DISCLOSURE SLIDE

Employment: None; Stock Ownership: None

Consultant or Advisory Role: Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas.

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Grant support: Merck Serono, Roche.

Others: Executive Board member of ESMO, Chair of Education ESMO, General and Scientific Director INCLIVA, Associate Editor: Annals of Oncology and ESMO Open, Editor in chief: Cancer Treatment Reviews.
CURRENT STANDARD OF CARE AND PRACTICE
CHANGING STUDIES IN OPERABLE COLON CANCER

Andrés Cervantes
Professor of Medicine
CURRENT APPROACH TO LOCALISED COLON CANCER

Clinical Staging

Surgical resection

Pathology assessment and estimation of risk

Treatment based upon TNM stage

Postoperative chemotherapy for 3 months: standard of care in stage III

Postoperative chemotherapy of value for some stage II colon cancers
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. EMMERSON, M.D., DOUGLAS C. TORMEY, M.D.,
JOHN H. GLICK, M.D., MICHAEL H. VEEDER, M.D., AND JAMES A. MAILLIARD, M.D.*

5-FU + Levamisol 12 months in 1990

Historical landmarks in localised colon cancer

**5-FU + Levamisol in 1990**

**DFS HR: 0.55 p:0.0001**

**OS HR: 0.67 p:0.006**

Absolute increase in OS at 3.5 years: 16%

ESMO MAGNITUDE OF THE CLINICAL BENEFIT SCALE

- 5-FU + Levamisol in 1990  DFS HR. 0.55 p:0.0001 OS HR:67 p:0.006

### Historical landmarks in stage III colon cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>12 months 5-FU + Levamisol</td>
</tr>
<tr>
<td>1996</td>
<td>6 months 5-FU+ Folinic acid</td>
</tr>
</tbody>
</table>
| 2004 | 6 months FOLFOX4 is better than LV5FU2  

Capecitabine at least as active as IV 5-FU/FA  
UFT/LV similar activity compared to IV 5-FU/FA |
| 2006 | Bolus 5-FU/FA/oxaliplatin better than bolus 5-FU/FA |
| 2008 | CAPOX better than bolus 5-FU-LV |
| 2018 | 3 months as good as 6 for stage III colon cancer |
Historical landmarks in stage III colon cancer

1990  12 months 5-FU + Levamisol
1996  6 months 5-FU + Folinic acid
2004  6 months FOLFOX4 is better than LV5FU2
       Capecitabine at least as active as IV 5-FU/FA
       UFT/LV similar activity compared to IV 5-FU/FA
2006  Bolus 5-FU/FA/oxaliplatin better than bolus 5-FU/FA
2008  CAPOX better than bolus 5-FU-LV
2018  3 months as good as 6 for stage III colon cancer
Adjuvant therapy increases the chance of survival: Evidence in 13,793 stage III colon cancer patients.

Absolute increase at 8 years 10.3%
# Adding Oxaliplatin to 5-FU based adjuvant therapy in localised colon cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Control</th>
<th>Exp.</th>
<th>Stage</th>
<th>DFS HR P value</th>
<th>OS HR P value</th>
<th>Absolute Gain in OS</th>
<th>G3 Neurotox</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIC⁴</td>
<td>2246</td>
<td>FULV2</td>
<td>FOLFOX4</td>
<td>II/III</td>
<td>0.80 0.003</td>
<td>0.84 0.046</td>
<td>4.2% at 6 y stage III</td>
<td>12%</td>
</tr>
<tr>
<td>NSABP-C07²</td>
<td>2407</td>
<td>FULV Roswell</td>
<td>FLOX</td>
<td>II/III</td>
<td>0.80 0.0034</td>
<td>0.82 0.002</td>
<td>2.7 % at 5 y Stage III</td>
<td>8.2%</td>
</tr>
<tr>
<td>XELOXA³</td>
<td>1886</td>
<td>FULV Mayo</td>
<td>CAPEOX</td>
<td>III</td>
<td>0.80 0.0038</td>
<td>0.83 0.04</td>
<td>6 % at 7 y</td>
<td>11%</td>
</tr>
</tbody>
</table>

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3Schmoll HJ et al. J Clin Oncol 2015; 33:3733-3740
ESMO MAGNITUDE OF THE CLINICAL BENEFIT SCALE

- MOSAIC: No Grade A
- NSABP C07: No Grade A
- XELOXA: Grade A in OS over 5%

Adding Oxaliplatin to 5-FU based adjuvant therapy in localised colon cancer: Stage II vs III

