Adjuvant Chemotherapy for Stage II colon Cancer: for which patients?

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Adjuvant Chemotherapy of colon cancers

- Adjuvant chemotherapy is a concept with proven efficacy in several human solid tumors including colon cancer.
- Most of the data were generated in the past 20 years.
- Adjuvant chemotherapy benefits to a very limited number of patients, most of them are cured after surgery and numerous patients are over-treated.
- The Risk/benefit ratio has to be considered.
- This is particularly true in stage II colon cancer.

Recommended references:
Early colon cancer ESMO Guidelines Annals of Oncology 24 Suppl 6 2013
ESMO Consensus Guidelines for CRC Annals of Oncology 23; 2479 2012
Adjuvant Chemotherapy for Stage II colon Cancer: for which patients?

- What defines a stage II colon cancer?
- Risk factors and outcome of stage II colon cancer
- Adjuvant chemotherapy results from trials
- Could biomarkers help?
- ESMO recommendations
TNM staging system
AJCC/UICC 7th edition 2010
Stage II Colon Cancer

T3  Tumour invades through the muscularis propria into the pericololectal tissues
T4a  Tumour penetrates into the surface of the visceral peritoneum
T4b  Tumour directly invades or is adherent to other organs or structures

IIA  T3  N0  M0
IIB  T4a  N0  M0
IIC  T4b  N0  M0

N0: 0 node involved out of at least 12 lymph nodes
TNM staging system
AJCC/UICC 7th edition 2010
Stage II Colon Cancer

T

TX  Primary tumour cannot be assessed
T0  No evidence of primary tumour
Tis Carcinoma in situ: intraepithelial or invasion of lamina propria
T1  Tumour invades submucosa
T2  Tumour invades muscularis propria
T3  Tumour invades through the muscularis propria into the pericolorectal tissues
T4a Tumour penetrates into the surface of the visceral peritoneum
T4b Tumour directly invades or is adherent to other organs or structures
Colon cancer: stage II subgroups
Stage II colon cancer

- The quality of the pathology report is ESSENTIAL
  - T size 3 or 4
  - T4a or T4b
  - Number of lymph nodes retrieved and examined

- Additional features to be described:
  - Perineural invasion
  - Lympho-Vascular invasion
  - Lymphocytic reaction?
  - Stroma reaction?
High risk group according to ASCO NCCN and ESMO

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>T4 primary tumor</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Inadequately sampled nodes</td>
<td>+ (&lt;13)</td>
<td>+ (&lt;12)</td>
<td>+ (&lt;12)</td>
</tr>
<tr>
<td>Poorly differentiated tumor</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Perforation</td>
<td>+</td>
<td>+ (localized)</td>
<td>+</td>
</tr>
<tr>
<td>Obstruction</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LVI</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PNI</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Close/indeterminate or positive margins</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LVI: lymphovascular invasion; PNI: perineural invasion.
* I.e., the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO).
Adjuvant Chemotherapy for Stage II colon Cancer: for which patients?

Risk factors and outcome of stage II colon cancer
Stage II: bad prognostic factors

• **Clinical factors:**
  - Obstruction (subjective)
  - Perforation

• **Histological factors:** (sometime subjective)
  - Differentiation
  - Lymphovascular invasion
  - Neuro invasion

- Depth of invasion
  - pT4a: serosal invasion
    - May be missed
    - May be difficult to recognize (mesothelial hyperplasia, inflammation)
  - pT4b: invasion of adjacent organs
    - May be difficult to differentiate from inflammatory adhesion

Most of the studies published refer to previous TNM Classifications and not to TNM 7 (AJCC 2010)
SEER database 48,500 stage II colon cancer Observed 5-year survival by TN category. (TNM VI)

Stage II

- A
- B
- C

Stage IIIA

Stage IIIB

TN Category

- T1N0
- T2N0
- T3N0
- T4aN0
- T4bN0
- T1-2N1
- T1N2a
- T2N2a
- T3N1a
- T4aN1a
- T3N1b
- T1N2b
- T4aN2a
- T4bN1b
- T3N2a
- T2bN2b
- T3N2b
- T4aN2b
- T4bN1
- T4bN2a
- T4bN2b

