Adjuvant / neoadjuvant systemic treatment in colorectal cancer

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8th ESO ARAB AND SOUTHERN EUROPEAN COUNTRIES
MASTERCLASS IN CLINICAL ONCOLOGY,
23-27/1/2020, LIMASSOL, CYPRUS
• Conflict of Interest:

None
• **Outline**
  • Adjuvant therapy
  • Stage II
  • Stage III disease
  • Biological agents, Irinotecan
  • Prognostic tools, genomic assays, molecular pathology - optimal decision making
  • Elderly
  • Neo-adjuvant therapy
  • Chemotherapy
  • Immunotherapy
## Survival by surgical stage

<table>
<thead>
<tr>
<th>Surgical stage</th>
<th>5-year survival (%) – surgery alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>85–95%</td>
</tr>
<tr>
<td>II</td>
<td>55–80%</td>
</tr>
<tr>
<td>III</td>
<td>30–60%</td>
</tr>
<tr>
<td>IV</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Adapted from O’Connell In: ASCO Educational Book 1994
Adjuvant therapy

• Goal
  – To destroy potentially remaining undetected foci of microscopic disease
  – To increase chances of cure

• Treatment efficacy only based on studies and statistics
  – Patients are not diseased
  – Prescription based on prognostic factors
  – No tumour or parameter for monitoring
Adjuvant chemotherapy

Adjuvant setting groups

Adjuvant chemotherapy

Stage III disease

Adjuvant Therapy Increases OS: ACCENT Database of 20,898 Patients

Stage II

- Surgery alone: 66.8%
- Surgery + FU-based chemotherapy: 72.2%

\[\Delta = 5.4\% \quad P = .026\]

Stage III

- Surgery alone: 42.7%
- Surgery + FU-based chemotherapy: 53.0%

\[\Delta = 10.3\% \quad P < .0001\]

Prognostic factors in Stage II/III colon cancer: TNM remains the main determinant

<table>
<thead>
<tr>
<th>Disease-free survival</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥5</td>
<td>4.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tumour depth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>1.2</td>
<td>0.2545</td>
</tr>
<tr>
<td>T4</td>
<td>1.8</td>
<td>0.0033</td>
</tr>
<tr>
<td>High grade</td>
<td>1.3</td>
<td>0.0017</td>
</tr>
<tr>
<td>Age ≥ 60 yrs</td>
<td>1.0</td>
<td>0.6447</td>
</tr>
<tr>
<td>Female</td>
<td>0.94</td>
<td>0.4130</td>
</tr>
<tr>
<td>Right colon</td>
<td>0.92</td>
<td>0.2537</td>
</tr>
</tbody>
</table>

7 studies; n=3341

Adjuvant Therapy Options for Stage III Colon Cancer

• **Oxaliplatin-based chemotherapy:** standard adjuvant treatment of stage III colon cancer in good performance score patients
  – FOLFOX
  – XELOX (CapeOx)

• **Fluoropyrimididine monotherapy:** considered for patients who cannot tolerate more aggressive oxaliplatin-based regimens
  – 5-FU/LV
  – Capecitabine
## Adjuvant Therapy
### Stage III Colon Cancer

<table>
<thead>
<tr>
<th>Trials</th>
<th>vs 5FU/ folinic</th>
<th>Survival difference (%)</th>
<th>HR(CI 95%)</th>
<th>Follow up (yr)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIQ</td>
<td>FOLFOX</td>
<td>4.2</td>
<td>0.8(0.65-0.97)</td>
<td>6</td>
<td>0.023</td>
</tr>
<tr>
<td>X-act</td>
<td>Capecitabine</td>
<td>3</td>
<td>0.86(0.74-1.01)</td>
<td>6.9</td>
<td>0.06</td>
</tr>
<tr>
<td>NO16968 (XELOXA)</td>
<td>XELOX</td>
<td>4</td>
<td>0.83(0.7-0.99)</td>
<td>7</td>
<td>0.037</td>
</tr>
<tr>
<td>NSABP C-07</td>
<td>FLOX</td>
<td>2.7</td>
<td>0.85(0.72-1)</td>
<td>5</td>
<td>0.052</td>
</tr>
</tbody>
</table>
Stage II

• Should adjuvant chemotherapy be offered?
• Prognostic risk factors better defined
• Do they also predict therapeutic outcome?

