T1, 7.3% T4 disease
  - 4.6% (n = 987) had PNI
  - 86.8% no PNI and no CT; 8.7% no PNI and CT; 3.7% (n = 785) PNI and no CT, and 0.9% (n = 202) PNI and CT
  - Patients with PNI who had CT: younger, private insurance, fewer comorbidities greater T stage
  - PNI and CT improved OS in T3-4 disease (P<0.001), but not in T1-2 disease.
  - Multivariate analysis: PNI greater HR mortality 1.38, CT decreased the hazard of mortality by 43%
MSI + tumours, no benefit from 5FU based CT

No benefit in Stage III patients, could be even deleterious in stage II patients

ColoPrint, useful to select patients??
Immunoscore: an hope

Good reproducibility

Immunoscore and stage II disease: DFS

High
- Events/Total: 83/375
- 5-year KM: 76.8 [72.3 – 81.5]
- HR: 0.59 [0.43 – 0.81]

Int
- Events/Total: 88/694
- 5-year KM: 85.9 [83.1 – 88.8]
- HR: 0.36 [0.23 – 0.56]

Low
- Events/Total: 28/364
- 5-year KM: 91.2 [87.9 – 94.5]
- HR: 0.0001

C-index = 0.65 (0.54-0.75)

Galon J. et al., ASCO 2016, OS 3500
Tumor associated macrophages (TAM)

- Two types:
  - Good TAM M1
  - Bad TAM M2

- Definition of a prognostic tool:
  - stage II colon cancer receiving or not adjuvant CT
  - First step: cohort of 521 patients
  - Validation on a cohort of 314 patients
  - Best tool: IHC CD206/CD68 ratio
TAM: a predictive effect???

![Graph E: Low CD206/CD68 ratio](image1)

- **Overall survival (%)**
- **Time (month)**
- **Adjuvant chemotherapy**
- Yes, event = 18 Log rank $P = 0.706$
- No, event = 21 HR (95%CI), 1.129 (0.601–2.119)

![Graph F: High CD206/CD68 ratio](image2)

- **Overall survival (%)**
- **Time (month)**
- **Adjuvant chemotherapy**
- Yes, event = 13 Log rank $P = 0.029$
- No, event = 18 HR (95%CI), 0.460 (0.225–0.942)

No. at risk
- Yes: 190, 190, 188, 182, 155, 121, 78, 0
- No: 245, 245, 241, 236, 217, 169, 109, 0

Interaction analysis HR = 0.406 (0.157–1.052), $P = 0.063$
Prognostic impact of postoperative ctDNA?

N=130
ctDNA samples n=829

Postoperative detection (6 weeks after surgery)
N = 93
ctDNA +, n=8

Post-CT detection
N = 58
ctDNA +, n = 10

→ Delay between ctDNA and radiological recurrence n = 14

T. Reinart et al., ESMO® 2018, Abs P456PD
Prognostic impact of postoperative ctDNA?

- Results: prognostic impact of postoperative ctDNA (N=93)

- Post-operative (n=93): positive ctDNA in 8/93 (9%)
  - recurrence observed in 6/8 (75%) ctDNA+ vs 10/85 (12%) in ctDNA-.
  - PFS significantly different in ctDNA+ vs ctDNA- patients (HR 9.7, p = 0.000018)
Algorithm of decision in stage II disease

Stage II colon cancer

- Age < 70y
  - pT4
    - pMMR / MSS: Consider adj. CTx
    - dMMR / MSI-H: No adj. CTx
  - pT3
    - Additional marker: less than 12 LN / PNI ? / Gene signature / Immunoscore?

- Advanced age or comorbidities: No adj. CTx
Stage III disease

Complete resection

Adjuvant CT has to be discussed

DPD measure before tmt

Reference

Options

Folfox4 or Xelox

>70 y:
Capecitabine or LV5FU2

CI oxaliplatin:
LV5FU2 or cap

pT3N1 3 months
XELOX

PT3N2 6 months
XELOX or FOLFOX

Options

CI oxaliplatin:
LV5FU2 or cap

>70 y:
Capecitabine or LV5FU2

Reference

DPD measure before tmt

Complete resection

Adjuvant CT has to be discussed
# Nut Consumption and Survival in Patients With Stage III Colon Cancer: Results From CALGB 89803 (Alliance)

Temidayo Fadelu, Sui Zhang, Donna Niedzwiecki, Xing Ye, Leonard B. Saltz, Robert J. Mayer, Rex B. Mowat, Renaud Whittom, Alexander Hantel, Al B. Benson, Daniel M. Atienza, Michael Messino, Hedy L. Kindler, Alan Venook, Shuji Ogino, Kimmie Ng, Kana Wu, Walter Willett, Edward Giovannucci, Jeffrey Meyerhardt, Ying Bao, and Charles S. Fuchs

## Categories of Intake (servings)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Never</th>
<th>&lt; 1 per Month</th>
<th>1-3 per Month</th>
<th>≥ 1 per Week</th>
<th>P_{trend}</th>
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<tr>
<td>Tree nuts</td>
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<tr>
<td>DFS</td>
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<td>No. of events/total No. of patients</td>
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<td>77/287</td>
<td>40/152</td>
<td>25/120</td>
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<td>HR (95% CI), adjusted 1†</td>
<td>Ref</td>
<td>0.72 (0.53 to 0.97)</td>
<td>0.66 (0.46 to 0.96)</td>
<td>0.53 (0.34 to 0.84)</td>
<td>.02</td>
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<tr>
<td>HR (95% CI), adjusted 2‡</td>
<td>Ref</td>
<td>0.68 (0.51 to 0.93)</td>
<td>0.66 (0.45 to 0.96)</td>
<td>0.54 (0.34 to 0.85)</td>
<td>.04</td>
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<td>HR (95% CI), adjusted 1†</td>
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<td>0.84 (0.61 to 1.16)</td>
<td>0.67 (0.44 to 1.02)</td>
<td>0.55 (0.33 to 0.91)</td>
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<td>HR (95% CI), adjusted 2‡</td>
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<td>0.79 (0.57 to 1.10)</td>
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