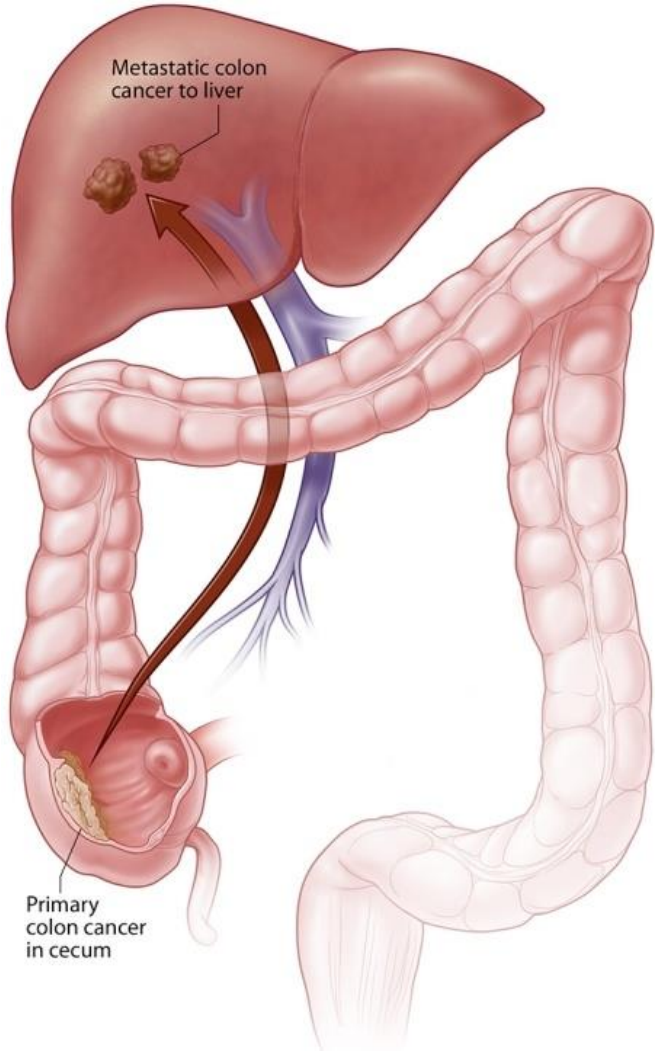
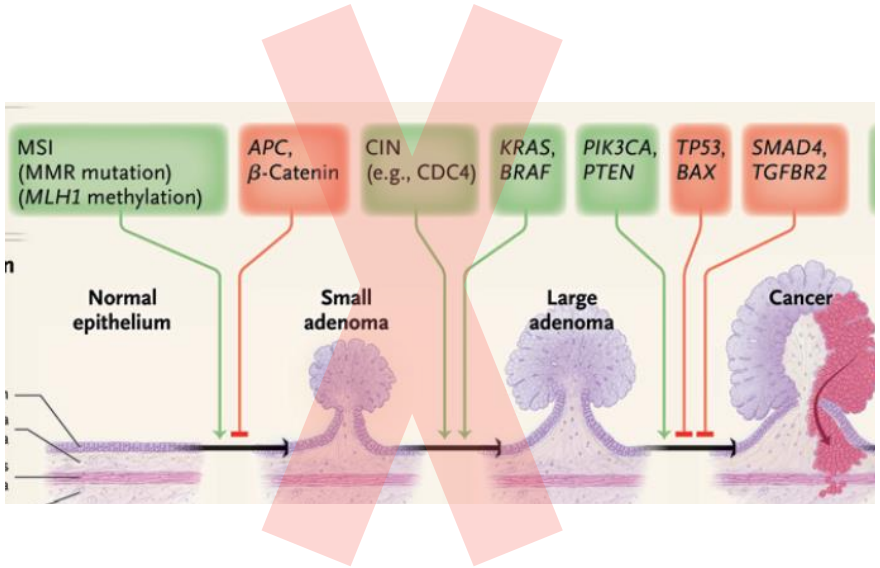
Are we making progress in the molecular taxonomy of colon cancer?

Sabine Tejpar
University of Leuven
Belgium

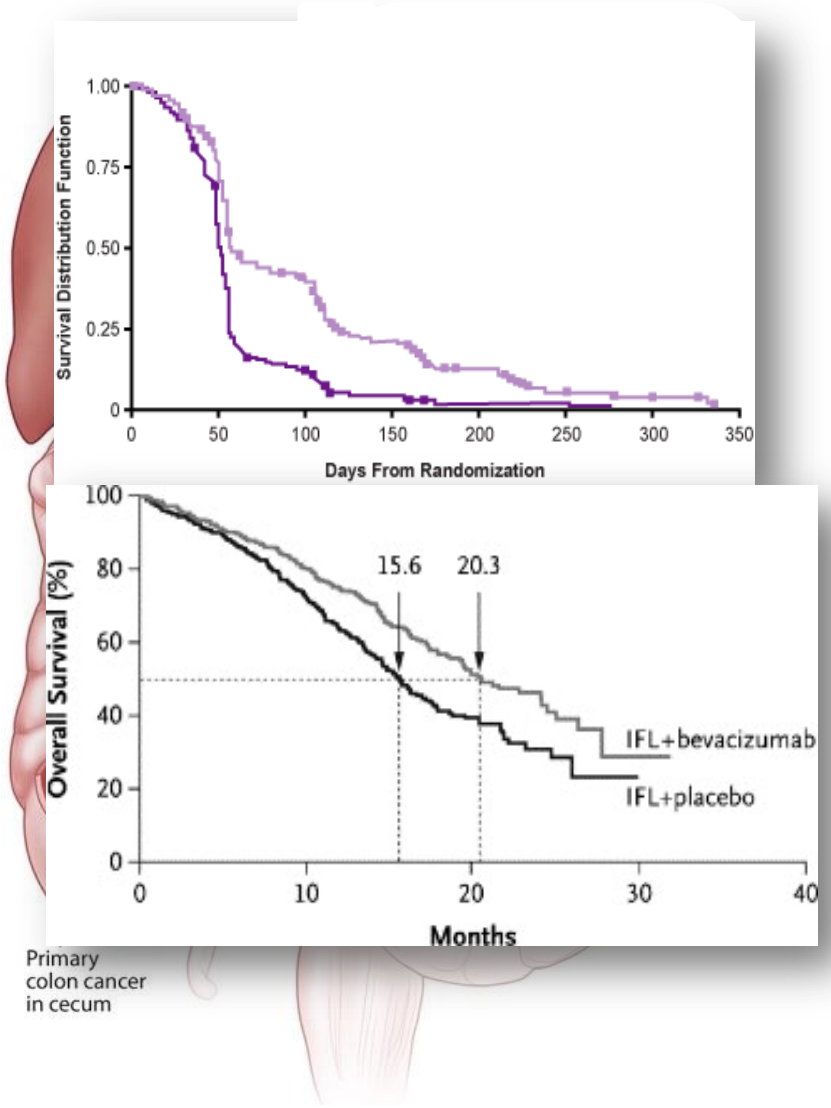
Colorectal cancer: from one disease to hetereogenous entities

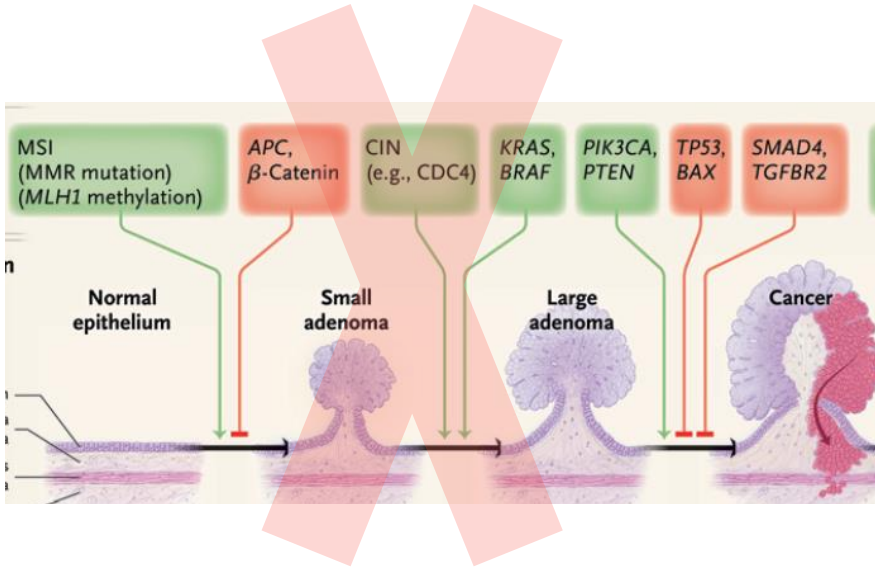




Many diseases hitting the same organ

Colorectal cancer: from one disease to hetereogenous entities





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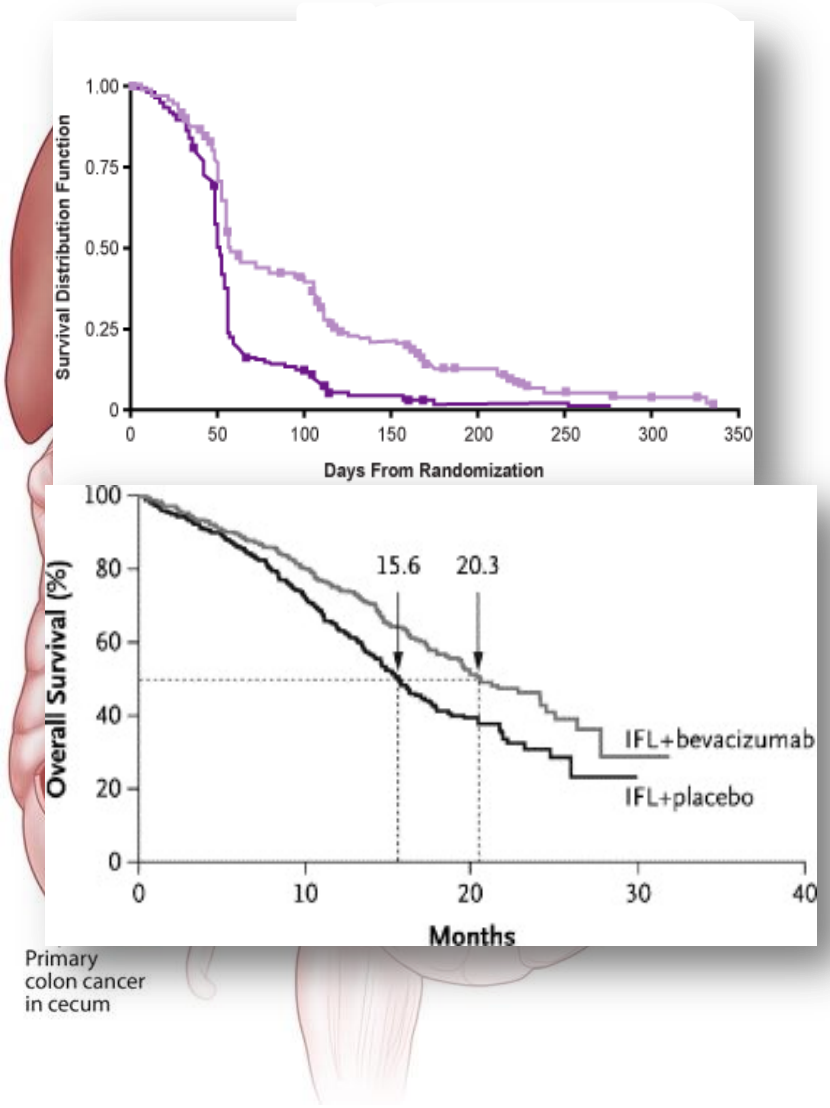