Area of controversy
Stage II disease: not always better prognosis than a stage III!!!

Stage II / Risk factors

- Clinical obstruction
- T4 lesions
- Perforation
- Poorly differentiated tumour
- Lymphovascular invasion
- Poor yield of lymph nodes in the resected surgical specimen (min.12)
Stage II: Risk of cancer death and death from any other cause by age

### IMPACT – pooled analysis

**Efficacy of 5FU/LV in Duke’s B2 colon cancer**

5 year results: 1016 pts/5 trials

<table>
<thead>
<tr>
<th></th>
<th>5FU/LV</th>
<th>Control</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>76%</td>
<td>73%</td>
<td>0.83</td>
<td>0.061</td>
</tr>
<tr>
<td>OS</td>
<td>82%</td>
<td>80%</td>
<td>0.81</td>
<td>0.057</td>
</tr>
</tbody>
</table>

“Recommended that adjuvant chemotherapy should not be offered routinely for patients with stage II colon cancer”

**IMPACT B2 Investigators, JCO 1999, 1356-1363**
SEER database retrospective review

- 3151 “usual” risk patients with stage II disease
- 27% > 70 yrs old
- OS: Chemotherapy 75% vs 73% for observation

D Schrag et al. JCO 2002;20:3999-4005
QUASAR: adjuvant chemotherapy significantly reduces recurrence in stage II

Hazard ratio = 0.78
(95% CI: 0.67–0.91)
p=0.001

Also a modest improvement in overall survival (3.6%) (p=0.04)

Quasar Collaborative Group, Lancet 2007, 370 (604): 2020-2029
Quasar Collaborative Group, Lancet 2007, 370 (604): 2020-2029

Figure 3: Relative risk of recurrence with chemotherapy by site, stage, sex, age, chemotherapy schedule, and timing
QUASAR

• Limitations:
  a. included population with rectal cancer as well stage I and III disease
  b. median number of lymph nodes examined per specimen only 6 (64% patients < 12 lymph nodes)!!!
  c. some patient received: RT, levamisole, portal vein 5FU
Adjuvant therapy-Irinotecan

- CALGB 89803: IFL vs bolus 5-FU/folinic
- PETACC3: FOLFIRI vs infusional 5-FU/folinic
- ACCORD02/FFCD9802: FOLFIRI vs infusional 5-FU/folinic
- N0147: FOLFIRI (140 pts) ± Cetuximab (40 pts)* vs FOLFOX ± Cetuximab
  * 3yr survival rate: 92.3 vs 69.8%,
  DFS, HR=0.53, 0.26-1.1, p=0.09, OS, HR=0.45, 0.17-1.16, p=0.1 (med fup: 5.95 yrs)

Adjuvant therapy - Bevacizumab

- **NSABP C-08** (2,000 pts, stage II-III): FOLFOX+Bev vs FOLFOX:
  no advantage

- **AVANT** (3,451 pts, stage II-III): FOLFOX vs FOLFOX+Bev vs XELOX+Bev:
  no advantage

Allegra CJ et al. JCO 2011; 29(1):11-16, Andre T et al. JCO 2011; 29: Abstract 3509
Adjuvant therapy - Cetuximab

- 2686 pts, stage III:
  FOLFOX + Cetuximab vs FOLFOX: 
  no advantage

MSI-H (microsatellite unstable)

- More frequently in the right colon
- Poorly differentiated histology
- Mucinous appearance
- Lymphocytic expression

