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

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

Many diseases hitting the same organ
Colorectal cancer: from one disease to heterogeneous entities

Many diseases hitting the same organ
Colorectal cancer: from one disease to heterogeneous entities

Many diseases hitting the same organ

Many new targets to pursue, new ways to pursue them
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>%</th>
<th>Features</th>
<th>Survival Outcomes</th>
</tr>
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Mutation frequencies in human CRC.

(a) Graph showing mutation rates per 10^6 bases, with distinction between non-silent (circles) and silent (diamonds) mutations. The graph also includes a legend for epigenetic silencing, frameshift mutations, and missense/nonsense mutations, and represents different tumor sites, MSI status, CIMP status, and MLH1 silencing.

(b) Bar charts comparing mutation frequencies in hypermutated and non-hypermutated tumors for various genes.
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

Budinska et al J Clin Oncol 30, 2012 (abstr 3511)
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

mFF6: 128 Pts, 31 Deaths
mFF6+Bev: 124 Pts, 18 Deaths

HR = 0.52, 95% CI = 0.29 to 0.94
P = .03

mFF6: 873 Pts, 172 Deaths
mFF6+Bev: 868 Pts, 177 Deaths

HR = 1.03, 95% CI = 0.84 to 1.27
P = .78

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>118</th>
<th>111</th>
<th>106</th>
<th>95</th>
<th>85</th>
<th>28</th>
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<tr>
<td>MSI</td>
<td>119</td>
<td>112</td>
<td>107</td>
<td>106</td>
<td>90</td>
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<tr>
<th></th>
<th>831</th>
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<td>MSS</td>
<td>837</td>
<td>800</td>
<td>760</td>
<td>711</td>
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WT RAS

OS in Patients With WT RAS mCRC

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<th>Treatment</th>
<th>Events</th>
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<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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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

OS estimate vs Time

Survival Percent Event Free vs months
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

Aflibercept biomarker analysis
Retrospective stratification

Survival after relapse of CMS

Arm A vs Arm B
SNP Arrays → Functional shRNA Screen → Next Gen Sequencing
Expression Arrays → Integrated Analysis → Functional validation

Integrated Analysis

Discovery of novel therapeutic targets
RTKs activation by effectors inhibition

EGFR

ERBB3

IGF1R

P

Ras

B-Raf

MEK

MAPK

PI3K

p85

PTEN

AKT

S6K

mTORC inhibitors

BRAF/MEK inhibitors

MEK inhibitors

AKT inhibitors

SOS

Grb2 Shc

Ras

B-Raf

C-RAF

MEK

MAPK

DUSPs

Ebi et al., J Clin Invest October 10, 2011

Chandarlapaty S et al., Cancer Cell. 2011 Jan 18;19(1):58-71
Rodrik-Outmezguine et al., Cancer Discovery 2011;1:248-259

Prahallad et al., Nature January 26, 2012
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

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

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

#### Enrich, stratify

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SPECTAcolor

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

Molecular subtypes

1

Subtype A → Regimen A
Subtype B → Regimen B
Subtype C → Regimen C

Biomarker profiling

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

- Charities
- Patients Organizations
- Academia
- Policy

Efficiency!

Discovery of novel therapeutic targets

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Let’s organize it for CRC

New Model of Collaboration

Public Funding

Charities

Industry

Patients Organizations

Policy Makers

Academia

EFFICIENCY!