Can we refine the selection for adjuvant treatment in stage III colon cancer?
High vs Low Risk

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Disclosure

Consultant and or Advisory board:
Amgen, BMS, Gritstone, HalioDx, MSD Oncology, Roche, Sevier

Honoraria:
Amgen, Bayer, BMS, MSD Oncology, Roche/Genentech, Xbiotech
Sanofi Aventis
## SEER Colon Cancer Analysis, Relative Survival by NT Category of Disease

<table>
<thead>
<tr>
<th>NT Category</th>
<th>No. of Patients</th>
<th>5-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>95</td>
<td>87.3</td>
</tr>
<tr>
<td>T1-2</td>
<td>3,134</td>
<td>87.7</td>
</tr>
<tr>
<td>T1</td>
<td>968</td>
<td>87.6</td>
</tr>
<tr>
<td>T2</td>
<td>2,166</td>
<td>87.7</td>
</tr>
<tr>
<td>T3</td>
<td>17,866</td>
<td>68.7</td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td>4,545</td>
<td>50.5</td>
</tr>
<tr>
<td>T4a</td>
<td>2,771</td>
<td>60.6</td>
</tr>
<tr>
<td>T4b</td>
<td>1,774</td>
<td>34.9</td>
</tr>
<tr>
<td><strong>N2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>19</td>
<td>83.2</td>
</tr>
<tr>
<td>T1-2</td>
<td>499</td>
<td>75.0</td>
</tr>
<tr>
<td>T1</td>
<td>104</td>
<td>68.7</td>
</tr>
<tr>
<td>T2</td>
<td>395</td>
<td>76.6</td>
</tr>
<tr>
<td>T3</td>
<td>8,566</td>
<td>47.3</td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td>3,036</td>
<td>27.1</td>
</tr>
<tr>
<td>T4a</td>
<td>1,653</td>
<td>33.3</td>
</tr>
<tr>
<td>T4b</td>
<td>1,383</td>
<td>19.7</td>
</tr>
</tbody>
</table>

Gunderson et al, JCO 2009
Stage III Colon Cancer

Cured with Surgery Alone (55%)

Patients cured by FOLFOX or CAPOX

Patients cured by chemo: 20%

Patients with recurrence: 25%

OS with 10 yr Follow Up : ITT
Stage III

- Hazard ratio 0.80
- 95% CI: 0.66 to 0.96
- P = 0.015

André T et al et al. JCO 2015
Year Overall Survival: Stage III

Stage III N1 (1 to 3 N+): -6.6%
Stage III N2 (≥ 4N+): +13%

André T et al et al. JCO 2015
Stage III ACCENT Database
Fluoropyrimidines ± Oxali (n=8993)

- Higher risk of recurrence over time was associated with higher T and N Stage
- Oxaliplatin demonstrating more benefit in patients with more advanced T and nodal stage
- Addition of oxaliplatin to FU is associated with benefit for T4 and T3, however this benefit exist but is little for T1 and T2

Shah MA et al et al. JCO 2016
TNM staging of colorectal cancer should be reconsidered by T stage weighting

- Open SEER population-based data from 1992-2004
- The relative weights of the T and N stages were calculated by multiple linear regressions
- For colon cancer, Relative T and N stage weight were 0.58 and 0.42
- Conclusion: T stage affects colon cancer survival more significantly than the N stage
<table>
<thead>
<tr>
<th>T4</th>
<th>Perforates serosa</th>
<th>Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4a</td>
<td>Tumor penetrates to the surface of the visceral peritoneum</td>
<td>Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor directly invades or is adherent to other organs or structures</td>
<td>Tumor directly invades or is adherent to other organs or structures</td>
</tr>
</tbody>
</table>
Prospective Pooled Analysis of Six Phase III Trials Investigating Duration of Adjuvant Oxaliplatin-based therapy (3 vs. 6 months) for Patients with Stage III Colon Cancer:

The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration

Grothey A et al. NEJM 2018
André T et al. JCO 2018
Sobrero A et al. JCO 2018
Ivenson T et al. Lancet Oncol 2018
Study Schema

Total planned accrual ≥ 10,500

Stage III Colon Cancer Patients

R

1:1

Investigator’s choice FOLFOX or CAPOX

3 months

6 months

FOLFOX: 5FU/LV + Oxaliplatin

CAPOX: Capecitabine + Oxaliplatin

Grothey A et al. NEJM 2018
Results: mITT Population

<table>
<thead>
<tr>
<th>N patients</th>
<th>12,834</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>72%</td>
</tr>
<tr>
<td>N2</td>
<td>28%</td>
</tr>
<tr>
<td>T1-2</td>
<td>13%</td>
</tr>
<tr>
<td>T3</td>
<td>66%</td>
</tr>
<tr>
<td>T4</td>
<td>21%</td>
</tr>
<tr>
<td>T1-T3 N1</td>
<td>59%</td>
</tr>
<tr>
<td>T4 or N2</td>
<td>41%</td>
</tr>
<tr>
<td>FOLFOX / CAPOX</td>
<td>60% / 40%</td>
</tr>
</tbody>
</table>
Primary DFS Analysis (mITT)

DFS HR = 1.07
95% CI, 1.00 to 1.15

Grothey A et al. NEJM 2018
DFS Comparison by Regimen, cont.

**FOLFOX**

- 3m TRT better
- 6m TRT better

**CAPOX**

- 3m TRT better
- 6m TRT better

**DFS HR**

- **FOLFOX**
  - HR: 1.0
  - DFS HR = 1.16
  - 95% CI: 1.06 to 1.26
  - Inferiority

- **CAPOX**
  - HR: 1.0
  - DFS HR = 0.95
  - 95% CI: 0.85 to 1.06
  - Non-Inferiority

**NI Margin**

- **FOLFOX**
  - NI Margin

- **CAPOX**
  - NI Margin

**Interaction p-value** = 0.0051

TRT: treatment

Grothey A et al. NEJM 2018
DFS Comparison by Risk Groups, cont
mITT all patients independently of the
duration of chemotherapy

IDEA, Shi Q et al, personal data
Analysis by Risk Groups and Regimens

- Large difference in overall prognosis observed between (T1-3 N1) and (T4 or N2) cancers*
  - 3 year DFS Δ 20%
  - Analysis of 3m vs 6m adjuvant therapy for these groups

* Shah MA et al et al. JCO 2016
DFS Comparison by Risk Groups, cont.

T1-3 N1 (58.7%)

3m TRT better

6m TRT better

DFS HR = 1.01
95% CI, 0.90 to 1.12

Non-Inferiority

HR 1.0 1.12

NI Margin

Interaction p-value = 0.11

T4 or N2 (41.3%)

3m TRT better

6m TRT better

DFS HR = 1.12
95% CI, 1.03 to 1.23

Inferiority

HR 1.0 1.12

NI Margin

TRT: treatment

Grothey A et al. NEJM 2018
mITT: DFS Comparison by N Groups: N1 vs N2

IDEA, Shi Q et al, personal data
mITT: DFS Comparison by N Groups: T1-T3 vs T4

IDEA, Shi Q et al, personal data
mITT: DFS Comparison by N Groups: Low Risk vs High risk

IDEA, Shi Q et al, personal data

| T1-3 N1 | 3744 | 3313 | 2796 | 1934 | 1064 | 527 | 211 |
| T1-T3 N1 | 3727 | 3336 | 2788 | 1949 | 1081 | 566 | 221 |
| T4 or N2 | 2634 | 2099 | 1640 | 1044 | 531 | 292 | 107 |
| T4 or N2 | 2622 | 2151 | 1655 | 1094 | 586 | 301 | 110 |
mITT: DFS T4 and/or N2
FOLFOX vs XELOX

mITT population
T4 or N2 FOLFOX

Stratified Non Inferiority P-value: 0.8825

mITT population
T4 or N2 XELOX

Stratified Non Inferiority P-value: 0.0974

IDEA, Shi Q et al, personal data
### mITT: DFS Comparison by Stage, cont.