They look ominous but have better prognosis
## MSI probability by surgical stage

<table>
<thead>
<tr>
<th>Source</th>
<th>ACCENT</th>
<th>NSABP</th>
<th>PETACC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No pts</td>
<td>No pts</td>
<td>No pts</td>
</tr>
<tr>
<td>All pts</td>
<td>1,027</td>
<td>1,589</td>
<td>1,217</td>
</tr>
<tr>
<td></td>
<td>16.6</td>
<td>13</td>
<td>15.1</td>
</tr>
<tr>
<td>Stage II</td>
<td>530</td>
<td>420</td>
<td>398</td>
</tr>
<tr>
<td></td>
<td>19.2</td>
<td>18.1</td>
<td>21.4</td>
</tr>
<tr>
<td>Stage III</td>
<td>497</td>
<td>1,169</td>
<td>829</td>
</tr>
<tr>
<td></td>
<td>12.7</td>
<td>9.1</td>
<td>11.9</td>
</tr>
</tbody>
</table>

Sargent D et al. JCO 2010; 28: 3219-3226,
Roth AD et al. JCO 2010; 28: 466-474
Fig 2. (A) Disease-free survival (DFS) in patients with stage II disease and defective DNA mismatch repair (dMMR) by treatment status. (B) DFS in patients with stage III disease and dMMR by treatment status. (C) DFS in patients with stage II disease and proficient MMR (pMMR) by treatment status. (D) DFS in patients with stage III disease and pMMR by treatment status. HR, hazard ratio; FU, fluorouracil.

Sargent D et al. JCO 2010; 28: 3219-3226
Potential Prognostic Role of BRAF in Stage II (and III) Colon Cancer

- Results from a translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial

Proportion With RFS

- No BRAF mutation
- BRAF mutation

\( p = 0.330 \)

Proportion With OS

- No BRAF mutation
- BRAF mutation

\( p = 0.007 \)
Oncotype DX for stage II colon cancer

- QUASAR validation study to predict likelihood of recurrence for stage II colon cancer – “Oncotype DX colon cancer recurrence score”
- 1800 colon cancer patients / 760 candidate genes were evaluated
- Resulting genes were then studied in just over 1200 pts with stage II disease from the QUASAR trial
- Study met its primary end-point in predicting risk of recurrence
- “Useful” for MSS tumours
- What happens when factors such as e.g. oxaliplatin or T4 tumours come into the equation?
Genomic Tests for CRC Risk Stratification

- Gene signatures provide **prognostic, not predictive**, information
- 12-gene recurrence score assay validated for recurrence risk in stage II patients

QUASAR: 12% (low risk) vs 22% (high risk) 3-yr recurrence risk

CALGB 9581: 13% (low risk) vs 21% (high risk) 5-yr recurrence in T3, MMR proficient disease

Stage II –
tumor gene expression profiles

• Prognostic data independent of other factors

BUT

• No predictive information to guide us for an optimal treatment decision
International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study


Interpretation The Immunoscore provides a reliable estimate of the risk of recurrence in patients with colon cancer. These results support the implementation of the consensus Immunoscore as a new component of a TNM-Immune classification of cancer.
Survival according to Immunoscore and MSI

- Immunoscore has a significant prognostic value ($P<0.0001$)
- Immunoscore performs as well in MSS and in MSI patients, and MSI is statistically dependent on Immunoscore

