



# Biomarkers in lung cancer

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Alberto Bardelli

Institute for Cancer Research and Treatment  
University of Torino - Medical School



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# Prognostic and Predictive Values of *KRAS* in *EGFR*-based Subgroups and Combined with *TP53* in Completely Resected Non-Small Cell Lung Cancer (NSCLC): a LACE-Bio Study

P.A. Jänne, F. A. Shepherd, C. Domerg, G. Le  
Teuff, R.A. Kratzke, P. Hainaut, J.-P. Pignon, R.  
Rosell, J.C. Soria and M. Tsao

on behalf of the  
LACE-Bio Collaborative Group

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# Predictive Value of *TP53* and *KRAS* Mutations on Overall Survival

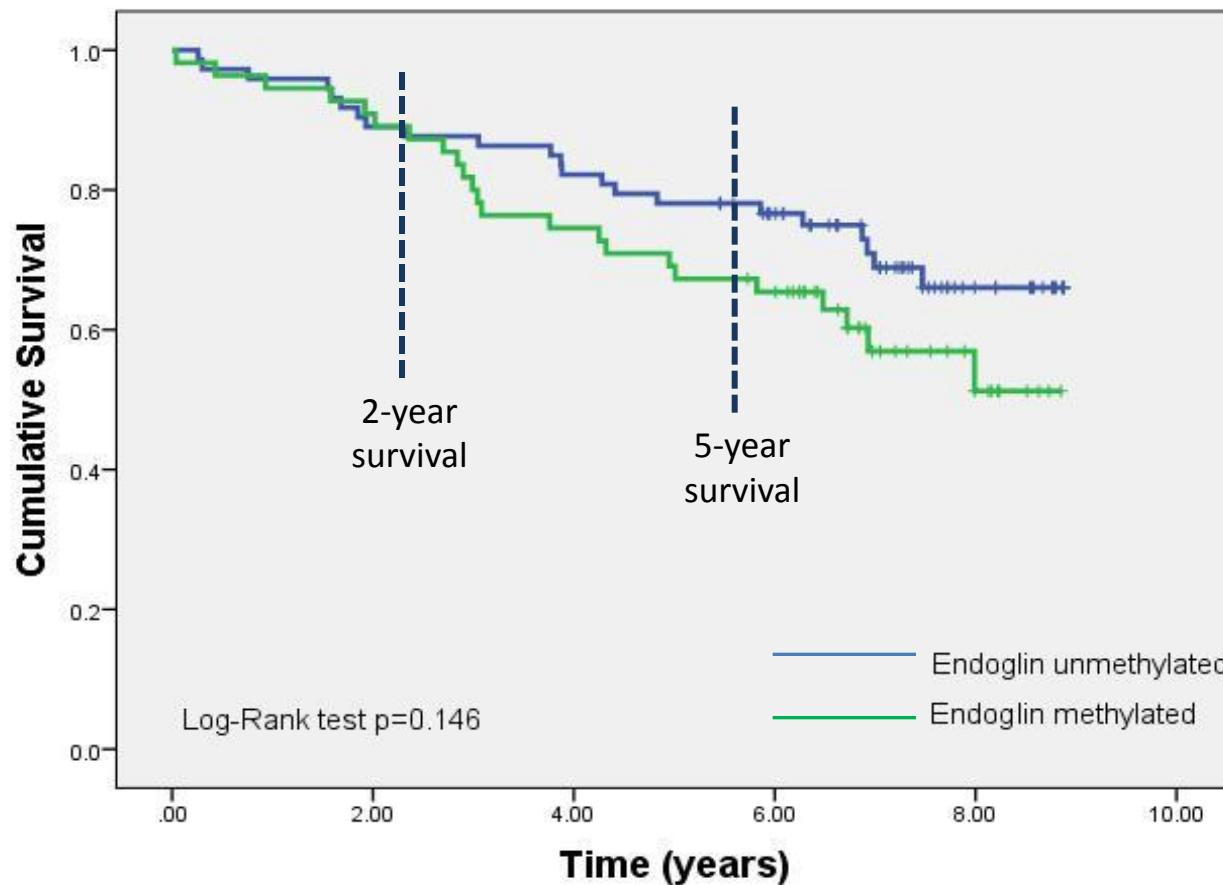
	Chemotherapy (Deaths / Pts)	Observation (Deaths / Pts)	HR for death CT vs. no CT
<i>KRAS/TP53</i> wild type n=567*	109 / 268	141 / 299	0.82 [0.64 - 1.06] p = 0.13
<i>KRAS</i> mutant n= 184*	41 / 98	41 / 86	0.73 [0.47 - 1.13] p = 0.16
<i>TP53</i> mutant n= 373	108 / 202	89 / 171	0.97 [0.73 - 1.29] p = 0.84
Double mutant n=49	17 / 25	9 / 24	2.49 [1.10 - 5.66] p = 0.03
HR Double mutation vs. WT	2.76 [1.62 - 4.68] P = 0.0002	0.91 [0.46 - 1.80] P = 0.79	3.03 [1.29 - 7.15] <sub>12</sub> P = 0.01