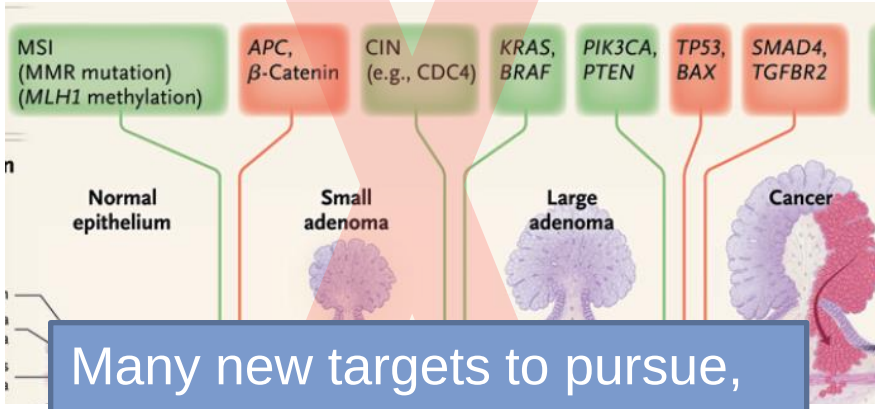

Many new targets to pursue, new ways to pursue them

Many diseases hitting the same organ

Progress in molecular taxonomy

- Knowledge

- Application

Colorectal cancer subtyping consortium (CRCSC) identifies consensus molecular subtypes

Rodrigo Dienstmann, Justin Guinney, Mauro Delorenzi, Aurelien De Reynies, Paul Roepman, Anguraj Sadanandam, Louis Vermeulen, Andreas Schlicker, Edoardo Missiaglia, Charlotte Soneson, Laetitia Marisa, Krisztian Homicsko, Xin Wang, Iris Simon, Pierre Laurent-Puig, Lodewyk F. A. Wessels, Jan Paul Medema, Scott Kopetz, Stephen H. Friend, Sabine Tejpar, **Colorectal Cancer Subtyping Consortium**

PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

CRCSC – Results Summary

CMS1	**13%**	Females, older age, right colon, MSI, hypermutation, *BRAF* mut, immune activation	Better RFS, intermediate OS, worse SaR
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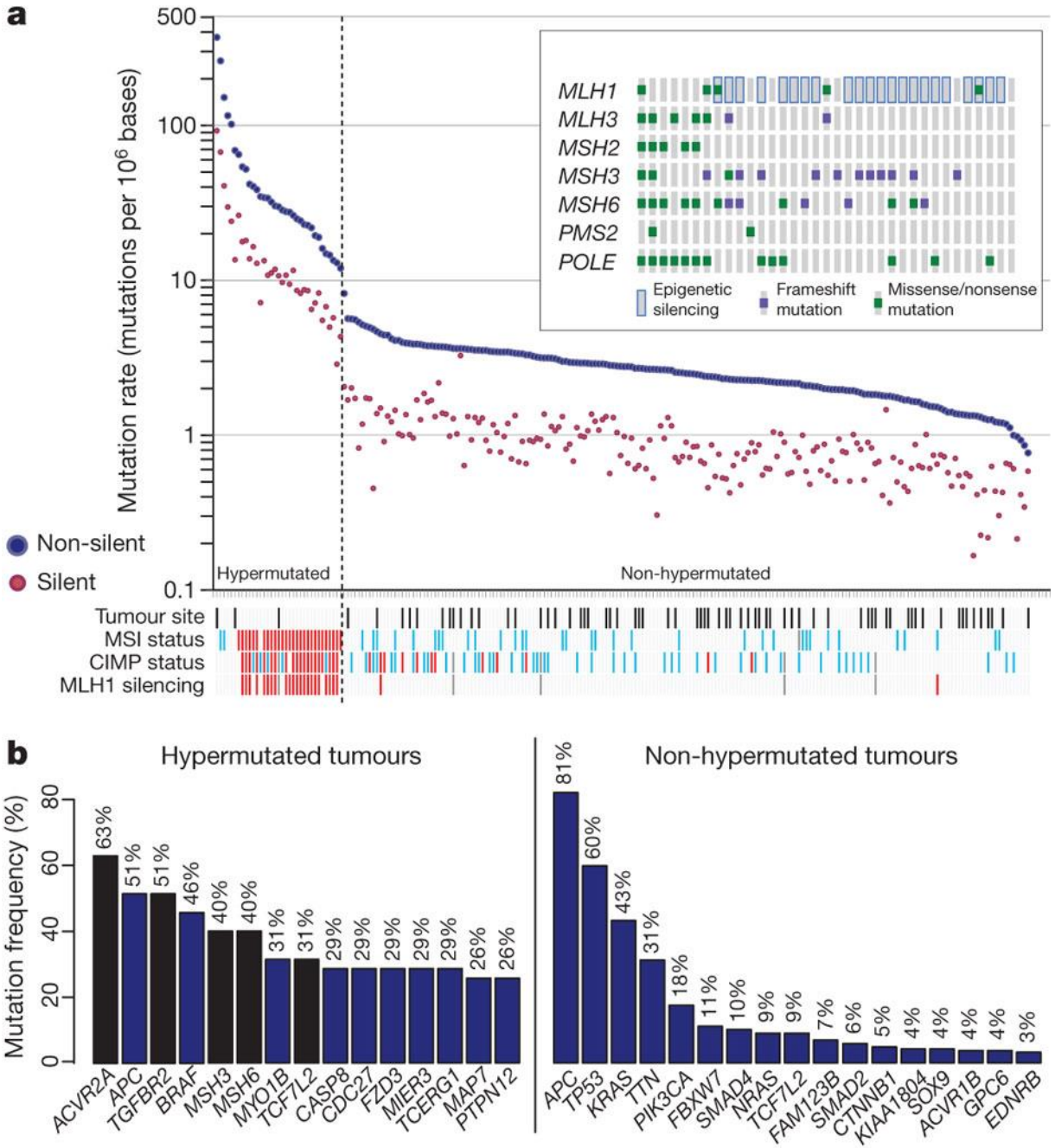
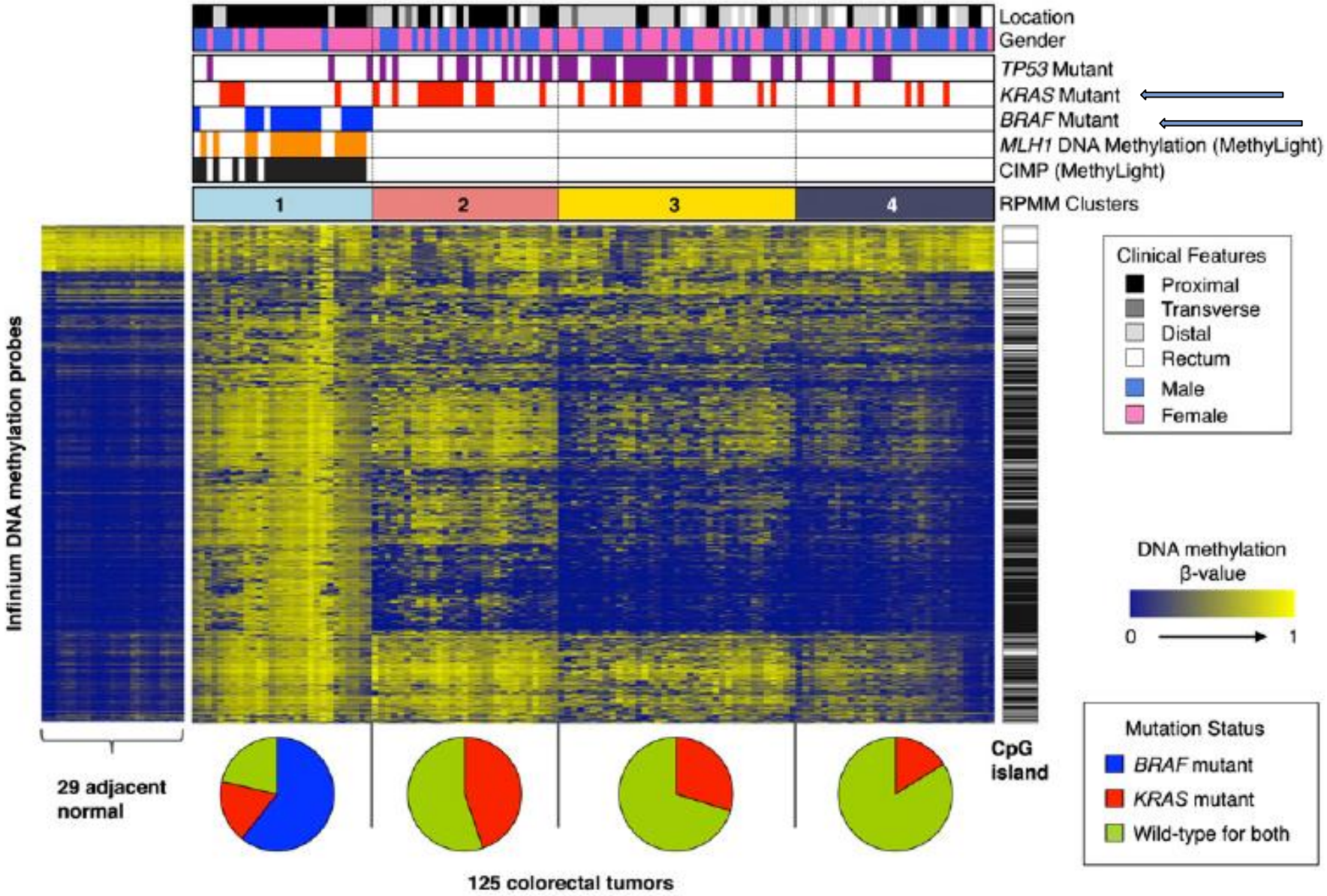
Mutation frequencies in human CRC.