*The Lancet 2018*
# Multivariate analyses for Immunoscore

## Multivariate Overall Survival (OS) analysis stratified by center

<table>
<thead>
<tr>
<th>Individual Parameters</th>
<th>Hazard ratio (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender Female vs Male</td>
<td>0.90 (0.72-1.12)</td>
<td>0.34</td>
</tr>
<tr>
<td>T Stage T2 vs T1</td>
<td>1.49 (0.62-3.57)</td>
<td>0.37</td>
</tr>
<tr>
<td>T Stage T3 vs T1</td>
<td>1.91 (0.84-4.38)</td>
<td>0.12</td>
</tr>
<tr>
<td>T Stage T4 vs T1</td>
<td>2.36 (1.01-5.55)</td>
<td>0.0484</td>
</tr>
<tr>
<td>N Stage N1 vs N0</td>
<td>1.16 (0.89-1.52)</td>
<td>0.28</td>
</tr>
<tr>
<td>N Stage N2 vs N0</td>
<td>1.58 (1.15-2.17)</td>
<td>0.0052</td>
</tr>
<tr>
<td>MSI Status MSI vs MSS</td>
<td>0.93 (0.68-1.27)</td>
<td>0.64</td>
</tr>
<tr>
<td>VELIPI Yes vs No</td>
<td>1.20 (0.94-1.54)</td>
<td>0.15</td>
</tr>
<tr>
<td>Differentiation moderate vs Well</td>
<td>0.91 (0.66-1.24)</td>
<td>0.54</td>
</tr>
<tr>
<td>Differentiation poor-undif vs Well</td>
<td>1.37 (0.9-2.08)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mucinous (Colloid) Yes vs No</td>
<td>1.02 (0.78-1.33)</td>
<td>0.87</td>
</tr>
<tr>
<td>Sidedness distal vs proximal</td>
<td>0.96 (0.76-1.21)</td>
<td>0.74</td>
</tr>
<tr>
<td>Immunoscore Int vs Lo</td>
<td>0.67 (0.52-0.86)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Immunoscore Hi vs Lo</td>
<td>0.47 (0.33-0.65)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Cox multivariate regression model for OS stratified by center, combining Immunoscore with T-stage, N-stage, gender, VELIPI, histological grade, mucinous-colloide type, sidedness, and microsatellite status (MSI).
- Immunoscore is the most significant parameter in multivariate analysis
Conclusions

- In patients with stage II or III CRC, ctDNA detected 4–10 weeks post-surgery was associated with a significantly worse OS, CRC-specific survival and a shorter time to recurrence.
- The prognostic value of ctDNA detection could be enhanced by combining with an analysis of mutation allele frequency.
### Impact of older age on the efficacy of newer adjuvant therapies in >12,500 patients with stage II / III colon cancer: Findings from the ACCENT Database

<table>
<thead>
<tr>
<th>Trial</th>
<th>Accrual Period</th>
<th># pts</th>
<th>% pts ≥70 yrs</th>
<th>Experimental treatment arm†</th>
<th>% stage III‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIC</td>
<td>1998-01</td>
<td>2246</td>
<td>14</td>
<td>FOLFOX4</td>
<td>60</td>
</tr>
<tr>
<td>NSABP C-07</td>
<td>2000-02</td>
<td>2434</td>
<td>16</td>
<td>FLOX</td>
<td>71</td>
</tr>
<tr>
<td>CALGB 89803</td>
<td>1999-01</td>
<td>1263</td>
<td>24</td>
<td>IFL</td>
<td>98</td>
</tr>
<tr>
<td>PETACC-3</td>
<td>2000-02</td>
<td>3186</td>
<td>13</td>
<td>FOLFIRI</td>
<td>71</td>
</tr>
<tr>
<td>NSABP C-06</td>
<td>1997-99</td>
<td>1557</td>
<td>23</td>
<td>Uracil/tegafur</td>
<td>53</td>
</tr>
<tr>
<td>X-ACT</td>
<td>1998-01</td>
<td>1983</td>
<td>20</td>
<td>Capecitabine</td>
<td>100</td>
</tr>
<tr>
<td>XELOXA</td>
<td>2003-04</td>
<td>1962</td>
<td>22</td>
<td>XELOXA</td>
<td>100</td>
</tr>
</tbody>
</table>

† Compared to control arm of intravenous 5-flourouracil (IV 5-FU) and leucovorin (LV)
‡ Remaining patients were stage II or unknown

McCleary NJ et al. JCO 2013, 31(20): 2600-2606
Forest Plots of Hazard Ratios
Disease-Free Survival