Rectum
Colon

Gunderson L L et al. JCO 2010;28:264-271
SEER data base 48 500 stage II colon cancer
Observed 5-year survival by T category. (TNM VI)

Revised TN Classification for Colon Cancer
Based On National Survival Outcomes Data

<table>
<thead>
<tr>
<th>NT Category</th>
<th>Number of Patients</th>
<th>5-Yr Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>74,690</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>2,383</td>
<td>95.6%</td>
</tr>
<tr>
<td>T1-2</td>
<td>23,861</td>
<td>97.1%</td>
</tr>
<tr>
<td>T1</td>
<td>10,930</td>
<td>97.4%</td>
</tr>
<tr>
<td>T2</td>
<td>13,931</td>
<td>96.8%</td>
</tr>
<tr>
<td>T3</td>
<td>40,338</td>
<td>87.5%</td>
</tr>
<tr>
<td>T4</td>
<td>8,108</td>
<td>71.5%</td>
</tr>
<tr>
<td>T4a</td>
<td>5,020</td>
<td>79.6%</td>
</tr>
<tr>
<td>T4b</td>
<td>3,088</td>
<td>58.4%</td>
</tr>
</tbody>
</table>

Adapted from Goldberg R, ASCO GI 2014
Documenting the Natural History of Patients With Resected Stage II Adenocarcinoma of the Colon After Random Assignment to Adjuvant Treatment With Edrecolomab or Observation: Results From CALGB 9581

From the Cancer and Leukemia Group B Statistical Center; Duke University Medical Center, Durham; Southeast Cancer Control Consortium, Goldsboro; University of North Carolina, Chapel Hill, NC; Brigham and Women’s Hospital; Eastern Cooperative Oncology Group; Dana-Farber Cancer Institute; and the University of North Carolina at Chapel Hill, NC.

Patients registered
(N = 1,738)

Nonrandom treatment assignment
(n = 8)

Patients randomly allocated
(n = 1,713)

Allocated to MoAb 17-1A
(n = 857)
Received allocated intervention
(n = 834)
Did not receive allocated intervention
(n = 23)

Allocated to observation
(n = 856)
Received allocated intervention
(n = 856)
Did not receive allocated intervention
(n = 0)

Completed treatment
(n = 722)
Lost to follow-up
(n = 4)
Discontinued intervention early
(n = 108)
Adverse events
(n = 54)
Withdrawn
(n = 31)
Other disease
(n = 3)
Progressed during treatment
(n = 2)
Nonprotocol therapy
(n = 1)
Other/unknown reason
(n = 17)

Completed treatment
(n = 856)
Lost to follow-up
(n = 4)
Refused further follow-up
(n = 9)

Analyzed
(n = 857)
Excluded from analysis
(n = 8)

Analyzed
(n = 856)
Excluded from analysis
(n = 17)
Smoothing splines of (A) the log hazard for disease-specific disease-free survival by number of nodes examined truncated at 32 nodes, representing 95% of the data, and (B) the log hazard for disease-specific overall survival by age at trial entry.
Risk factors in CALGB 9581 (Edrecolomab trial)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cancer Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>0.004</td>
</tr>
<tr>
<td>Age &gt; 70</td>
<td>0.03</td>
</tr>
<tr>
<td>Differenciation</td>
<td>0.004</td>
</tr>
<tr>
<td>Lympho-Vascular Invasion</td>
<td>0.013</td>
</tr>
<tr>
<td>Perineural Invasion</td>
<td>0.001</td>
</tr>
<tr>
<td>Depth of invasion T 3 vs 4</td>
<td>0.001</td>
</tr>
</tbody>
</table>
## Stage II colon cancer subgroups

