Can We Refine the Selection for Adjuvant Treatment in Stage II Colon Cancer?

Elena Élez MD PhD
Colon Cancer Program
Medical Oncology Department
Vall d’Hebron Institute of Oncology (VHIO), Barcelona
meelez@vhio.net
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Estimates incidence and Mortality of CRC

- Colorectal cancer (CRC) ranks third in terms of incidence and second in terms of mortality\(^1\)
- Mortality declines in developed countries\(^2\):
  - Improved cancer management
  - Screening and early detection programs
- Early stages may increase
- CC Stage II 5y OS ranges from 60-87\(^3\)

DECISIONS IN STAGE II DISEASE

The benefit obtained in 5 year OS from adjuvant 5FU is poor ranging 2 to 5% \(^1-5\)

1. **TREATMENT**: Yes vs No
   I. Patient related factors (age, comorbidities)
   II. Tumor related factors

2. **OXALIPLATIN**: Yes vs No

3. **FOR HOW LONG**: 3 vs 6 months

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TREATMENT: YES vs NO

- TNM stage system and clinico-pathological patterns are the main factors that guide treatment decisions
- In stage II disease, only patients defined as high-risk are considered for adjuvant treatment
- However, we can find some variability across guidelines

<table>
<thead>
<tr>
<th>EXPERT ORGANIZATIONS</th>
<th>pT4</th>
<th>PERFORATION/OBSTRICTION</th>
<th>POOR DIFFERENTIATION</th>
<th>LN&lt;13</th>
<th>LN&lt;12</th>
<th>CLOSE/INTERMEDIATE/+ MARGINS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESMO¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>NCCN²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X*</td>
</tr>
<tr>
<td>ASCO³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*Except in MSI tumors

PROGNOSIS VS TREATMENT BENEFIT

- Stage III and II (pT4, obstruction/perforation, poor histology, LN<12, emergent admission)
- 5y survival CT benefit observed in stage III (HR, 0.64; 95% CI, 0.60 to 0.67).
- No survival benefit was observed for chemo in high risk stage vs low risk stage II.
OXA Li PLATIN: YES VS NO

- NSABP C-07 and MOSAIC investigated the value of the addition of ox to 5FU in stage II and III
- MOSAIC (10y follow-up):
  - Non significant improvement in DFS and OS in stage II high risk group
  - No benefit of oxaliplatin for low risk stage II patients

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**FOR HOW LONG: IDEA STAGE II**

### IDEA Trials Summary (High Risk Stage II)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen(s)</th>
<th>HR stage II Colorectal Cancer Patients</th>
<th>Enrolling Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOSCA</td>
<td>CAPOX or FOLFOX4</td>
<td>1268</td>
<td>Italy</td>
</tr>
<tr>
<td>SCOT</td>
<td>CAPOX or mFOLFOX6</td>
<td>1078*</td>
<td>UK, Denmark, Spain, Australia, Sweden</td>
</tr>
<tr>
<td>HORG</td>
<td>CAPOX or FOLFOX4</td>
<td>413</td>
<td>Greece</td>
</tr>
<tr>
<td>ACHIEVE2</td>
<td>CAPOX or mFOLFOX6</td>
<td>514</td>
<td>Japan</td>
</tr>
</tbody>
</table>

*Included 130 rectal patients

High risk definition:
- T4
- Poorly differentiated
- Invasion
  - Vascular
  - Lymphatic
  - Perineural
- Inadequate nodal harvest
  - <10 SCOT
  - <12 others
- Obstruction
- Perforation

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Ireson T, Solimero A, Yoshino T et al. Prospective pooled analysis of four randomized trials investigating duration of adjuvant (ad) oxaliplatin-based therapy (3 vs 6 months [m]) for patients (pts) with high-risk stage II colorectal cancer (CC). J Clin Oncol 37, 2019 (suppl; abstr 3505)
FOR HOW LONG: IDEA STAGE II

Results: DFS Comparison by Regimen

**CAPOX**
- **Duration**
  - 3m: 81.7%
  - 6m: 82.0%

**FOLFOX**
- **Duration**
  - 3m: 79.2%
  - 6m: 86.5%

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Ireson A, Sobrero A, Yoshino T et al. Prospective pooled analysis of four randomized trials investigating duration of adjuvant (neo)oxaliplatin-based therapy (3 vs 6 months [m]) for patients (pts) with high-risk stage II colorectal cancer (CC). J Clin Oncol 37, 2019 (suppl; abstr 3500)
These trials did not yet report biomarkers, which may influence survival and predict response to treatment.
MICROSATELLITE STATUS

- Validated prognostic factor with positive impact on survival in early stage disease
- Stage II-MSI patients:
  - Low recurrence rates without CT\(^1,2\)
  - Adjuvant FU-based CT do not decrease distant relapses in these patients\(^3\)
  - The potential detrimental effect of 5FU has not been confirmed\(^4\)
- Current data in MSI stage II CC support observation

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Integrated Analysis of Molecular and Clinical Prognostic Factors in Stage II/III Colon Cancer