Oxaliplatin

Irinotecan

Overall

Hazard Ratio

Age < 70

Age >= 70

Oral

Age < 70

Age >= 70

Oxaliplatin

Irinotecan

Overall

Hazard Ratio

0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2 2.2
Forest Plots of Hazard Ratios
Overall Survival
MOSAIC data in patients > 70 years

Benefit is lost at 5 years
MOSAIC data in patients > 70 years

OS

No clinically relevant Benefit in OS

HR 1.096 [0.73-1.65]
## Comparison with ACCENT Analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CIs)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DFS</td>
</tr>
<tr>
<td><strong>ACCENT analysis</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;70 years, n=3877</td>
<td>0.77 (0.68,0.86)</td>
</tr>
<tr>
<td>≥70 years, n=703</td>
<td>1.04 (0.80,1.35)</td>
</tr>
<tr>
<td><strong>XELOXA</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;70 years, n=1477</td>
<td>0.79 (0.66,0.94)</td>
</tr>
<tr>
<td>≥70 years, n=409</td>
<td>0.87 (0.63,1.18)</td>
</tr>
</tbody>
</table>

McCleary et al. ASCO 2009 (Abstract 4010)
Impact of Age on the Efficacy of Newer Adjuvant Therapies in Patients With Stage II/III Colon Cancer: Findings From the ACCENT Database


ABSTRACT

Purpose
Prior studies have suggested that patients with stage I/II colon cancer receive similar benefit from intravenous (IV) fluoropyrimidine adjuvant therapy regardless of age. Combination regimens and oral fluoropyracil (FU) therapy are now standard. We examined the impact of age on colon cancer recurrence and mortality after adjuvant therapy with these newer options.

Patients and Methods
We analyzed 11,953 patients age < 70 and 2,575 age ≥ 70 years from seven adjuvant therapy trials comparing IV FU with oral fluoropyrimidines (capecitabine, uracil, or tegafur) or combinations of fluoropyrimidines with oxaliplatin or irinotecan in stage II/III colon cancer. End points were disease-free survival (DFS), overall survival (OS), and time to recurrence (TTR).

Results
In three studies comparing oxaliplatin-based chemotherapy with IV FU, statistically significant interactions were not observed between treatment arm and age (P interaction = .09 for DFS, .05 for OS, and .36 for TTR), although the stratified point estimates suggested limited benefit from the addition of oxaliplatin in elderly patients (DFS hazard ratio [HR], 0.94; 95% CI, 0.78 to 1.13; OS HR, 1.04; 95% CI, 0.85 to 1.27). No significant interactions by age were detected with oral fluoropyrimidine therapy compared with IV FU; noninferiority was supported in both age populations.

Conclusion
Patients age ≥ 70 years seemed to experience reduced benefit from adding oxaliplatin to fluoropyrimidines in the adjuvant setting, although statistically, there was not a significant effect modification by age, whereas oral fluoropyrimidines retained their efficacy.

J Clin Oncol 31:2600-2606. © 2013 by American Society of Clinical Oncology
The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration: Prospective Combined Analysis of Phase III Trials Investigating Duration of Adjuvant Therapy with the FOLFOX (FOLFOX4 or Modified FOLFOX6) or XELOX (3 versus 6 months) Regimen for Patients with Stage III Colon Cancer: Trial Design and Current Status

Thierry André • Timothy Iveson • Roberto Labianca • Jeffrey A. Meyerhardt • Ioannis Souglakos • Takayuki Yoshino • James Paul • Alberto Sobrero • Julien Taieb • Anthony E. Shields • Atsushi Ohtsu • Axel Grothey • Daniel J. Sargent • for the IDEA Steering Committee