The Cancer Genome Atlas Network Nature **487**, 330-337 (2012) doi:10.1038/nature11252

nature

Methylation based subgrouping

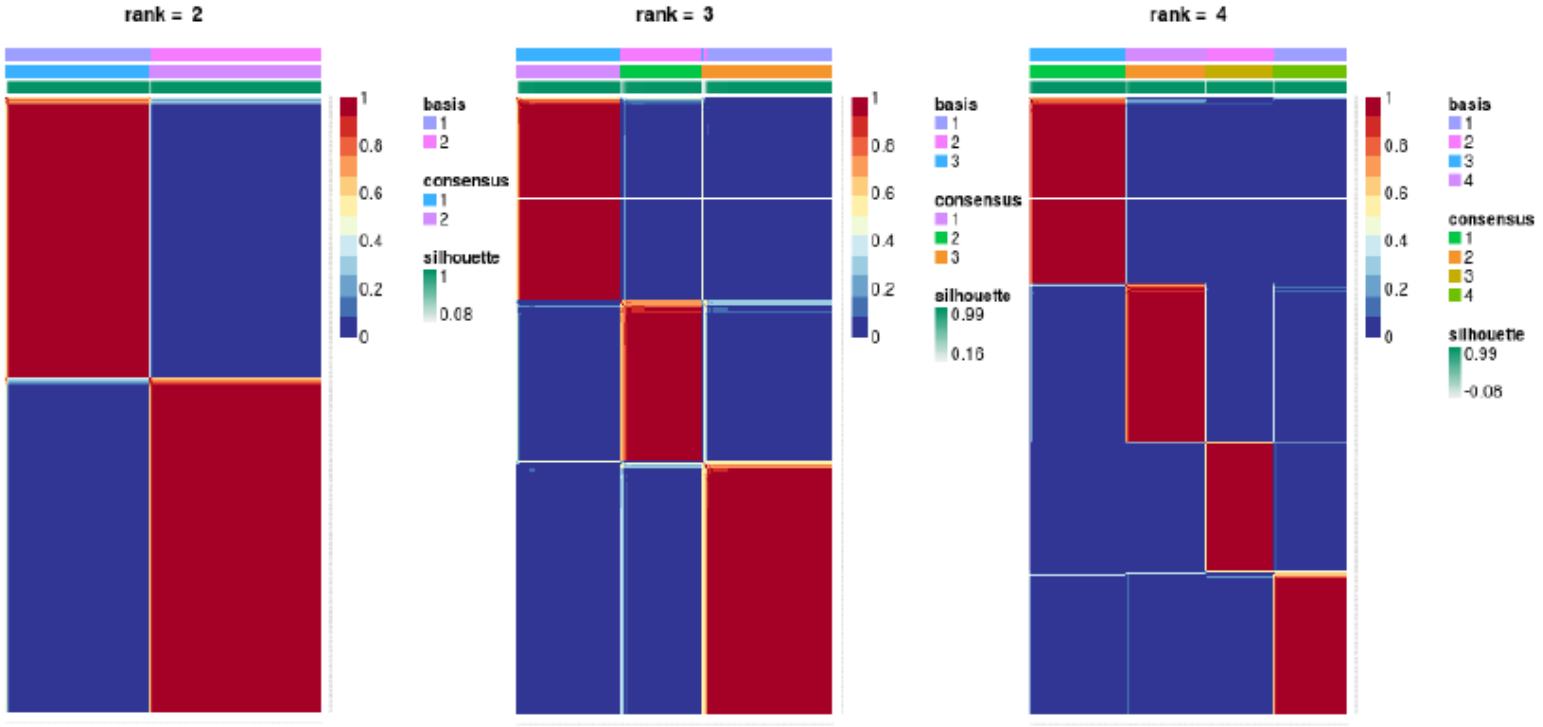


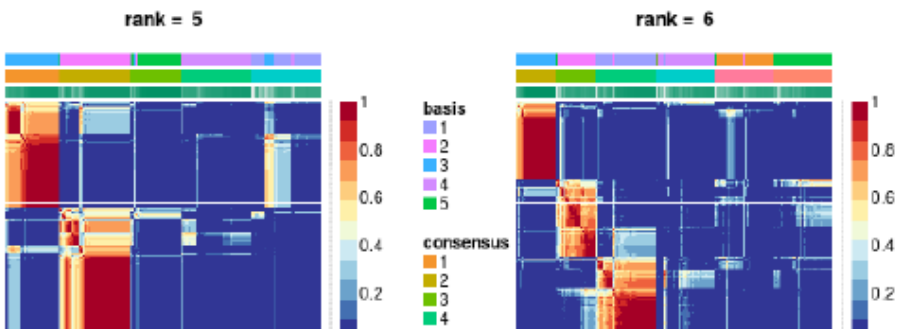
Hinoue et al

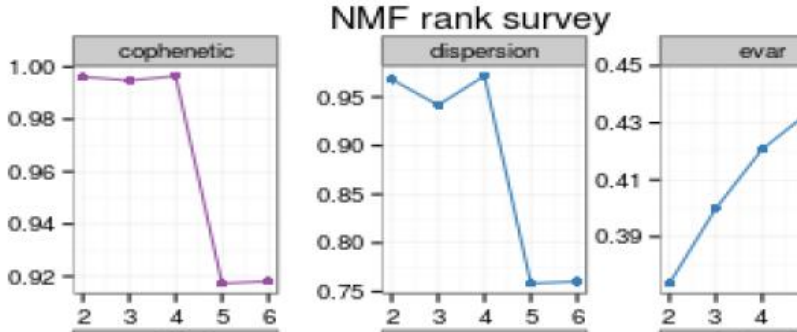
miRNA based subgrouping. 960 colon specific miRNA

Bioinformatics Core Facility
Swiss Institute of Bioinformatics

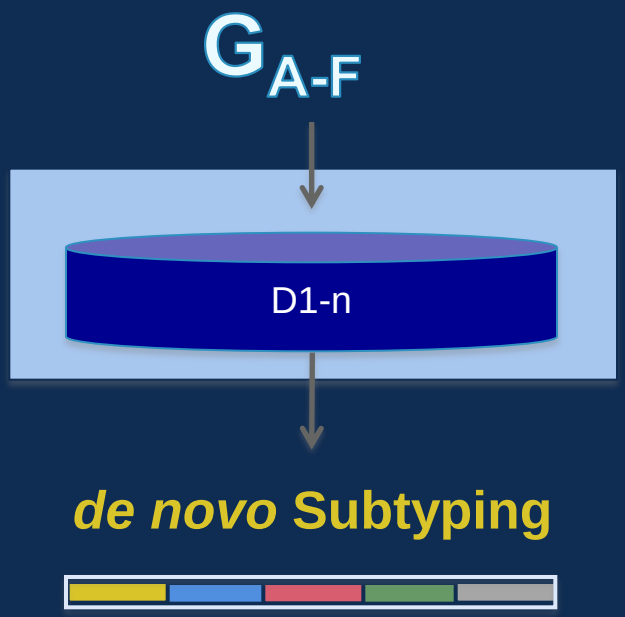
PETACC-3 miRNA
April 14, 2014







CRCSC – Future directions

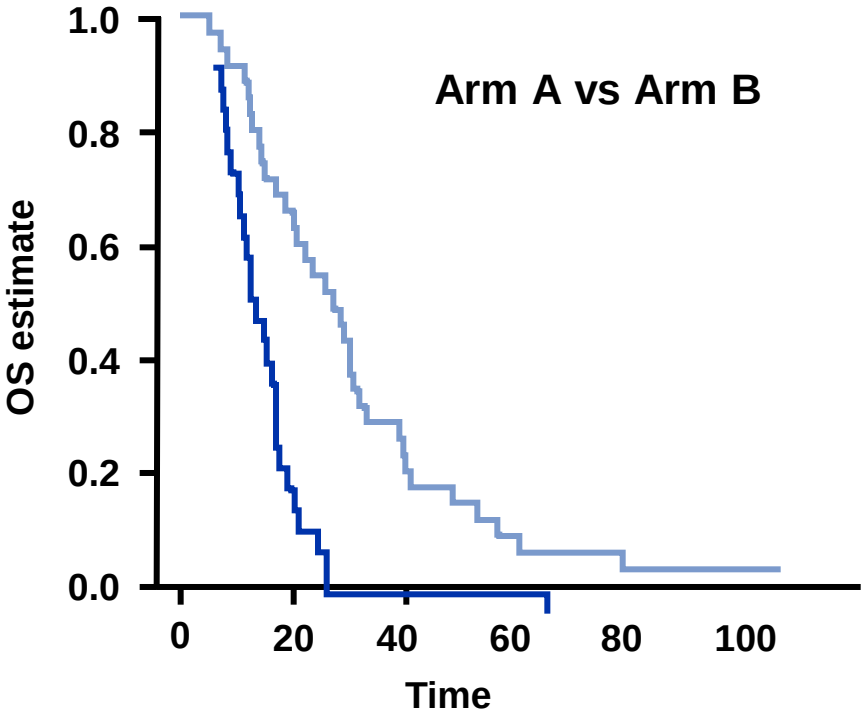


Ongoing work (complete analyses Fall 2014):

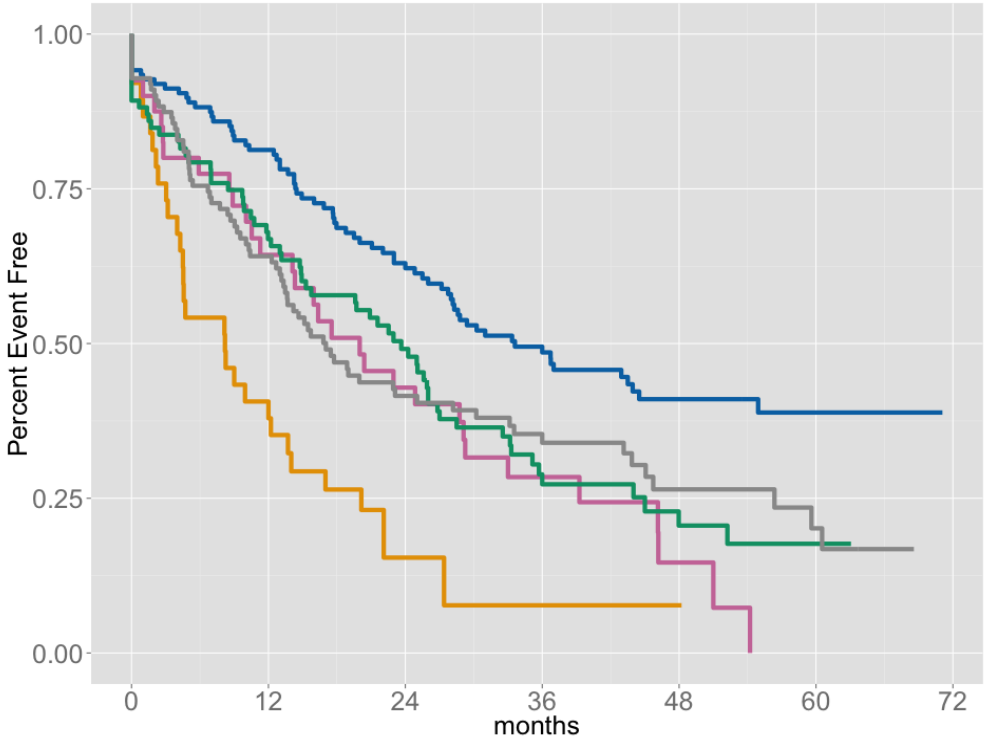
- Refinement of potential "mixed" subtype (CMS5)
- Development of a CRC subtype classifier that is robust and reproducible
- Integrate other markers