<table>
<thead>
<tr>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>T4b</td>
</tr>
<tr>
<td>T4a?</td>
<td>T4a?</td>
</tr>
<tr>
<td>No obstruction (subjective)</td>
<td>Obstruction (subjective)</td>
</tr>
<tr>
<td>No perforation</td>
<td>Perforation</td>
</tr>
<tr>
<td>No lymphovascular invasion</td>
<td>Lymphovascular invasion</td>
</tr>
<tr>
<td>No perineural invasion</td>
<td>Perineural invasion</td>
</tr>
<tr>
<td>Well differentiated</td>
<td>Poorly differentiated</td>
</tr>
</tbody>
</table>
Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study

QUASAR Collaborative Group
QUASAR Patient consort diagram

7559 patients with complete resection of colon or rectal cancer

4320 patients with clear indication for chemotherapy

3239 patients with uncertain indication for chemotherapy

1617 patients randomly assigned to observation alone
6 patients received chemotherapy
1611 did not

1622 patients randomly assigned to receive chemotherapy (607 up to 1997, 1015 after 1997*)
45 did not receive any chemotherapy
1577 start chemotherapy, of whom 13% receive <80%, 19% receive 80–99% and 58% receive 100% of scheduled chemotherapy

47 not flagged or follow-up not received
3 lost to follow-up

1567 patients with recent follow-up available for analysis

54 not flagged or follow-up not received
7 lost to follow-up

1561 patients with recent follow-up available for analysis
### QUASAR

<table>
<thead>
<tr>
<th></th>
<th>CT* 1622</th>
<th>No CT 1617</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>II</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Rectum or Both</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Gender male</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>Age &lt;70</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>&gt;70</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>

*All CT was 5FU/LV 27% with levamisol*

### OS

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.82</td>
<td>0.78</td>
</tr>
<tr>
<td>P</td>
<td>0.008</td>
<td>0.001</td>
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</tbody>
</table>

### RECURRENCE RATE

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<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>
QUASAR CONCLUSION

• Improvement of borderline clinical significance
  • Significant reduction in recurrence rate
    • Mostly early recurrences (2 years)
    • More pronounced in rectum

• In colon cancer stage II:
  • 18% reduction in the risk of death (absolute benefit + 3.6%)
  • No benefit > 70 years of age

• No data on benefit in high-risk patients (T4, vascular invasion, < 8 LN)
QUASAR vs. older trials

- **5FU/Levamisol (MOERTEL 1990)**
  - Stage II: 3.5y Recurrence-free survival:
    - 84 vs. 77% (ns)

- **IMPACT B2 (1999)**
  - Stage II: 5y Relapse-free survival:
    - 76 vs. 73% (ns)

- **Meta-analysis (Figueroedo JCO 2004)**
  - 37 trials, 11 meta-analysis
    - HR for recurrence: 0.87 (ns)
SEER (Medicare) Database
24 847 Patients > 65y Stage II

O'Connor E S et al. JCO 2011;29:3381-3388
Adjuvant chemotherapy for stage II

The issue of Oxaliplatin
DFS (A) by treatment arm and (B) by treatment arm and by stage

A

MOSAÏC

B

©2009 by American Society of Clinical Oncology André T et al. JCO 2009;27:3109-3116
OS (A) by treatment arm and (B) by treatment arm and by stage

MOSAÏC
MOSAÏC outcome according to subgroup stage II TNM VII + clinical factors

<table>
<thead>
<tr>
<th>FOLFOX4 v FL by Subgroup</th>
<th>No. of Patients</th>
<th>Five-Year DFS</th>
<th></th>
<th></th>
<th>Five-Year TTR</th>
<th></th>
<th></th>
<th>Six-Year OS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Stage II</td>
<td>899</td>
<td>0.84</td>
<td>0.62 to 1.14</td>
<td>.258</td>
<td>0.70</td>
<td>0.49 to 0.99</td>
<td>.045</td>
<td>1.00</td>
<td>0.7 to 1.41</td>
</tr>
<tr>
<td>High risk</td>
<td>569</td>
<td>0.72</td>
<td>0.51 to 1.01</td>
<td>.062</td>
<td>0.62</td>
<td>0.41 to 0.92</td>
<td>.002</td>
<td>0.91</td>
<td>0.61 to 1.36</td>
</tr>
<tr>
<td>Low risk</td>
<td>330</td>
<td>1.36</td>
<td>0.76 to 2.45</td>
<td>.305</td>
<td>1.01</td>
<td>0.5 to 2.05</td>
<td>.972</td>
<td>1.36</td>
<td>0.67 to 2.5</td>
</tr>
</tbody>
</table>