<table>
<thead>
<tr>
<th>N stage</th>
<th>Patients 3m Arm</th>
<th>Patients 6m Arm</th>
<th>HR (3m/6m)</th>
<th>Favors 3m</th>
<th>Favors 6m</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>4583</td>
<td>4585</td>
<td>1.07</td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>N2</td>
<td>1798</td>
<td>1769</td>
<td>1.07</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T stage</th>
<th>Patients 3m Arm</th>
<th>Patients 6m Arm</th>
<th>HR (3m/6m)</th>
<th>Favors 3m</th>
<th>Favors 6m</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/T2</td>
<td>849</td>
<td>841</td>
<td>1.07</td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>T3</td>
<td>4219</td>
<td>4181</td>
<td>1.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>1320</td>
<td>1335</td>
<td>1.16</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Risk Group

- **T1-3 N1**: 3744 3727 1.01  
  Interaction P-value: 0.11
- **T4 or N2**: 2634 2622 1.12  
  Interaction P-value: 0.11

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Grothey A et al. NEJM 2018
mITT: DFS Comparison by Regimen, N, T and Low versus High risk

### Disease-free Survival at 3 Yr, According to Subgroup

<table>
<thead>
<tr>
<th>Treatment Duration</th>
<th>3 Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX +2.4%</td>
<td>73.6-76.0</td>
<td></td>
</tr>
<tr>
<td>CAPOX -1.1%</td>
<td>75.9-74.8</td>
<td></td>
</tr>
<tr>
<td>N1 +1.1%</td>
<td>79.7-80.8</td>
<td></td>
</tr>
<tr>
<td>N2 +0.2%</td>
<td>61.6-61.8</td>
<td></td>
</tr>
<tr>
<td>T1-T3 +0.3%</td>
<td>79.0-79.3</td>
<td></td>
</tr>
<tr>
<td>T4 +3.3%</td>
<td>58.1-61.4</td>
<td></td>
</tr>
<tr>
<td>Low Risk +0.2%</td>
<td>83.1-83.3</td>
<td></td>
</tr>
<tr>
<td>High Risk +1.7%</td>
<td>62.7-64.4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX +2.4%</td>
<td>7763</td>
<td></td>
</tr>
<tr>
<td>CAPOX -1.1%</td>
<td>5071</td>
<td></td>
</tr>
<tr>
<td>N1 +1.1%</td>
<td>9168</td>
<td></td>
</tr>
<tr>
<td>N2 +0.2%</td>
<td>3567</td>
<td></td>
</tr>
<tr>
<td>T1-T3 +0.3%</td>
<td>10,090</td>
<td></td>
</tr>
<tr>
<td>T4 +3.3%</td>
<td>2655</td>
<td></td>
</tr>
<tr>
<td>Low Risk +0.2%</td>
<td>7471</td>
<td></td>
</tr>
<tr>
<td>High Risk +1.7%</td>
<td>5256</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hazard Ratio 3 vs. 6 Mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX +2.4%</td>
</tr>
<tr>
<td>CAPOX -1.1%</td>
</tr>
<tr>
<td>N1 +1.1%</td>
</tr>
<tr>
<td>N2 +0.2%</td>
</tr>
<tr>
<td>T1-T3 +0.3%</td>
</tr>
<tr>
<td>T4 +3.3%</td>
</tr>
<tr>
<td>Low Risk +0.2%</td>
</tr>
<tr>
<td>High Risk +1.7%</td>
</tr>
</tbody>
</table>

Grothey A et al. NEJM 2018
My Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer

Stage

T1-3 N1
CAPOX or (FOLFOX)

3 months
End of therapy

T4 and/or N2
CAPOX or FOLFOX

3 months
Stop at 3 months if CAPOX T1-T3 N2?