<table>
<thead>
<tr>
<th>Stage</th>
<th>FL Survival %</th>
<th>FL + Oxaliplatin Survival %</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>86.8</td>
<td>86.9</td>
<td>1.00 (0.70 to 1.41)</td>
<td>.986</td>
</tr>
<tr>
<td>Stage III</td>
<td>68.7</td>
<td>72.9</td>
<td>0.80 (0.65 to 0.97)</td>
<td>.023</td>
</tr>
</tbody>
</table>
Current approach to localised colon cancer
MUST DO

Postoperative chemotherapy standard of care in stage III

Oxaliplatin–based treatment for 3 months

FOLFOX4, CAPOX,

FLOX not recommended due to higher incidence of diarrhea

In patients without comorbidities and younger than 70

Pay attention to sensory peripheral neurotoxicity during treatment
Current approach to localised colon cancer
MUST NOT DO

Never use Irinotecan, Bevacizumab or anti-EGFR antibodies
Current questions to adjuvant therapy colon cancer

- Should we check for Microsatellite instability (MIS)?
- How to select stage II colon cancer patients for adjuvant therapy?
- What about DDP genotyping or fenotyping?
- Duration of treatment: 3 versus 6 months?
- Any role for Precision Medicine?
MSI is strongly prognostic,

... but not clearly predictive


Fig 3. Recurrence by mismatch repair (MMR) status: (A) all patients, (B) colon stage II only. Obs., observed number of recurrences; Exp., expected number of recurrences.
Current questions to adjuvant therapy colon cancer

- Should we check for Microsatellite instability (MIS)?
- How to select stage II colon cancer patients for adjuvant therapy?
- What about DDP genotyping or fenotyping?
- Duration of treatment: 3 versus 6 months?
- Any role for Precision Medicine?
Characterization of high risk stage II colon cancer

- Risk factors
  - Perforation
  - Occlusion
  - pT4
  - Less than 12 LN
  - Poorly differentiated tumors
  - Vascular invasion
  - Lymphatic invasion
  - Perineural invasion
  - High CEA

In MSS cancers

Adjuvant-FU based CT to be discussed with patients
Adjuvant therapy increases the chance of survival: Evidence in 7,105 stage II colon cancer patients

Absolute increase at 8 years 5.4%

Current questions to adjuvant therapy colon cancer

- Should we check for Microsatellite instability (MIS)?
- How to select stage II colon cancer patients for adjuvant therapy?
- What about DDP genotyping or phenotyping?
- Duration of treatment: 3 versus 6 months?
- Any role for Precision Medicine?
Dihydropyrimidin dehydrogenase (DPD) as predictive marker of toxicity

- DPD is the main enzyme involved in fluoropyrimidine catabolism
- 3-5% of patients have deficiencies of DPD function due to genetic polymorphisms
- These deficiencies may lead to fatal toxicity
- EMA based on the recommendation of the Pharmacovigilance Risk Assessment Committee indicates that testing for DPD insufficiency should be conducted before initiating fluoropyrimidines (March, 13th, 2020)
Current questions to adjuvant therapy colon cancer

- Should we check for Microsatellite instability (MIS)?
- How to select stage II colon cancer patients for adjuvant therapy?
- What about DDP genotyping or phenotyping?
- Duration of treatment: 3 versus 6 months?
- Any role for Precision Medicine?
Duration of Adjuvant Chemotherapy for Stage III Colon Cancer


HR 1.07 (1.00-1.15), Δ3 yr DFS = -0.9%
Statistical non-inferiority of 3 months of therapy was not confirmed

Debates over the clinical interpretation considering the huge reduction in toxicity

No. at Risk

<table>
<thead>
<tr>
<th>Years since Randomization</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>6 Months</td>
<td>6410</td>
<td>5530</td>
<td>4477</td>
<td>3065</td>
<td>1679</td>
<td>873</td>
<td>334</td>
</tr>
<tr>
<td>3 Months</td>
<td>6424</td>
<td>5446</td>
<td>4464</td>
<td>3000</td>
<td>1609</td>
<td>826</td>
<td>321</td>
</tr>
</tbody>
</table>

6 trials, 12,834 pts

- TOSCA
- SCOT
- IDEA FRANCE
- ACHIEVE
- HORG
- CALGB/SWOG 80702

Presented by Alberto Sobrero at TBD
IDEA overall population OS

Δ OS at 5 yr = -0.4%  95%CI +1.5% to -2.4%

HR: 1.02 (0.95-1.11)