Tournigand C et al. JCO 2012;30:3353-3360
Rates of (A) disease-free, (B) relapse-free, (C) overall, and (D) post–disease-free survival in high-risk stage II colon cancer treated with LV5FU2 or FOLFOX4.
Adjusted* Kaplan Meier Estimate of OS in Stage II

**NSABP experience: 4 trials**

- **5-FU**: 2009 Pts, 483 Deaths
- **5-FU+Oxali**: 991 Pts, 100 Deaths

HR = 0.95, 95% CI 0.75 - 1.21
P = 0.67

*Adjusted for age, gender, race, nodes examined, and T-stage*
Adjuvant colon cancer: stade II
NSABP  C05-06-07-08

- 3000 patients stage II high (HR) and low risk (LR) treated in NSABP studies
- 2009 pts treated with 5-FU and 901 with 5-FU+ oxaliplatine

<table>
<thead>
<tr>
<th>At 5 years</th>
<th>oxaliplatin</th>
<th>No oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS HR</td>
<td>81%</td>
<td>76%</td>
</tr>
<tr>
<td>DFS LR</td>
<td>83%</td>
<td>80%</td>
</tr>
<tr>
<td>OS HR</td>
<td>90%</td>
<td>87%</td>
</tr>
<tr>
<td>OS LR</td>
<td>91%</td>
<td>89%</td>
</tr>
</tbody>
</table>

- Minimal benefit, Risk/benefit questionable, no consensus…

GA Yothers et al., ASCO 2011, A#3507
Adjuvant treatment of colon cancer stage II

The issue of age
Adjuvant chemotherapy of stage II colon cancer issues in the elderly

- Recent analysis showed that elderly (>70 years-old) may not benefit from adjuvant chemotherapy
  - Already seen in the Quasar trial (stage II)
  - Already seen in the Mosaïc trial (stage II and III)
  - Recently reported in NO 16968 (stage III, Xelox vs. 5FU/LV)
Adjuvant chemotherapy in the elderly with colon cancer

**XELOX versus 5FU/LV (NO16968)**

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>3 years</th>
<th>4 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>XELOX</td>
<td>71,0%</td>
<td>HR 0,80</td>
<td>68,4%</td>
<td>66,1%</td>
</tr>
<tr>
<td>5-FUL/LV</td>
<td>67,0%</td>
<td>P=0,004</td>
<td>62,3%</td>
<td>59,8%</td>
</tr>
</tbody>
</table>

Analysis according to age

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>3 years</th>
<th>4 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70 ans</td>
<td>HR 0,79 (95% CI 0,66-0,94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 70 ans</td>
<td>HR 0,87 (95% CI 0,63-1,18)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mosaic**

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX</th>
<th>LV5FU2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=315</td>
<td>155</td>
<td>160</td>
</tr>
<tr>
<td>DFS</td>
<td>HR 0,91 (95% CI 0,62-1,34)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>HR 1,10 (95% CI 0,73-1,65)</td>
<td></td>
</tr>
</tbody>
</table>

⇒ Relapse in FOLFOX in Elderly:
- fewer patients resected (p=0,01)
- fewer patients treated with combined therapy (p=0,01)

⇒ More 2nd cancer in FOLFOX

D.G. Haller et al. ASCO 2010. Abstract 3521
C. Tournigand et al. ASCO 2010. Abstract 3522
## Cross-trial comparison: Age