Clinical decision point
- Tolerability of therapy
- Regimen FOLFOX or CAPOX
- Patient preference
- T4 or N2

If FOLFOX and or T4
Continue oxaliplatin with stop if neuropathy ≥ grade 2
and continue fluoropyrimidines

Recommended duration of adjuvant therapy

6 months
Is molecular profiling going to help for adjuvant treatment?  
**KRAS, BRAF, MSI** assessments

- **Important for clinical research:**
  - Stratification factors for future clinical trials (Kras and Braf)

- **For daily practice:** No interest for the indication and choice of adjuvant treatment
  - except MSI / dMMR in elderly subjects because if a chemo is decided, indication to a combination of fluoropyrimidines and oxaliplatin is mandatory
IDEA and after?

- 20,000 patients included in 8 studies for evolution of 3 drugs: irinotecan, bevacizumab and cetuximab

- 1,000 Millions of Dollars (cost of one adjuvant trial with 2,000 patients with a new drug ≥ 80-130 Millions $)

- A disaster for patients, physicians, and companies

- Difficult to find a new industrial partner!

- No indisputable signals emerging from results of trials performed in the metastatic setting, which argue to go in adjuvant settings

- We need study with selected population with a predictive test for new drugs

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de Gramont A et al, Curr Colorectal Cancer Rep 2013
What is the future?
The consensus molecular subtypes of CRC

Clinical Outcome From Oxaliplatin Treatment in Stage II/III Colon Cancer According to Intrinsic Subtypes: Secondary Analysis of NSABP C-07/NRG Oncology Randomized Clinical Trial.

The stemlike subtype (CMS3 and 4) was associated with poor prognosis and lack of benefit from oxaliplatin (HR, 0.99 [95% CI, 0.73-1.34]; P = .96 [N = 367]).

Song N et al. JAMA Oncol 2016
International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study
Digital Droplet PCR for Circulating Tumor DNA

Taly V. et al., Detecting biomarkers with microdroplet technology, Trends in Molecular Medicine, 2012;18:405-16.
Colon Cancer Stage III: tumoral circulating DNA

- 95 patients with colon cancer stage III
- Fluoropyrimidine alone: 23% and Fluoropyrimidine + oxaliplatin: 77%

**ctDNA after surgery**

- **RFS**
  - ctDNA négatif
  - ctDNA positif

- HR = 2.9; p = 0.03

- n  |  Evts  | RFS at 2 Years |
------|--------|----------------|
- 75  | 12     | 84%            |
- 13  | 5      | 55%            |

- HR = 7.1; p < 0.001

- n  |  Evts  | RFS at 2 years |
------|--------|----------------|
- 74  | 11     | 82%            |
- 15  | 10     | 27%            |

Tie J et al., abstr. 3516 ASCO 2018
New Trials for stage III in 2018

• Strong prognostic factor: ctDNA
  - DYNAMIC-III, Phase III for stage III guided by ctDNA

• Focus on T4 or N2 because 40% relapse and need only between 500 to 800 patients to answer the question
  - IROCAS/PRODIGE study: FOLFOX6 vs FOLFIRINOX

• Predictive factor of efficacy
  - MSI/dMMR (NCT02912559 with atezolizumab)
  - Aspirin and mutation of PI3K (1 PRODIGE study in France with aspirin)
  - High Immuno-Score and Immuno-oncology ?
Take home message stage III

• T stage affects colon cancer survival more significantly than the N stage

• Prognosis if stage III T1-T3 N1: DFS is 83% with 3 or 6 months of fluoropyrimidines & oxaliplatin and 3 months of CAPOX will be the new standard

• Prognosis if stage III T4 or N2: DFS is 62.7% with 3 and 64.4% with 6 months of fluoropyrimidines & oxaliplatin: 6 months of CAPOX or FOLFOX are the standard, with stopping oxaliplatin in case of neuropathy grade ≥ 2
Thank you for your attention