FDR adjusted NI p-value = 0.0583 > 0.025
Statistical conclusion: Fail to reject null hypothesis after multiplicity adjustment


<table>
<thead>
<tr>
<th>Duration</th>
<th>Events/Total</th>
<th>HR (95% CI)</th>
<th>5 year rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Months</td>
<td>1314/6425</td>
<td>1.02 (0.95-1.11)</td>
<td>82.4 (81.4-83.3%)</td>
</tr>
<tr>
<td>6 Months</td>
<td>1270/6410</td>
<td>Reference</td>
<td>82.8 (81.8-83.8%)</td>
</tr>
</tbody>
</table>

FDR Adjusted Stratified Logrank p-value: 0.6434
FDR Adjusted Stratified NIF p-value: 0.0583
SUMMARY OF IDEA STAGE III STUDY

1. 12,835 patients randomized
2. 2 to 6 times lower toxicities; 3 times lower neurotoxicity grade 2+ : 14 vs 46%
3. Primary (3 yr DFS) and two secondary endpoints (5 yr OS and DFS) show minimal, clinically irrelevant differences for most patients with stage 3 colon cancer using 3 months of adjuvant therapy
4. Drug regimen effect was observed in every endpoint, although the trial was not randomized for regimen
   - No loss of efficacy was observed in low risk cancers with 3m CAPOX
   - Minimal loss with 3m CAPOX in high risk and 3m FOLFOX in low risk cancers
   - Relevant loss with 3m FOLFOX in high risk cancers
5. Strong correlation between DFS at 3yrs and 5yr OS data
IMPLICATIONS FOR CLINICAL PRACTICE

1. 60% of patients with stage 3 colon cancer are low risk and should receive 3 month of CAPOX

2. 40% of patients are high risk. For the majority of these, the risk-benefit assessment suggests 3 months of CAPOX as well. For those unwilling to loose even 1-2% of efficacy, 6 months of therapy is recommended.

3. For High risk cancers, novel prognostic factors including Immunoscore and/or ctDNA as marker for MRD, may help to define the best adjuvant therapy in the future\textsuperscript{1-2}

\textsuperscript{1}Pages F, Ann Oncol 2020; \textsuperscript{2}Taleb J, ESMO 2019 (abstract, Ann Oncol 2019. 30, 867-867)
Current questions to adjuvant therapy colon cancer

- Should we check for Microsatellite instability (MIS)?
- How to select stage II colon cancer patients for adjuvant therapy?
- What about DDP genotyping or phenotyping?
- Duration of treatment: 3 versus 6 months?
- Any role for Precision Medicine?
Circulating tumor cell-free DNA may detect residual disease and predict recurrence in patients with stage II colon cancer?

Tie J, et al. Sci Transl Med 2017; 8:
Circulating tumor cell-free DNA may detect Minimal Residual Disease and predict recurrence in patients with stage II-III colon cancer?

Results | Relapse-Risk Stratification by ctDNA Status

**Post-operative setting**

- **Strata:**
  - ctdNA=0
  - ctdNA=1

- **Graph:**
  - Disease-free Survival vs Time (months)
  - HR: 16.5; 95% CI: 7.2-38.0; P < 0.001
  - p < 0.0001

- **Number at risk**
  - ctdNA=0: 138, 132, 48, 18, 1
  - ctdNA=1: 14, 10, 1, 1, 0

- **MRD-Positive:** 9.2% (14/152)
- **Patients eventually relapsed:** 78.5%

**Post-ACT setting**

- **Strata:**
  - ctdNA=0
  - ctdNA=1

- **Graph:**
  - Disease-free Survival vs Time (months)
  - HR: 27.9; 95% CI: 9.2-85.1; P < 0.001
  - p < 0.0001

- **Number at risk**
  - ctdNA=0: 68, 66, 26, 12, 1
  - ctdNA=1: 16, 13, 2, 2, 0

**Post-definitive treatment setting**

- **Strata:**
  - ctdNA=0
  - ctdNA=1

- **Graph:**
  - Disease-free Survival vs Time (months)
  - HR: 47.5; 95% CI: 17.3-130.3; P < 0.001
  - p < 0.0001

- **Number at risk**
  - ctdNA=0: 120, 116, 59, 27, 2
  - ctdNA=1: 19, 14, 2, 2, 0

**ctDNA positivity:**

- In the post-operative setting, ctDNA positivity was strongly associated with inferior DFS.
- In the post-ACT setting, ctDNA positivity was associated with worse DFS.
- In the post-definitive treatment setting, ctDNA positivity was associated with worse DFS.
Thanks