# OTHER BIOMARKERS: STAGE II DISEASE EVIDENCE

<table>
<thead>
<tr>
<th>BIOMARKER</th>
<th>DATA IN STAGE II DISEASE</th>
</tr>
</thead>
</table>
| **BRAF**<sup>1</sup> | - Poor survival after relapse, strongly prognostic in terms of OS  
- To be considered together with MSI status |
| **KRAS**<sup>2</sup> | - Associated with poorly differentiated histology.  
- No major prognostic value OS or RFS |
| **CDX2**<sup>3</sup> | - Worse DFS for CDX2-negative tumors (5%) than CDX2-positive tumors  
- Stage II CDX2-negative could be candidates for adjuvant treatment.  
- To be validated in prospective CT |
| **POL-E**<sup>4</sup> | - 1% CRC. Positive prognostic factor for RFS and DFS in stage II patients.  
- To be validated in prospective CT |
| Sidedness<sup>5</sup> | - Left-sided CC may have reduced risk of death in all stages.  
- Sidedness must be considered in prospective CT |

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GENE EXPRESSION SIGNATURES

- Mandatory: Internal and external validation and contextualization with risk factors
- Several classifiers developed
- Oncotype DX:
  - Validated in 4 independent datasets:
    - QUASAR study: S II 5FU vs observation
    - CALGB 9581: S II, edrecolomab vs observation
    - NSABP C07 (S II/III, 5FU-LV +/- Ox)
    - SUNRISE (S II/III, no chemo)
  - T4 and MSI included in the multivariate analysis
  - High/intermediate/low risk
  - Limitations: Predictive?

Primary endpoint
The 12-RS assay significantly changed the treatment recommendations in 40% of patients. 95%CI, 34–45%; P<0.001

40% of pre-assay treatment recommendations changed
88 (32%) patients were recommended LESS* treatment
21 (8%) patients were recommended MORE* treatment

Watanabe J et al. SUNRISE-DI study. WJIC 2019. Abs O-017

IMMUNOSCORE

International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study

- Immunoscore may have the highest relative contribution to risk of all clinical parameters, including TNM.
- Predictive? Integration with pathological features and MSI. Pending prospective randomized studies.
Can We Refine the Selection for Adjuvant Treatment in Stage II Colon Cancer?
DETERMINANTS OF METASTATIC COMPETENCY IN CCR

Stem cells
Hierarchical cancer cell organization
Tumor cell phenotypes (invasion front)
Dormant cells
Microenvironment during progression and metastasis
Cancer associated fibroblasts
Endothelial cells
Immune cells
Innate immune cells
Adaptative immune cells

MINIMAL RESIDUAL DISEASE

Before surgery: MAF 13.4%
After surgery, day 3: MAF 0.015%
Day +48: MAF 0.11%
Day +244: MAF 0.66%

Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer

<table>
<thead>
<tr>
<th>Mutations</th>
<th>MAF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53 p.R342X</td>
<td>1.531</td>
</tr>
<tr>
<td>TP53 p.G245D</td>
<td>0.123</td>
</tr>
<tr>
<td>APC p.L858Q</td>
<td>0.11</td>
</tr>
<tr>
<td>TP53 p.R248Q</td>
<td>0.001</td>
</tr>
<tr>
<td>TP53 p.R248Q</td>
<td>0.006</td>
</tr>
<tr>
<td>TP53 p.R248Q</td>
<td>0.017</td>
</tr>
<tr>
<td>APC p.Q1405fs</td>
<td>0.059</td>
</tr>
<tr>
<td>APC p.E1379K</td>
<td>0.235</td>
</tr>
<tr>
<td>KRAS p.G13D</td>
<td>0.065</td>
</tr>
<tr>
<td>TP53 p.R248Q</td>
<td>0.578</td>
</tr>
<tr>
<td>APC p.C1578fs</td>
<td>0.140</td>
</tr>
<tr>
<td>KRAS p.G12D</td>
<td>0.027</td>
</tr>
<tr>
<td>KRAS p.G12V</td>
<td>0.006</td>
</tr>
<tr>
<td>TP53 p.P1515fs</td>
<td>0.003</td>
</tr>
<tr>
<td>APC p.S1436fs</td>
<td>0.046</td>
</tr>
<tr>
<td>TP53 p.R282W</td>
<td>1.774</td>
</tr>
<tr>
<td>APC p.D1178fs</td>
<td>0.007</td>
</tr>
<tr>
<td>APC p.E1408fs</td>
<td>0.045</td>
</tr>
<tr>
<td>TP53 p.I254fs</td>
<td>0.005</td>
</tr>
<tr>
<td>APC p.S1010fs</td>
<td>0.006</td>
</tr>
</tbody>
</table>

POTENTIAL OF ctDNA: STAGE II

Observation patients:

- ctDNA 14 of 178 (7.9%), 11 (79%) recurred
- ctDNA 164 patients, 16 (9.8 %) recurred

Recurrence free survival: Observation

*High-risk definition pMMR tumors with at least one of the following: T4, LN <1,2, LVI, poor differentiation

Postoperative ctDNA status remained an independent predictor of RFS for patients not treated with chemotherapy

Serial assessment of cell-free circulating tumor DNA (ctDNA) to assess treatment effect and minimal residual disease during neoadjuvant and adjuvant therapy in colorectal cancer

Results: Patients with persistent ctDNA were significantly more likely to experience disease recurrence (p<0.001) in a shorter time period.

