Are we making progress in the molecular taxonomy of colon cancer?

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University of Leuven
Belgium
Colorectal cancer: from one disease to heterogeneous entities

Many diseases hitting the same organ

Many new targets to pursue, new ways to pursue them

Many diseases hitting the same organ
Progress in molecular taxonomy

- Knowledge
- Application
Colorectal cancer subtyping consortium (CRCSC) identifies consensus molecular subtypes

### CRCSC – Results Summary

<table>
<thead>
<tr>
<th>CMS</th>
<th>Percentage</th>
<th>Characteristics</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>CMS1</td>
<td>13%</td>
<td>Females, older age, right colon, MSI, hypermutation, <em>BRAF</em> mut, immune activation</td>
<td>Better RFS, intermediate OS, worse SaR</td>
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<td>35%</td>
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</table>
Mutation frequencies in human CRC.

**a**

![Graph showing mutation frequencies and tumor site details](image)

**b**

<table>
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<tr>
<th>Gene</th>
<th>Hypermutated tumours</th>
<th>Non-hypermutated tumours</th>
</tr>
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<tbody>
<tr>
<td>APC</td>
<td>51%</td>
<td>46%</td>
</tr>
<tr>
<td>AKT1</td>
<td>46%</td>
<td>40%</td>
</tr>
<tr>
<td>CDH1</td>
<td>40%</td>
<td>31%</td>
</tr>
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<td>PIK3CA</td>
<td>40%</td>
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Methylation based subgrouping

Hinoue et al
miRNA based subgrouping. 960 colon specific miRNA
**CRCSC – Future directions**

Ongoing work (complete analyses Fall 2014):

- Refinement of potential “mixed” subtype (CMS5)
- Development of a CRC subtype classifier that is robust and reproducible
- Integrate other markers

Collaborations to assess predictive value and differential drug sensitivity patterns across CMSs.
Retrospective stratification

Survival after relapse of CMS

Arm A vs Arm B
Bevacizumab in Stage II-III Colon Cancer: the National Surgical Adjuvant Breast and Bowel Project C-08 Trial
Defective Mismatch Repair and Benefit from Bevacizumab for Colon Cancer: Findings from NSABP C-08

Kay Pogue-Geile, Greg Yothers, Yusuke Taniyama, Noriko Tanaka, Patrick Gavin, Linda Colangelo, Nicole Blackmon, Corey Lipchik, Seong Rim Kim, Saima Sharif, Carmen Allegra, Nicholas Petrelli, Michael J. O’Connell, Norman Wolmark, Soonmyung Paik

Manuscript received December 21, 2012; revised May 1, 2013; accepted May 6, 2013.

A

B

Percentage surviving

0 1 2 3 4 5 6

Years from Randomization

No. at risk

 MSI

MSS
**OS in Patients With WT RAS mCRC**

**WT RAS**

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<th>Treatment</th>
<th>Events n/N (%)</th>
<th>Median months (95% CI)</th>
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<tr>
<td>Panitumumab + FOLFOX4</td>
<td>128/259 (49)</td>
<td>26.0 (21.7 - 30.4)</td>
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<td>FOLFOX4 alone</td>
<td>148/253 (58)</td>
<td>20.2 (17.7 - 23.1)</td>
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Hazard ratio = 0.78 (95% CI, 0.62 - 0.99)  
P value = 0.043
OS in Patients With MT RAS mCRC

MT RAS

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<td>n/N (%)</td>
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Hazard ratio = 1.25 (95% CI, 1.02 - 1.55)
P value = 0.034
Retrospective stratification

Survival after relapse of CMS

Arm A vs Arm B

Survival estimates and comparison of Arm A vs Arm B.
Overall Survival - ITT Population

Symbol=Censor
Placebo/FOLFIRI  Median = 12.06 months
Aflibercept/FOLFIRI  Median = 13.50 months

Stratified HR=0.817 [95.34%CI, 0.713-0.937]
Log-rank p = 0.0032
Sample collection 128 sites worldwide, 28 countries, 1186 patients

Afiblercept biomarker analysis
Retrospective stratification

Survival after relapse of CMS

Arm A vs Arm B

OS estimate vs Time

Percent Event Free vs months
Discovery of novel therapeutic targets
RTKs activation by effectors inhibition


Rodrik-Outmezguine et al., *Cancer Discovery* 2011;1:248-259
Integrated Analysis

SNP Arrays

Functional shRNA Screen

Next Gen Sequencing

Expression Arrays

Functional validation

Discovery of novel therapeutic targets
CRCSC – Future directions

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- Refinement of potential “mixed” subtype (CMS5)
- Development of a CRC subtype classifier that is robust and reproducible
- Validation in external datasets

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Prospective testing of selected drugs based on subclass biology
## Prospective drug testing

### Enrich and stratify

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SPECTAcolor

Biomarker Screening Platform for Efficient Clinical Trials Access in Advanced Colorectal Cancer

1. Molecular subtypes
   - Subtype A → Regimen A
   - Subtype B → Regimen B
   - Subtype C → Regimen C

2. Escape

Adapted from Mallmann MR, et al. EPMA J 2010;1:421–437
EORTC SPECTAprogram

Screen and Treat

SPECTAplatforms
- SPECTAcolor
- SPECTAbrain
- SPECTAmel
- SPECTAlung
- SPECTApros

SPECTAforum
- Patient representatives
- Industry
- Regulators
- Technology companies
- Governments
- Payers

SPECTApath
- PathoBiology
- Biobanking
- Scientific/operational support

SPECTAreg
- Competent bodies
- Regulatory affairs research

The future of cancer therapy
Let's organize it for CRC

**New Model of Collaboration**

- ** Patients Organizations **
- ** Charities **
- ** Policy **

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**Efficiency!**

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**Unclassified** 21% Mixed subtype with variable epithelial mesenchymal activation? Intermediate RFS, OS and SoR