<table>
<thead>
<tr>
<th></th>
<th>NSABP C-07&lt;sup&gt;1&lt;/sup&gt;</th>
<th>MOSAIC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>NO16968</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FLOX*</td>
<td>FOLFOX*</td>
<td>XELOX*</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>&lt;70</td>
<td>≥70</td>
<td>&lt;70</td>
</tr>
<tr>
<td><strong>DFS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.76 (0.66–0.88)</td>
<td>1.03 (0.77–1.36)</td>
<td>na</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.80 (0.68–0.95)</td>
<td>1.18 (0.86–1.62)</td>
<td>na</td>
</tr>
</tbody>
</table>

*Comparison vs 5-FU/LV

na: not available

1. Yothers et al. JCO 2011;28:3768–74
2. Tournigand et al. JCO 2010;28:15s (abstr 3522)

Schmol H.J. ASCO GI 2012
Adjuvant chemotherapy of stage II colon cancer issues in the elderly

- Recent analysis showed that elderly (>70 years-old) may not benefit from adjuvant chemotherapy
  - Already seen in the Quasar trial (stage II)
  - Already seen in the Mosaïc trial (stage II and III)
  - Also reported in NO 16968 (stage III, Xelox vs. 5FU/LV)

- Considering the absence of clear benefit of adjuvant chemotherapy in stage II, elderly patients > 70 years of age should not be treated
Adjuvant chemotherapy for stage II colon cancer

Can we get help from biomarkers?
Microsatellite instability

Colorectal Cancer: Genomics

15%
MIN (MSI+)
(Microsatellite Instability)

Lynch Sx
Germline Mutation
MMR genes
MLH1, MSH2,
MSH6 & PMS2

2-3%

13%
Sporadic MSI(+)

• Epigenetic silencing of MLH1 by hypermethylation of its promoter region

<1%
FAP
Germline Mutation
APC

85%
CIN
(Chromosome Instability)

85%
Sporadic
Acquired
APC, p53,
DCC, kras,
LOH,...

Goldberg RASCO GI January 2014
MSI-H as a consistent favorable prognostic marker

<table>
<thead>
<tr>
<th>Source</th>
<th>Stage / Treatment</th>
<th>Endpoint</th>
<th>MMR-D vs MMR-P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Ribic et al (^1)</td>
<td>II/III Surgery alone</td>
<td>Overall survival</td>
<td>0.31</td>
</tr>
<tr>
<td>Sargent et al (^2)</td>
<td>II/III Surgery alone</td>
<td>Disease-free survival</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall survival</td>
<td>0.51</td>
</tr>
<tr>
<td>Gray et al (^3)</td>
<td>II Surgery alone</td>
<td>Recurrence-free interval</td>
<td>0.31</td>
</tr>
<tr>
<td>Gray et al (^3)</td>
<td>II Surgery alone</td>
<td>Recurrence-free interval</td>
<td>0.31</td>
</tr>
<tr>
<td>Roth et al (^4)</td>
<td>II 5FU ± irinotecan</td>
<td>Relapse-free survival</td>
<td>0.30</td>
</tr>
</tbody>
</table>

QUASAR
Recurrence by mismatch repair (MMR) status: (A) all patients, (B) colon stage II only.

Hutchins G et al. JCO 2011;29:1261-1270

©2011 by American Society of Clinical Oncology
A. DFS in **untreated** patients by DNA mismatch repair (MMR) status.

B. DFS in **treated** patients by DNA mismatch repair (MMR) status.

Sargent D J et al. JCO 2010;28:3219-3226
Predictive value of MMR status in stage II colon cancer

Sargent D J et al. JCO 2010;28:3219-3226
MSI as an indicator for adjuvant CT in stage II

Conclusions

- dMMR is a prognostic marker in untreated patients
- No suggestion of benefit from 5-FU based treatment in dMMR patients
- Significant OS decrement to 5-FU based treatment in stage II patients
Kaplan-Meier survival estimates of individuals with microsatellite-stable colon cancers by stage and V600E BRAF mutation status.