Published online: 23 July 2013
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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TOSCA (N = 2402)</th>
<th>SCOT (N = 3983)</th>
<th>IDEA France (N = 2010)</th>
<th>CALGB/SWOG 80/02 (N = 2440)</th>
<th>HORG (N = 708)</th>
<th>ACHIEVE (N = 1291)</th>
<th>All Patients (N = 12,834)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries</td>
<td>Italy</td>
<td>U.K., Denmark, Spain, Australia, Sweden, New Zealand</td>
<td>France</td>
<td>U.S., Canada</td>
<td>Greece</td>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>Median age (range) — yr</td>
<td>64 (20–83)</td>
<td>65 (20–84)</td>
<td>64 (18–85)</td>
<td>61 (19–88)</td>
<td>67 (20–75)</td>
<td>66 (28–85)</td>
<td>64 (18–88)</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>1348 (56.1)</td>
<td>2356 (59.2)</td>
<td>1144 (56.9)</td>
<td>1348 (55.3)</td>
<td>398 (56.2)</td>
<td>649 (50.3)</td>
<td>7,243 (56.4)</td>
</tr>
<tr>
<td>ECOG performance status — no. (%)</td>
<td>2268 (94.4)</td>
<td>2827 (71.0)</td>
<td>1479 (73.6)</td>
<td>1734 (71.1)</td>
<td>579 (81.8)</td>
<td>10,132 (79.0)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>130 (5.4)</td>
<td>1156 (29.0)</td>
<td>502 (25.0)</td>
<td>680 (27.9)</td>
<td>128 (18.1)</td>
<td>2,642 (20.6)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>29 (1.4)</td>
<td>26 (1.1)</td>
<td>1 (0.1)</td>
<td>57 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>3 (0.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (&lt;0.1)</td>
</tr>
<tr>
<td>Tumor stage — no. (%)</td>
<td>76 (3.2)</td>
<td>128 (3.2)</td>
<td>78 (3.9)</td>
<td>135 (5.5)</td>
<td>1 (0.1)</td>
<td>75 (5.8)</td>
<td>493 (3.8)</td>
</tr>
<tr>
<td>T1</td>
<td>216 (9.8)</td>
<td>333 (8.4)</td>
<td>161 (8.0)</td>
<td>288 (11.8)</td>
<td>60 (8.5)</td>
<td>119 (9.2)</td>
<td>1,197 (9.3)</td>
</tr>
<tr>
<td>T2</td>
<td>1773 (73.8)</td>
<td>2347 (58.9)</td>
<td>1399 (69.6)</td>
<td>1598 (65.5)</td>
<td>549 (77.5)</td>
<td>734 (56.9)</td>
<td>8,400 (65.5)</td>
</tr>
<tr>
<td>T3</td>
<td>291 (12.1)</td>
<td>1174 (29.5)</td>
<td>372 (18.5)</td>
<td>359 (14.7)</td>
<td>96 (13.6)</td>
<td>363 (28.1)</td>
<td>2,655 (20.7)</td>
</tr>
<tr>
<td>T4</td>
<td>26 (1.1)</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>2 (0.3)</td>
<td>3 (&lt;0.1)</td>
<td>89 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Nodal stage — no. (%)</td>
<td>1748 (72.8)</td>
<td>2749 (69.0)</td>
<td>1501 (74.7)</td>
<td>1739 (71.3)</td>
<td>472 (66.7)</td>
<td>9,168 (71.4)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>636 (26.5)</td>
<td>1233 (31.0)</td>
<td>506 (25.2)</td>
<td>630 (25.8)</td>
<td>230 (32.5)</td>
<td>3,567 (27.8)</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>18 (0.7)</td>
<td>1 (&lt;0.1)</td>
<td>3 (1.0)</td>
<td>71 (2.9)</td>
<td>6 (0.8)</td>
<td>99 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Risk group — no. (%)</td>
<td>1553 (65.5)</td>
<td>2032 (51.0)</td>
<td>1245 (62.0)</td>
<td>1507 (63.6)</td>
<td>416 (59.1)</td>
<td>7,471 (58.7)</td>
<td></td>
</tr>
<tr>
<td>T1, T2, or T3 N1</td>
<td>817 (34.5)</td>
<td>1950 (49.0)</td>
<td>764 (38.0)</td>
<td>864 (36.4)</td>
<td>288 (40.9)</td>
<td>5,256 (41.3)</td>
<td></td>
</tr>
<tr>
<td>T4, N2, or both</td>
<td>18 (0.7)</td>
<td>20 (1–99)</td>
<td>20 (1–132)</td>
<td>21 (1–123)</td>
<td>19 (0–132)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median no. of lymph nodes examined (range)</td>
<td>18 (0–85)</td>
<td>Not recorded</td>
<td>20 (1–99)</td>
<td>20 (1–132)</td>
<td>21 (1–123)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy regimen — no. (%)</td>
<td>CAPOX</td>
<td>840 (35.0)</td>
<td>201 (10.0)</td>
<td>0</td>
<td>412 (58.2)</td>
<td>5,071 (39.5)</td>
<td></td>
</tr>
<tr>
<td>FOLFOX</td>
<td>1562 (65.0)†</td>
<td>1334 (33.5)</td>
<td>1809 (90.0)</td>
<td>2440 (100)</td>
<td>296 (41.8)†</td>
<td>7,763 (60.5)</td>
<td></td>
</tr>
<tr>
<td>Median follow-up time — mo</td>
<td>61.7</td>
<td>36.8</td>
<td>51.3</td>
<td>34.9</td>
<td>47.5</td>
<td>36.7</td>
<td>41.8</td>
</tr>
</tbody>
</table>
**Figure 1.** Disease-free Survival with 3 Months versus 6 Months of Adjuvant Therapy.