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

Retrospective stratification



Survival after relapse of CMS

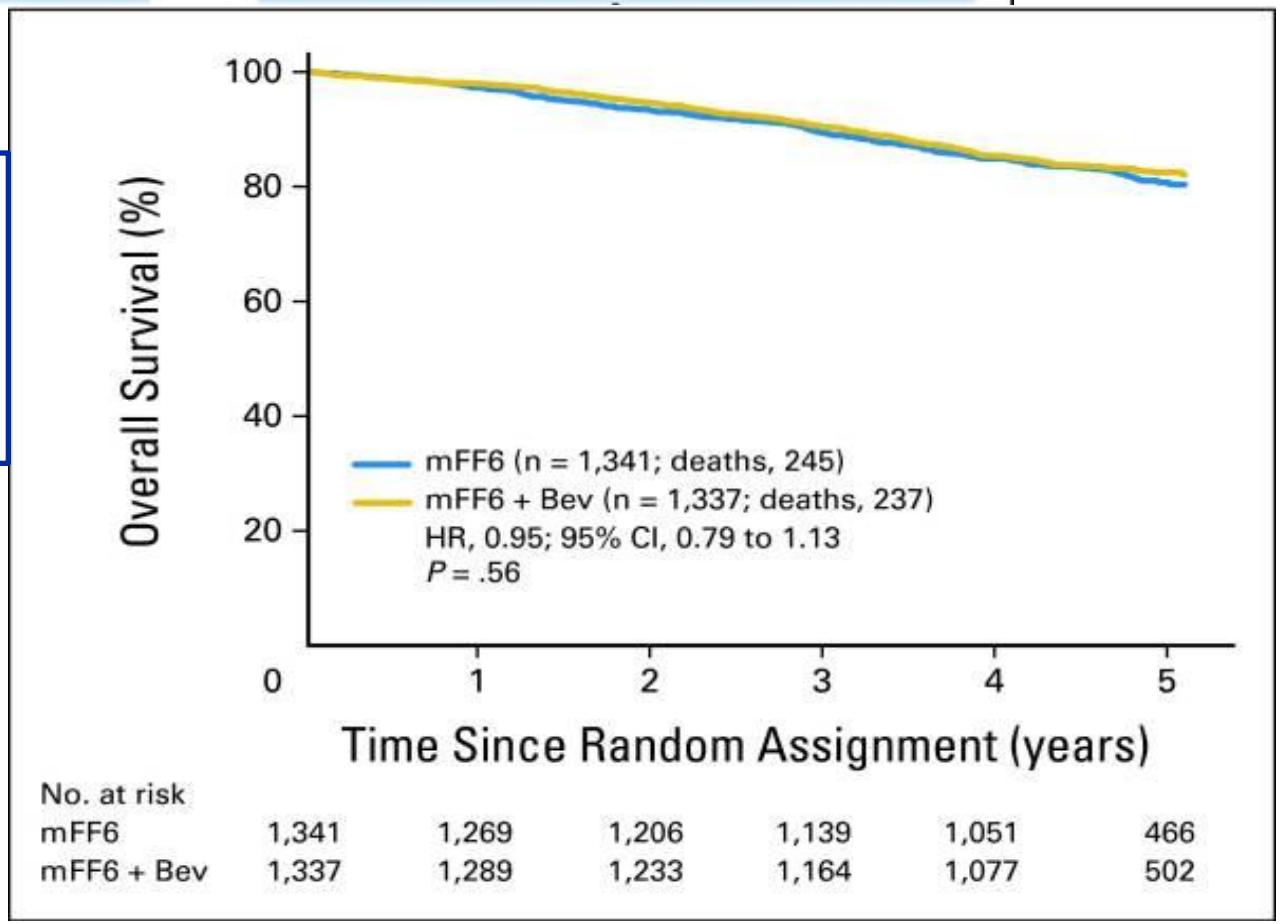


Randomly assigned
(N = 2,710)

Assigned to mFF6
(n = 1,356)

Assigned to mFF6 + Bev
(n = 1,354)

Bevacizumab in Stage II-III Colon Cancer: the National Surgical Adjuvant Breast and Bowel Project
C-08 Trial

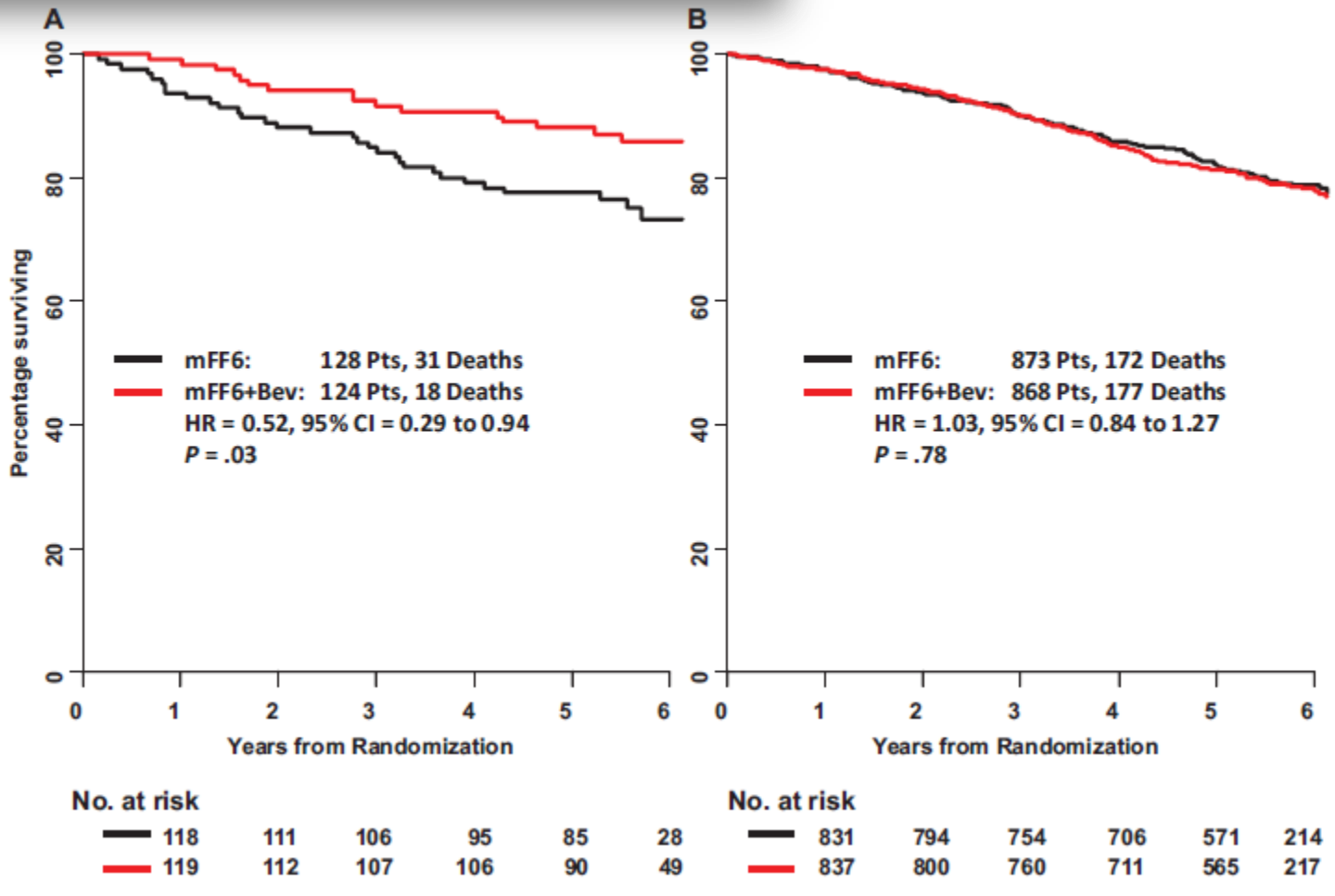


Defective Mismatch Repair and Benefit from Bevacizumab for Colon Cancer: Findings from NSABP C-08

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

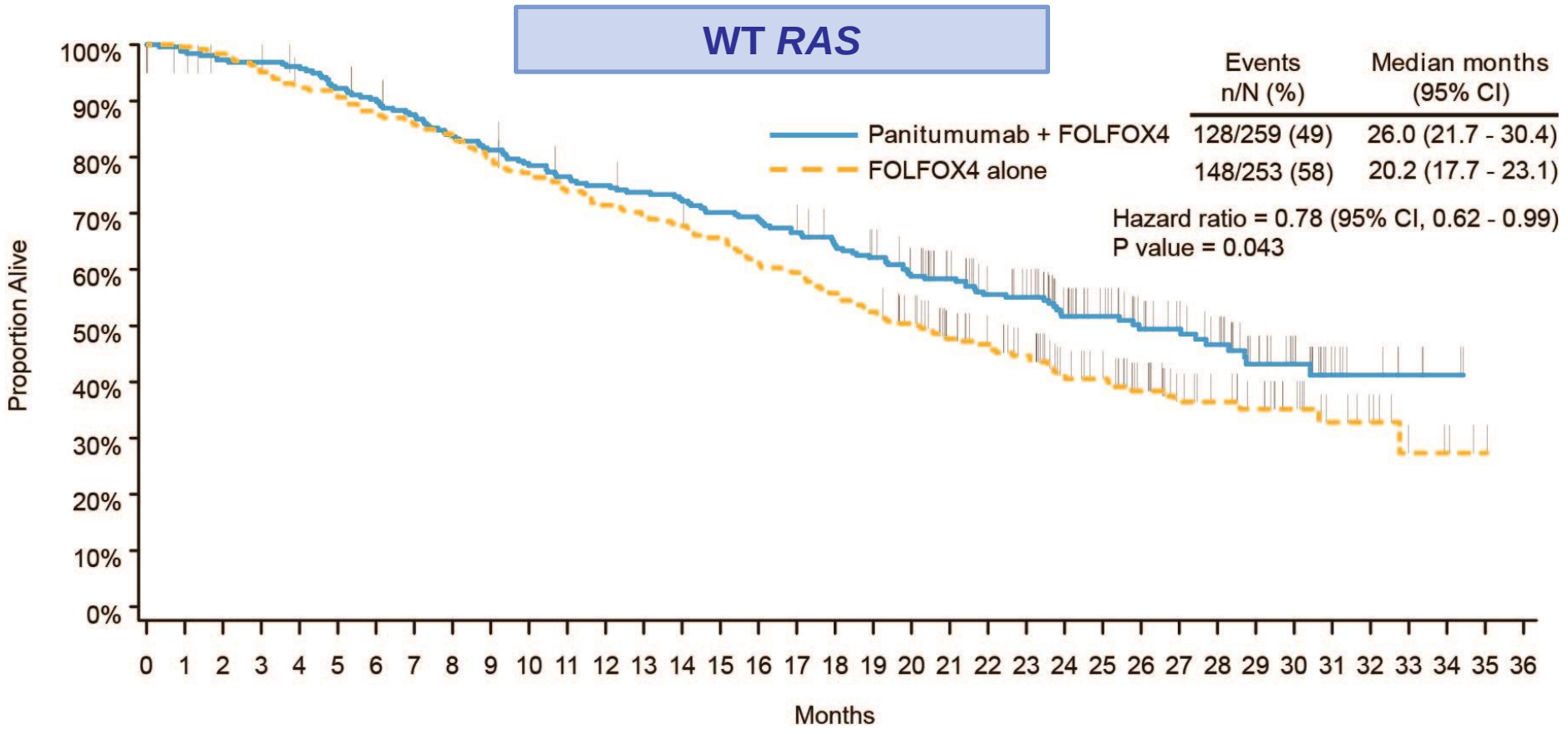
Manuscript received December 21, 2012; revised May 1, 2013; accepted May 6, 2013.