Gene signature in colon cancer

- Oncotype Dx (Genomic Health)
- CoIDx (Almac)
- ColonPRS (Signal Genetics LLC)
- ColoPrint (Agendia NV)
- GeneFx Colon (Precision Therapeutics)
- Onco-Defender-CRC (Everist Genomics)

- Still under investigation, Not approved
- Not routinely available
- Costly
Kaplan-Meier estimates of 3-year recurrence in surgery-alone patients by risk group. (Oncotype DX)

Gray R G et al. JCO 2011;29:4611-4619
Estimated absolute risk of recurrence at 3 years with and without FUFA chemotherapy, assuming the overall treatment effect for all stage II colon cancer patients in QUASAR Oncotype DX

Low risk - 3.1%
Intermediate risk - 4.7%
High risk - 5.7%
ColoPrint identifies patients at risk of distant and local-regional relapse (RFS)

Local, Regional and Distant Relapse

ColoPrint risk assessment

3-year RFS
Low Risk = 91%
High Risk = 74%

5-year RFS
Low Risk = 88% (83-93%)
High Risk = 71% (62-80.5%)

p=0.001

Tabernero J et al ASCO GI 2012
Subgroup analysis in T3-MSS patients (n=227)

Univariate Analysis of 3-year RFS

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ColoPrint</td>
<td>3.04</td>
<td>1.45-6.34</td>
<td>0.003</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>0.97-1.05</td>
<td>0.59</td>
</tr>
<tr>
<td>Localization</td>
<td>1.34</td>
<td>0.59-3.06</td>
<td>0.48</td>
</tr>
<tr>
<td>Grade</td>
<td>0.71</td>
<td>0.22-2.26</td>
<td>0.27</td>
</tr>
<tr>
<td>Gender</td>
<td>0.46</td>
<td>0.19-1.061</td>
<td>0.07</td>
</tr>
<tr>
<td>LN &gt; 12</td>
<td>0.83</td>
<td>0.37-1.85</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Low Risk = 91% (86-96%)
High Risk = 73% (63-83%)

Tabernero J et al ASCO GI 2012
ColoPrint in combination with clinical factors might give best risk stratification

According to that study, for stage II
ColoPrint is a better predictor than the clinico-pathologic HR and LR
Homeobox protein CDX-2 is a protein encoded by the CDX2 gene, a member of the caudal-related homeobox transcription factor family that is expressed in the nuclei of the GI track from the Duodenum to the rectum epithelial cells.
Study Design.

Step 1
Discovery of clinically actionable biomarkers of colon epithelial differentiation (i.e., markers for which a standardized diagnostic test is available) with use of Boolean logic analysis of a large database of gene-expression arrays.

Bioinformatics search for markers of colon epithelial differentiation, based on the fulfillment of the "X-negative implies ALCAM-positive" Boolean relationship and identification of 16 candidate genes.

Exclusion of 15 clinically nonactionable biomarkers (i.e., markers for which a standardized diagnostic test is not available).

Selection of 1 clinically actionable biomarker: CDX2

Step 2
Evaluation of CDX2 association with 5-yr disease-free survival in two independent data sets (discovery and validation) with use of multivariate analysis based on the Cox proportional-hazards method.

Discovery Data Set NCBI-GEO
- 466 Patients with disease-free survival and CDX2 information
- 32 Were CDX2-negative
- 434 Were CDX2-positive

Validation Data Set NCI-CDP
- 314 Patients with disease-free survival and CDX2 information
- 38 Were CDX2-negative
- 276 Were CDX2-positive

Step 3
Evaluation of CDX2 association with benefit from adjuvant chemotherapy in a pooled database of historical cohorts of treated and untreated patients with use of Kaplan-Meier curves and interaction tests.