Panel A shows the distribution of disease-free survival in the overall modified intention-to-treat population. At a median follow-up of 41.8 months, noninferiority of 3 months of treatment versus 6 months was not confirmed (hazard ratio, 1.07; 95% confidence interval [CI], 1.00 to 1.15; P = 0.11 for noninferiority of 3-month therapy; P = 0.045 for superiority of 6-month therapy). The 3-year rate of disease-free survival was 74.6% (95% CI, 73.5 to 75.7) in the 3-month therapy group, as compared with 75.5% (95% CI, 74.4 to 76.7) in the 6-month therapy group. Panel B shows the 3-year rate of disease-free survival according to subgroup, including treatment, tumor and nodal status, and risk.
Duration of Adjuvant Chemotherapy for Stage III Colon Cancer


CONCLUSIONS

Among patients with stage III colon cancer receiving adjuvant therapy with FOLFOX or CAPOX, noninferiority of 3 months of therapy, as compared with 6 months, was not confirmed in the overall population. However, in patients treated with CAPOX, 3 months of therapy was as effective as 6 months, particularly in the lower-risk subgroup. (Funded by the National Cancer Institute and others.)
Neo-adjuvant therapy

- Chemotherapy
- Immunotherapy
3504: FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer – Seymour MT, et al

**Study objective**
- To investigate the efficacy and safety of neoadjuvant chemotherapy in patients with colon cancer compared with surgery then chemotherapy

**Key patient inclusion criteria**
- Operable, non-obstructed colon cancer
- T3-4, N0-2, M0 (n=1052)

**Stratification**
- Primary location in colon (right vs. left)
- PS (0 vs. 1–2)

**Neoadjuvant chemotherapy**
- FOLFOX for 6 weeks followed by surgery then FOLFOX for 18 weeks (n=698)

**Surgery then**
- FOLFOX for 24 weeks (n=354)

**Primary endpoint**
- 2-year DFS

**Secondary endpoints**
- Resection rate, safety

**Key results (cont.)**

**Tumour regression grade (TRG)* at surgery**

91% scored blind by central pathologist
9% scored by local pathologists

<table>
<thead>
<tr>
<th></th>
<th>Neoadjuvant chemo (n=666)</th>
<th>Straight to surgery (n=332)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (TRG4)</td>
<td>3.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Marked regression (TRG3)</td>
<td>4.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Moderate regression (TRG2)</td>
<td>12.3%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Little regression (TRG1)</td>
<td>43.9%</td>
<td>16.7%</td>
</tr>
<tr>
<td>No regression (TRG0)</td>
<td>33.9%</td>
<td>78.8%</td>
</tr>
</tbody>
</table>

*p<0.0001


3504: FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer – Seymour MT, et al

Key results (cont.)