MSI

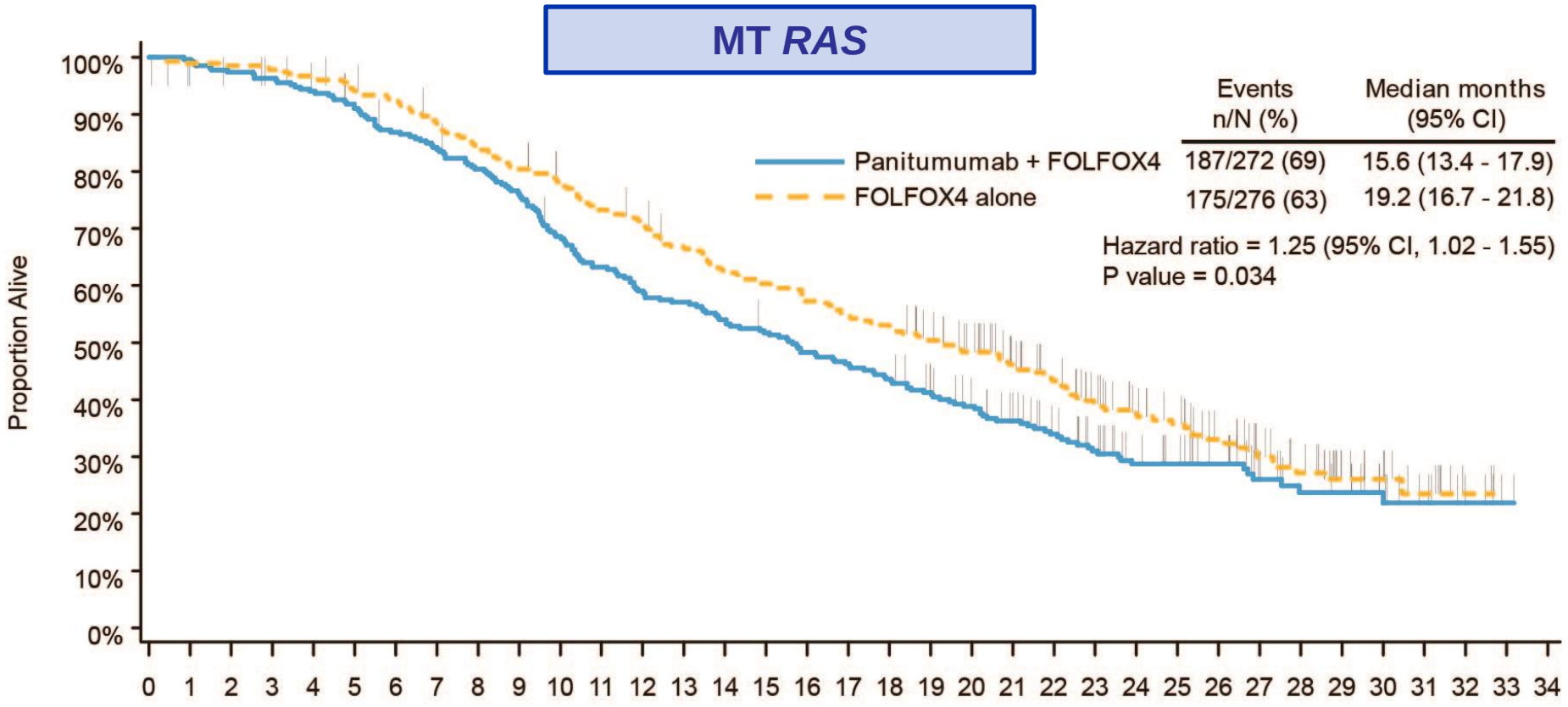


MSS

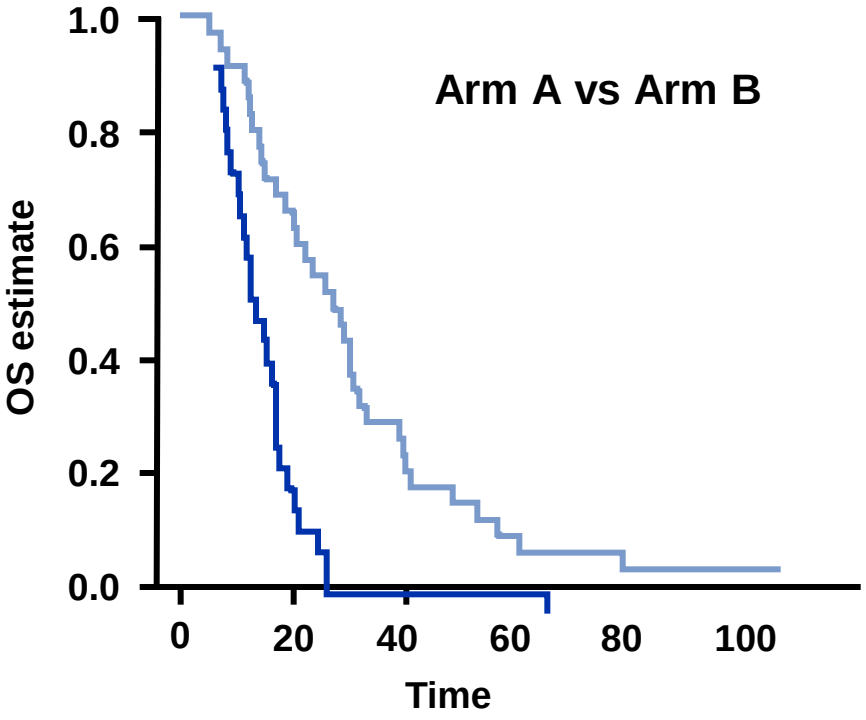
OS in Patients With WT RAS mCRC



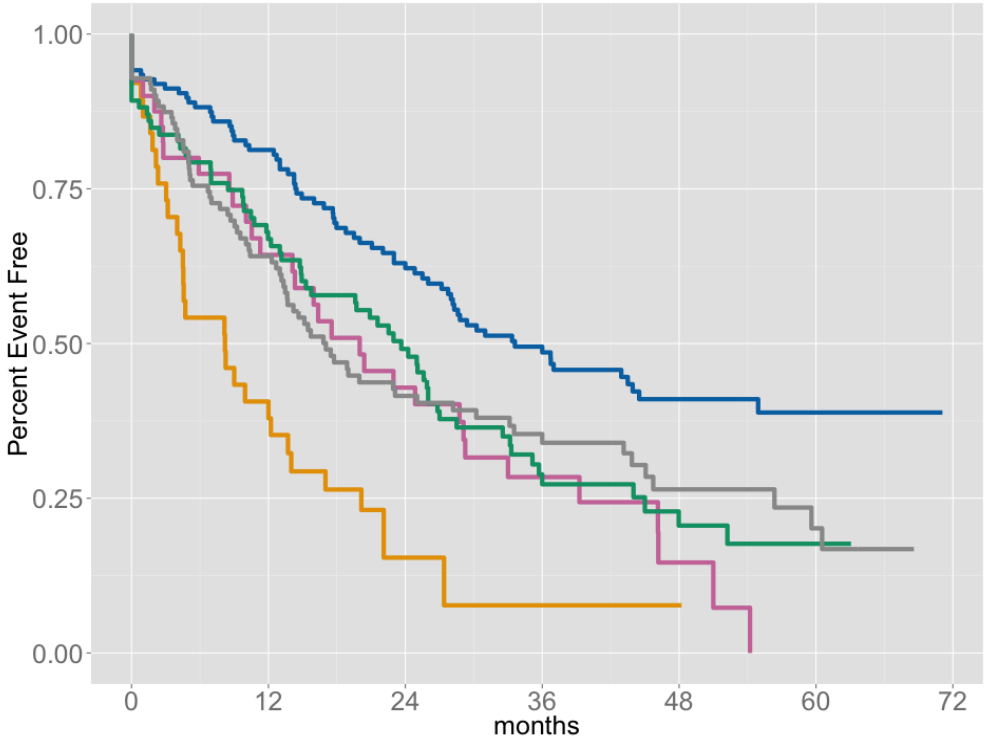
OS in Patients With MT RAS mCRC



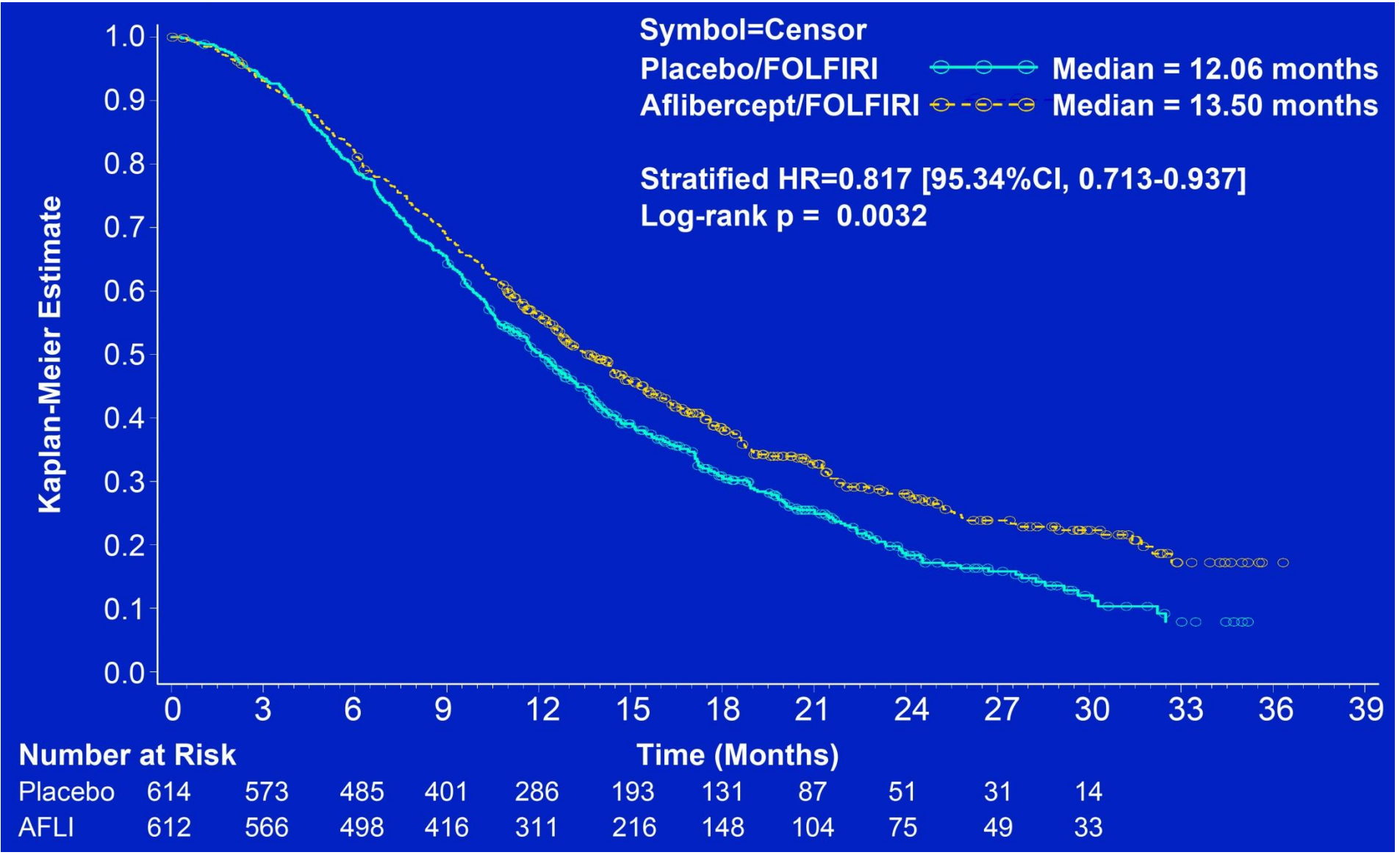
Retrospective stratification



Survival after relapse of CMS



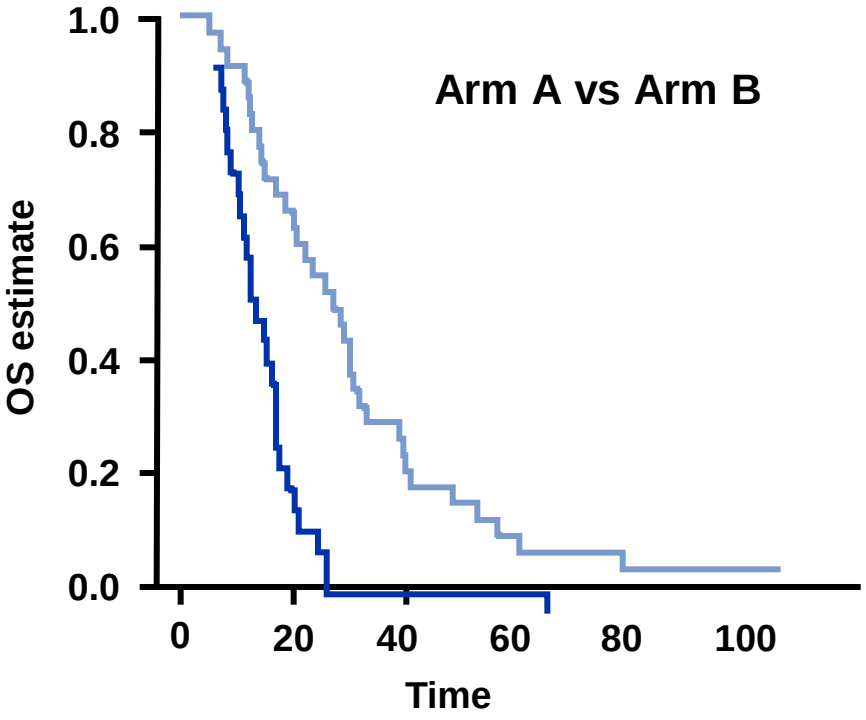