Expansion Data Set NSABP C07
- 1216 Patients with stage II or stage III disease with information on CDX2 expression status, disease-free survival, and treatment
- 67 Were CDX2-negative
- 1149 Were CDX2-positive

Expansion Data Set Stanford TMAD
- 194 Patients with stage II or stage III disease with information on CDX2 expression status, disease-free survival, and treatment
- 7 Were CDX2-negative
- 187 Were CDX2-positive

1897 Patients with stage II or stage III disease with annotated data on CDX2 status, disease-free survival, and treatment

669 Stage II
- 23 received chemotherapy
- 25 did not receive chemotherapy
- 389 received chemotherapy
- 232 did not receive chemotherapy

1228 Stage III
- 60 received chemotherapy
- 27 did not receive chemotherapy
- 1003 received chemotherapy
- 138 did not receive chemotherapy

CDX2 negative <10% stage II
Relationship between CDX2 Protein Expression and Disease-free Survival in the NCI-GDP Validation Data Set.

A Specimen without CDX2 Nuclear Expression

B Specimen with CDX2 Nuclear Expression

C Disease-free Survival, According to CDX2 Expression

D Multivariate Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDX2-negative</td>
<td>2.42 (1.36–4.29)</td>
<td>0.003</td>
</tr>
<tr>
<td>Tumor stage, according to increase in stage</td>
<td>2.71 (1.92–3.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor grade, according to increase in grade</td>
<td>0.79 (0.61–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Age, modeled as a continuous variable</td>
<td>1.00 (0.99–1.02)</td>
<td>0.68</td>
</tr>
<tr>
<td>Male vs. female sex</td>
<td>0.91 (0.61–1.35)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

E Disease-free Survival, According to CDX2 Expression and Tumor Grade

No. at Risk

<table>
<thead>
<tr>
<th>CDX2-positive, grade 1 or 2</th>
<th>257</th>
<th>241</th>
<th>209</th>
<th>183</th>
<th>167</th>
<th>137</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDX2-positive, grade 3 or 4</td>
<td>19</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>CDX2-negative, grade 1 or 2</td>
<td>16</td>
<td>11</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>CDX2-negative, grade 3 or 4</td>
<td>22</td>
<td>12</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

Relationship between CDX2 Expression and Benefit from Adjuvant Chemotherapy.

A  Patients with Stage II Disease

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Disease-free Survival (%)</th>
<th>Years</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDX2-Negative</td>
<td>100</td>
<td>0</td>
<td>412 388 365 344 326 310</td>
</tr>
<tr>
<td>CDX2-Positive</td>
<td>100</td>
<td>0</td>
<td>239 366 344 323 306 290</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>80</td>
<td>5</td>
<td>257 230 199 150 114 84</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>60</td>
<td>5</td>
<td>22 22 21 21 20 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 7 6</td>
</tr>
<tr>
<td>P=0.07</td>
<td></td>
<td></td>
<td>389 366 344 323 306 290</td>
</tr>
</tbody>
</table>

No. at Risk for Interaction: P=0.02

B  Patients with Stage III Disease

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Disease-free Survival (%)</th>
<th>Years</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Tumors</td>
<td>100</td>
<td>0</td>
<td>1063 935 796 721 654 607</td>
</tr>
<tr>
<td>CDX2-Negative</td>
<td>100</td>
<td>0</td>
<td>60 53 47 43 40 37 1003 882 749 678 614 570</td>
</tr>
<tr>
<td>CDX2-Positive</td>
<td>100</td>
<td>0</td>
<td>27 13 9 8 7 7 138 115 87 75 63 48</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>80</td>
<td>5</td>
<td>165 128 96 83 70 55</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>60</td>
<td>5</td>
<td>53 47 43 40 37 1003 882 749 678 614 570</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>138 115 87 75 63 48</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td></td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>
1: wide surgical resection and anastomosis.

2: Adjuvant therapy
    - should not be routinely recommended for unselected patients.
    - In HR patients, adjuvant therapy could be considered [II, B].

ASCO recommendation
Direct evidence from randomized controlled trials does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer. Features associated with an increased risk of recurrence include inadequate lymph node sampling, T4 disease, perforation and a poorly differentiated histology.
Adjuvant chemotherapy of stage II Colon cancer

- Adjuvant chemotherapy has a limited impact in stage II Colon cancer overall
- Patients should be carefully selected based on the pathology report and potentially additional biomarkers
- Older studies should be critically analyzed with the present improvement of imaging, surgical technics and biopathology results.