<table>
<thead>
<tr>
<th></th>
<th>Recurred</th>
<th>Recurrence Free</th>
<th>Median Time to Recurrence (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent ctDNA</td>
<td>11</td>
<td>0</td>
<td>182</td>
</tr>
<tr>
<td>Cleared ctDNA</td>
<td>3</td>
<td>3</td>
<td>333</td>
</tr>
<tr>
<td>Negative ctDNA</td>
<td>7</td>
<td>19</td>
<td>NR* (median follow-up: 550 days)</td>
</tr>
</tbody>
</table>

Sensitivity and whether the identification of ctDNA+ patients can improve their outcomes through early relapse diagnosis and therapeutic intervention remains to be proved.
POTENTIAL OF ctDNA: STAGE II

## POTENTIAL OF ctDNA: STAGE II

<table>
<thead>
<tr>
<th></th>
<th>DYNAMIC II(^1)</th>
<th>COBRA NGR GI005(^2)</th>
<th>IMPROVE-IT(^3)</th>
<th>IMPROVE(^4)</th>
<th>PEGASUS(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country</strong></td>
<td>Australia</td>
<td>US/Canada</td>
<td>Denmark</td>
<td>Denmark</td>
<td>Italy</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Enrolling (355/450)</td>
<td>Approved, opening May '19</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td>Safe-SeqS</td>
<td>Guardant LUNAR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td>II</td>
<td>II</td>
<td>Stage I/Low risk Stage II</td>
<td>High risk stage II/stage III</td>
<td>High risk stage II/stage III</td>
</tr>
<tr>
<td><strong>Methodology</strong></td>
<td>Escalate</td>
<td>Escalate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>De-escalation to:</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>Observation</td>
<td>N/A</td>
<td>5FU</td>
</tr>
<tr>
<td><strong>Escalate to:</strong></td>
<td>Chemo</td>
<td>FOLFOXx6m</td>
<td>CAPOX</td>
<td>r/a</td>
<td>CAPOX</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>450</td>
<td>1400</td>
<td>64</td>
<td>1800</td>
<td>140</td>
</tr>
<tr>
<td><strong>Phase</strong></td>
<td>II</td>
<td>III</td>
<td>II</td>
<td>Observational study</td>
<td>II</td>
</tr>
</tbody>
</table>

\(^1\) Dynamic II: Circulating tumour DNA (ctDNA) analysis informing adjuvant chemotherapy in Stage II Colon Cancer, ACTRN12615000381583; \(^2\) COBRA NCI NRG-G1 005 Phase II/III Study of Circulating Tumor DNA as a Predictive Marker for Response to Adjuvant Chemotherapy in Patients with Stage II Colon Cancer, presented by R Concannon, Asco Annual Meeting 2019; \(^3\) IMPROVE-IT: IMPROVE Intervention Trial Implementing Non-invasive Circulating Tumor DNA Analysis to Optimize the Operative and Postoperative Treatment for Patients With Colorectal Cancer (IMPROVE-IT) ClinicalTrials.gov Identifier: NCT03748680; \(^4\) Improve: Circulating Tumor DNA Analysis to Optimize Treatment for Patients With Colorectal Cancer (IMPROVE) ClinicalTrials.gov Identifier: NCT03897886; \(^5\) Pegasus trial
THE PEGASUS TRIAL

Molecular Adjuvant

1. Post Surgery LB (2-4 weeks)

2. LB ctDNA -

3. LB ctDNA +/-

4. LB ctDNA +/-

5. LB ctDNA +/-

6. LB ctDNA +/-

CAPOX

3 months

CAPE

6 months

Molecular Metastatic

7. Follow-Up

8. LB after 6 months from #8

9. LB after 6 months from #8

1. FOLFOX 6 months

2. Swallow-through

3. Post-Adjuvant LB

4. Post-Adjuvant LB

5. Pre-CAPE LB

6. Pre-CAPE LB

7. LB after 1 cycle of treatment

8. LB after 1 cycle of treatment

9. LB after 1 cycle of treatment

Switch to #6 months CAPOX
Switch to 12 months FOLFOX
Collection for prospective analysis (just-in-time)
1. Of interruption due to unacceptable toxicity

EUDRACT number: 2019-002074-32; Sponsor: IFOM – Istituto FIRC di Oncologia Molecolare; Sponsor representative: Silvia Marsoni
SUMMARY AND KEY MESSAGES STAGE II

- In 2019; TNM stage system is still the basis for therapeutic decisions in stage II disease.

- Patient related factors and tumor related risk factors (particularly T4) as well as mismatch repair status must be integrated in the decision.

- Supervised gene expression signatures / Immunoscore are strong prognostic tools but lack predictive value

- The incorporation of minimal residual disease may distinguish tumors with “real-limited disease” vs “molecular metastatic patients”

- The accurate diagnosis and management of ctDNA+ patients must be addressed in prospective clinical trials
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