Overall Survival - ITT Population



Sample collection 128 sites worldwide , 28 countries, 1186 patients

Aflibercept biomarker analysis

Retrospective stratification



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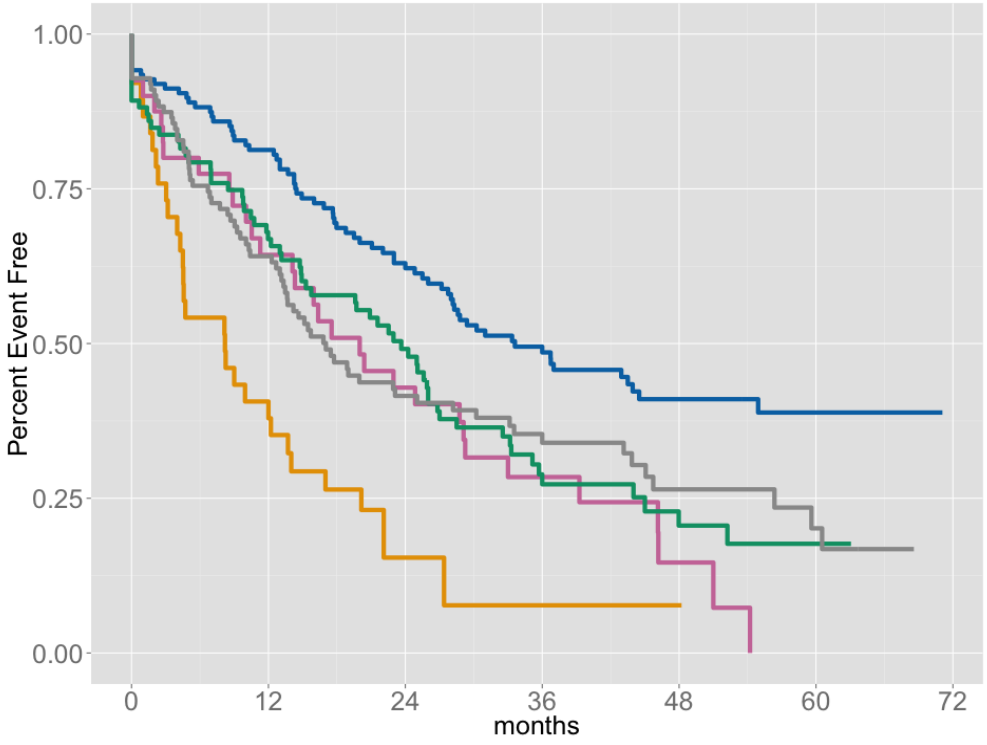
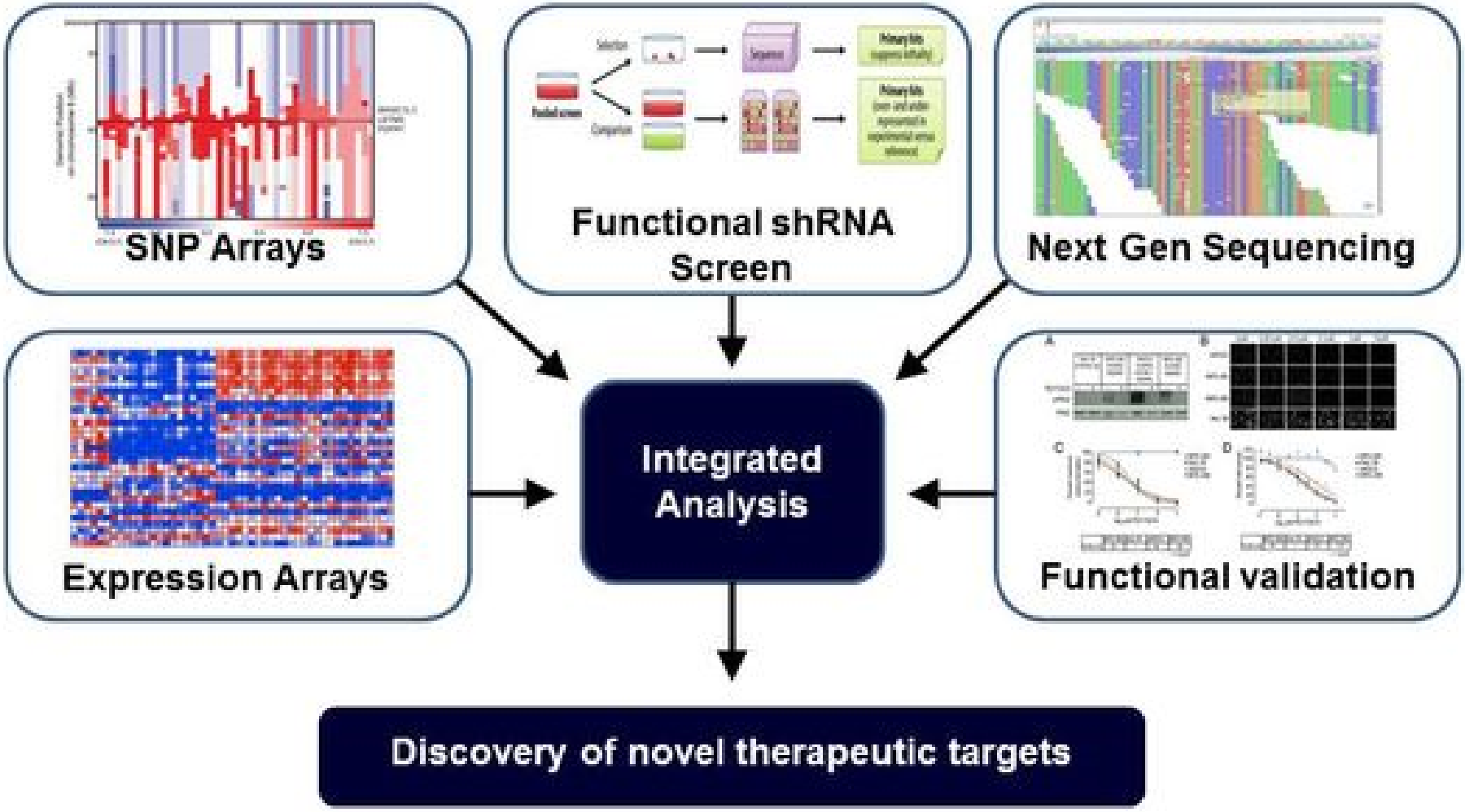
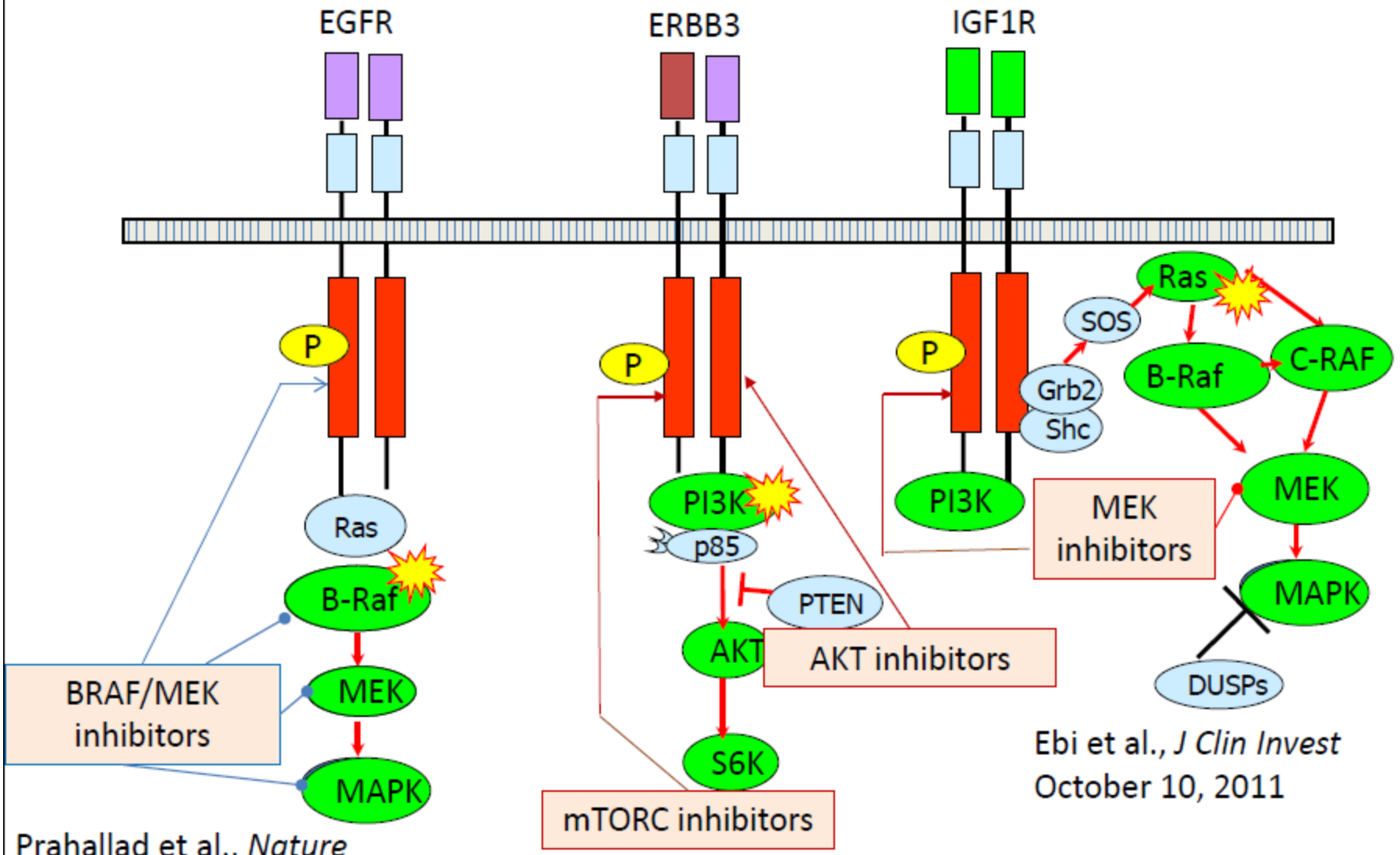