<table>
<thead>
<tr>
<th>Local pathologist score*, %</th>
<th>Pre &amp; postop CT (n=689)</th>
<th>Postop CT only (n=353)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not proceed to surgery</td>
<td>0.6</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Surgery but no resection</td>
<td>0.3</td>
<td>1.1</td>
<td>0.001</td>
</tr>
<tr>
<td>R2 – macroscopically incomplete</td>
<td>0.3</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>R1 – microscopically incomplete</td>
<td>4.2</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>R0 – microscopically complete</td>
<td>93.1</td>
<td>88.4</td>
<td></td>
</tr>
</tbody>
</table>

* Concordance of local vs. central assessment of resection margins = 99% (n=904)
3504: FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer – Seymour MT, et al

Key results

Recurrence – by treatment allocation

2-year recurrence (events, n/N), pre & postop vs. postop only:
13.6% (95/698) vs. 17.2% (61/354)
HR 0.75 (95%CI 0.55, 1.04); p=0.08

CAUTION: this subgroup analysis is exploratory, not prespecified in the initial trial design.
FOXTROT trial

- Neo-adjuvant CT did not reach significance for its primary endpoint DFS, but significantly downstaged tumours and reduced the number of incomplete resections
- No response seen in most dMMR CC
- No benefit adding Panitumumab in unselected KRAS wt (but NGS shows extended RAS or BRAF mut>35% pts)
- Trended towards improved 2 years cancer control (HR: 0.75, p= 0.081)
FOXTROT trial

• This approach may be considered as a potential new option for locally advanced colon cancer with less major postoperative morbidity
Study objective

- To assess the efficacy and safety of neoadjuvant ipilimumab + nivolumab in patients with early stage colon cancer

Key patient inclusion criteria

- Histologically confirmed colon cancer (no rectal cancer)
- No distant metastases
- No signs of perforation or clinical bowel obstruction

Primary endpoints

- Safety/feasibility

Secondary endpoints

- Efficacy, association between response and TMB, IFNγ, gene signatures, T-cell infiltration, TCR clonality

*Half of the MMR-P patients received celecoxib and other combinations in addition to study treatment

Key results (cont.)

- A major response was observed in all dMMR tumours
- Pre-treatment CD3 infiltration was not predictive of response to treatment

CD8+ T-cells increased in both dMMR and MMR-P tumours

IFNγ score significantly increased post-treatment

NICHE trial

• In early stage CC the Nivo+Ipi combination was safe and associated with excellent pathological responses in all dMMR tumours

• Tumor pre-treatment inflammation characteristics and immune gene signatures were not related with response

• These results needs to be further validated in prospective larger trials
Summary

• The adjuvant therapy could not “correct” a bad operation. Complete mesocolic excision is the “lege artis” surgical approach
Summary

• Stage II:
  - benefits are less certain from adjuvant therapy
  - who may benefit in this population?
  - do we treat and if so, with what?

• Stage III:
  - ~ 22% relative reduction in the risk of disease recurrence
  - ~ 20% relative reduction in mortality
Summary

- Bevacizumab, Cetuximab, Irinotecan should not be used in the adjuvant setting
- Capecitabine alone or 5FU, in stage III elderly patients, are the reasonable options
- XELOX or FOLFOX could still be considered for fit stage III elderly patients
Summary

• Capox for 3 months is an option for lower risk stage III CC

• Tumor gene expression platforms do not provide predictive information to guide as to treatment decision

• MMR testing should also be considered for all patients with stage II
Summary

• Neo-adjuvant approach may be considered as a potential new option for locally advanced colon cancer