SNP Arrays
Functional shRNA Screen
Next Gen Sequencing
Expression Arrays
Integrated Analysis
Functional validation
Discovery of novel therapeutic targets

RTKs activation by effectors inhibition

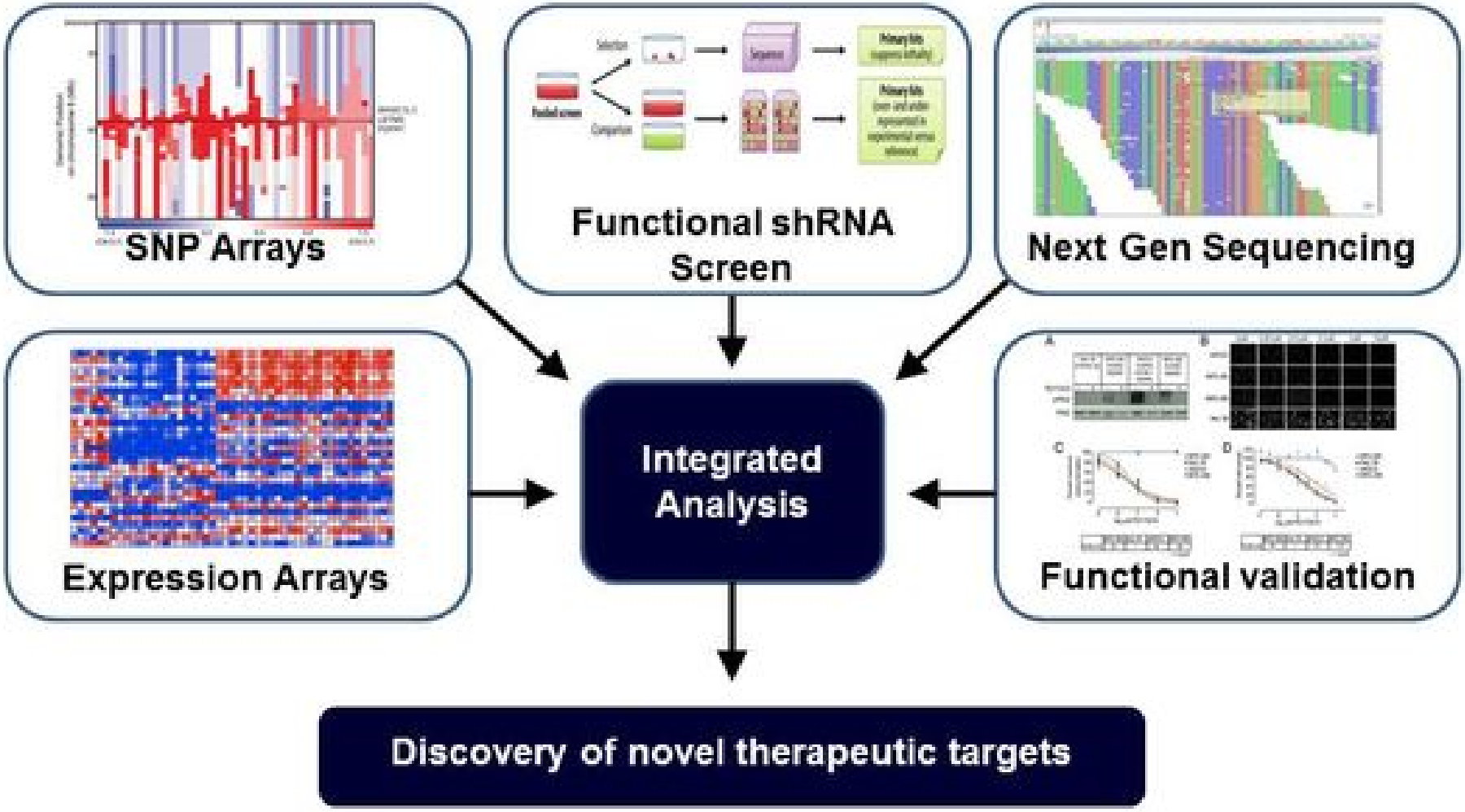


Prahallad et al., *Nature* January 26, 2012

Chandarlapaty S et al., *Cancer Cell*. 2011 Jan 18;19(1):58-71

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

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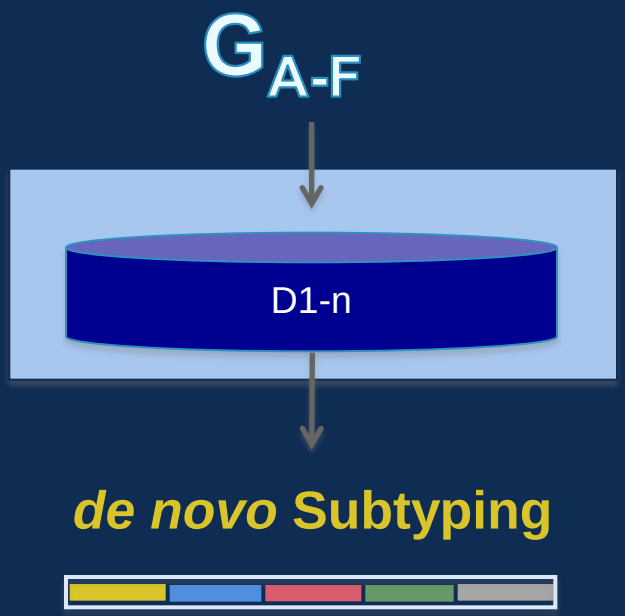

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Collaborations to assess predictive value and differential drug sensitivity patterns across CMSs.

→ Prospective testing of selected drugs based on subclass biology

Prospective drug testing

Enrich stratify

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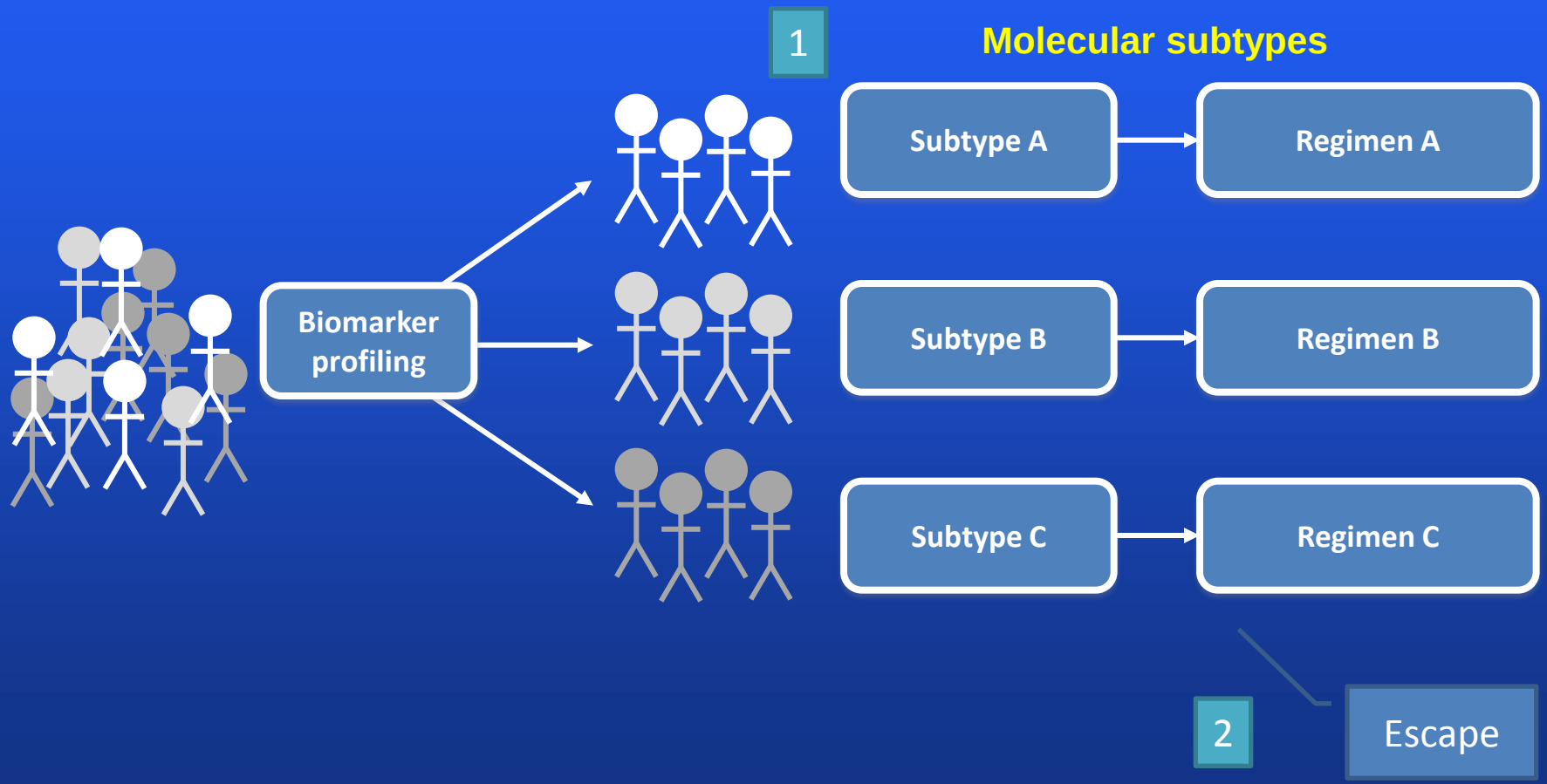
SPECTAcolor

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

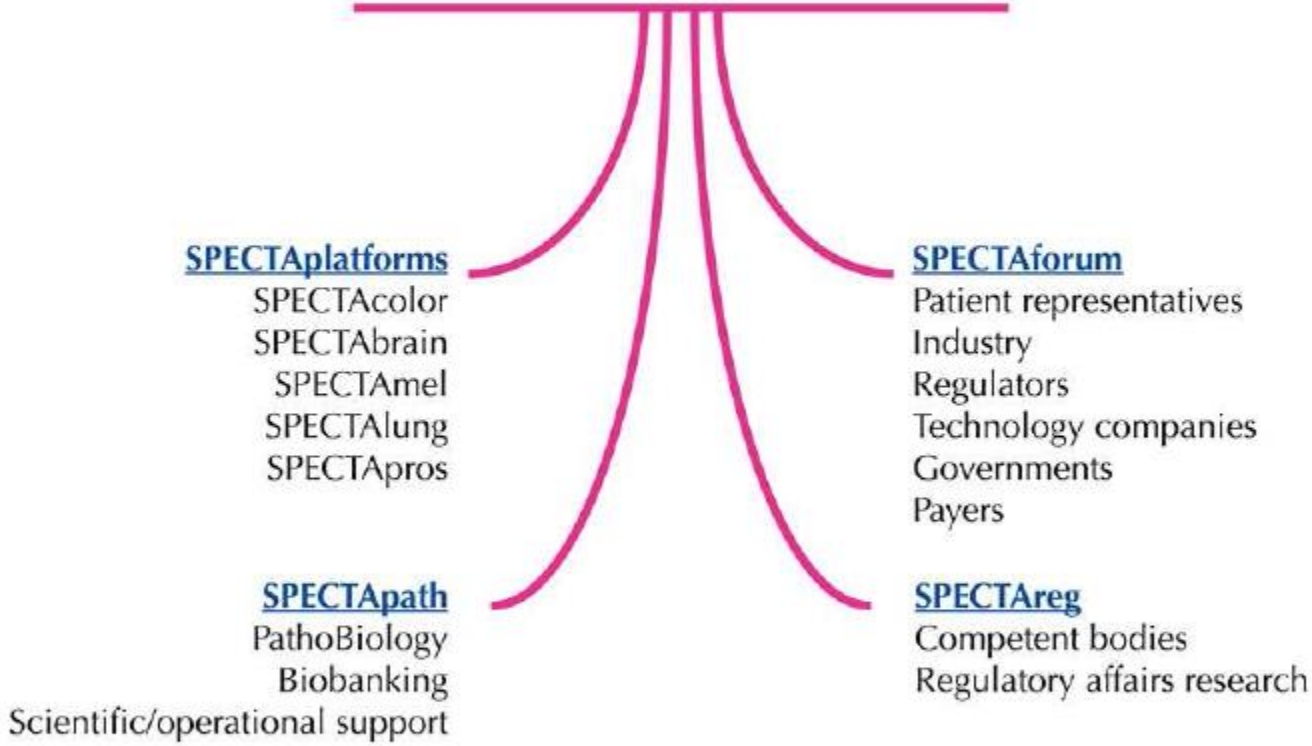


EORTC *The future of cancer therapy*

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

EORTC SPECTAprogram

Screen and Treat

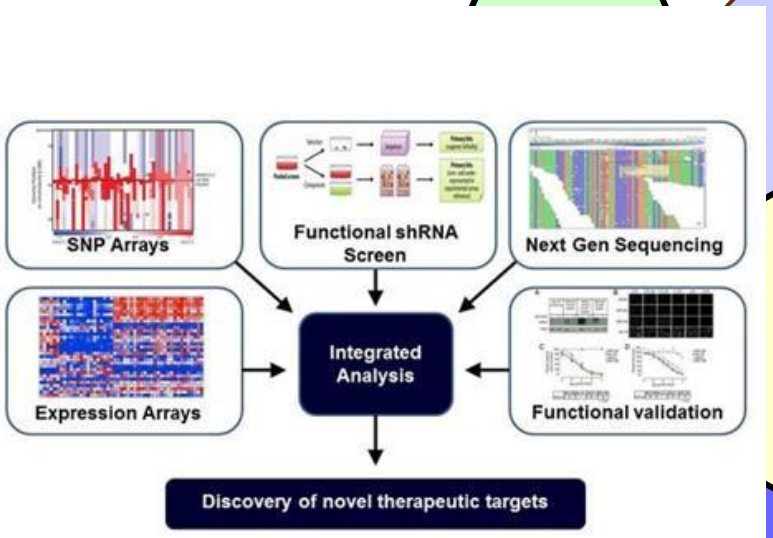


EORTC

The future of cancer therapy

EORTC *The future of cancer therapy*

Let’s organize it for CRC



Patients Organizations

Charities

New Model of Collaboration

Academi

Policy

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EFFICI

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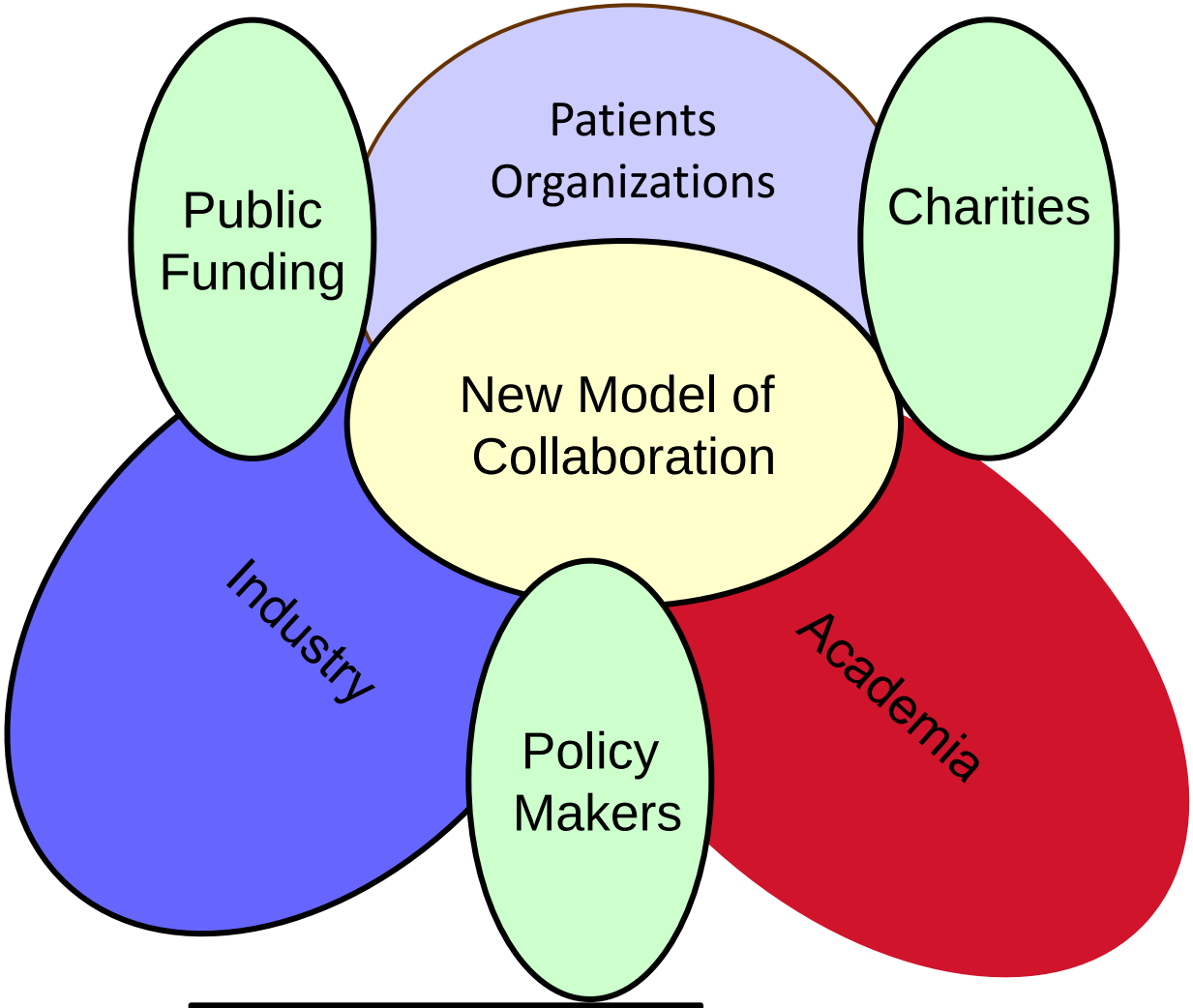

EFFICIENCY !