# Identification of Endoglin (CD105) as an epigenetically regulated candidate tumour suppressor gene in lung cancer

K.O'Leary<sup>1</sup>, F. Cavicchioli<sup>1</sup>, A.Shia<sup>1</sup>, V.  
Haley<sup>1</sup>, A. Comino<sup>2</sup>, M.B. Wischnewsky<sup>3</sup>,  
T. Crook<sup>4</sup>, C. Lo Nigro<sup>5</sup>, P. Schmid<sup>1</sup>.

# Eng Methylation and Survival

## Tumour pyrosequencing of operable stage I/II NSCLC patients



There is a strong trend towards shorter survival for patients with methylated Endoglin.

# **Quantification of cell-free DNA as a prognostic marker in advanced NSCLC**

Anneli Dowler Nygaard, M.D.  
Karen-Lise G. Spindler M.D. Ph.d, Niels Pallisgaard Ph.d,  
Rikke F. Andersen Ph.d, Anders Jakobsen M.D. DMSc.

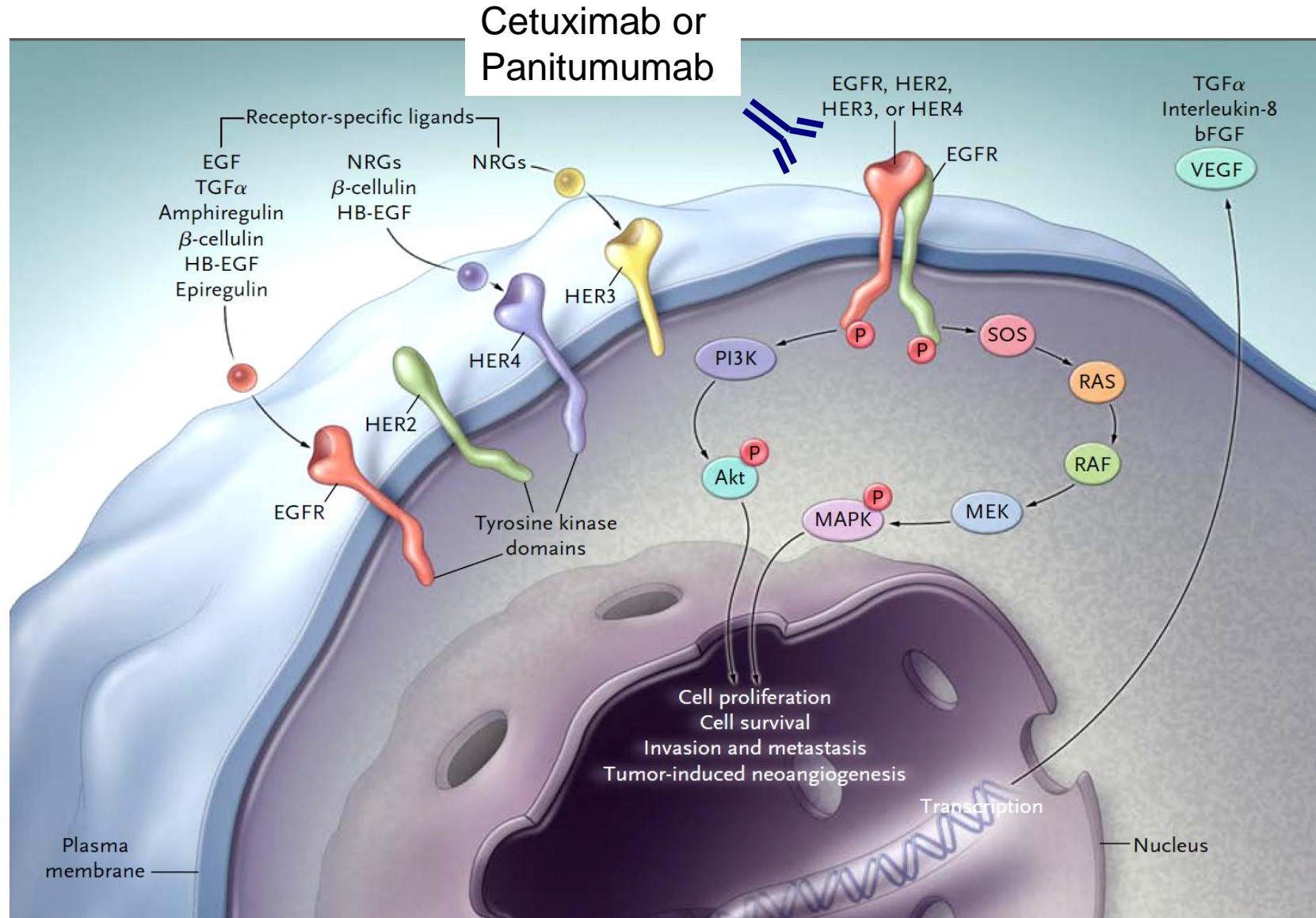
*Vejle Hospital  
Denmark*

# Introduction

- Cell-free DNA (cfDNA)
  - DNA circulating in the blood-stream
  - Normal cells, tumour cells, tumour surrounding tissue
  - Increased level under malignant conditions
    - Quantification
    - Qualification (tumour-specific mutations)
- "Liquid biopsy"

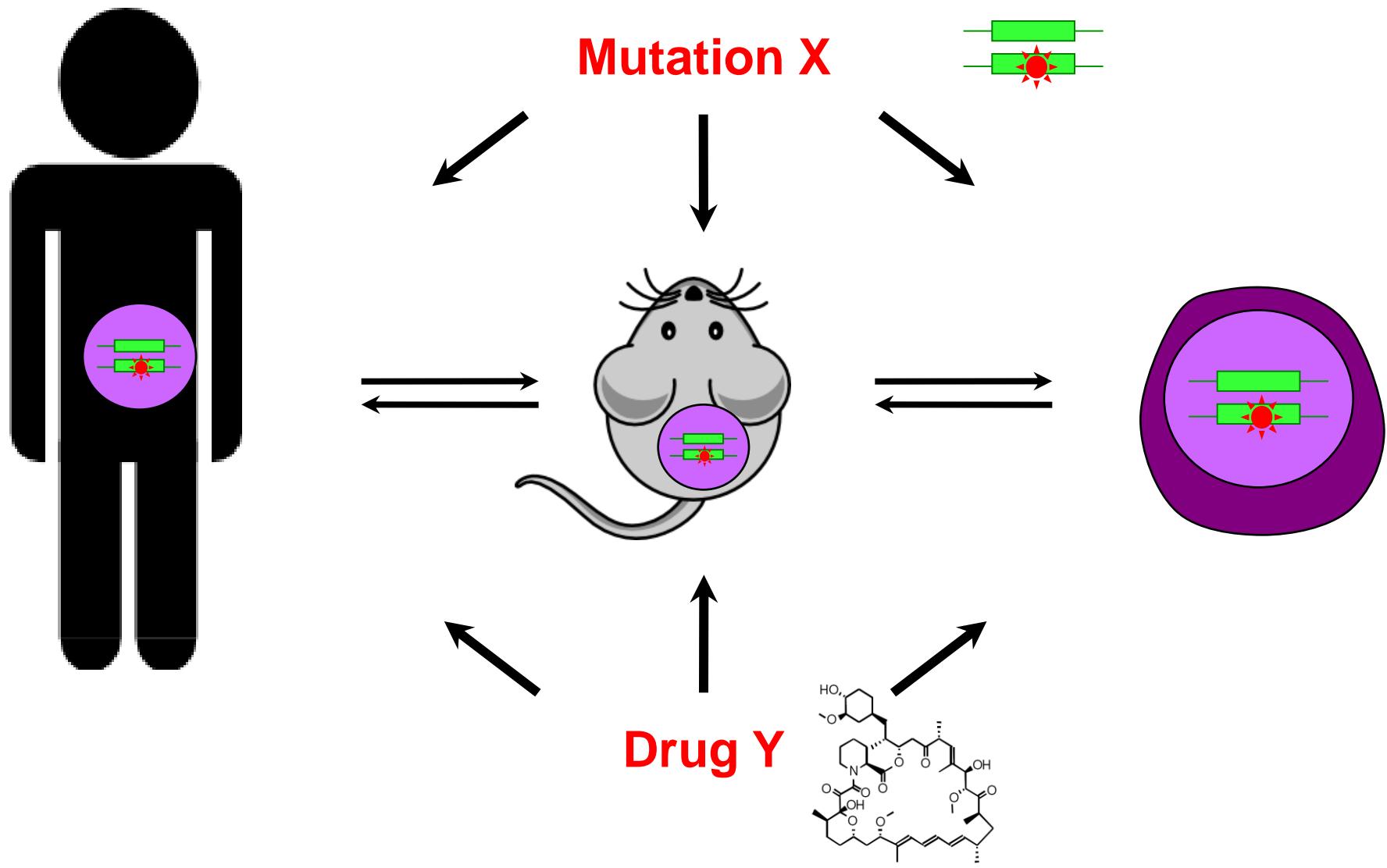
# Liquid Biopsies to monitor resistance to EGFR therapies in CRC patients

# Anti EGFR therapy and colorectal cancer



Adapted from Ciardiello F. and Tortora G. NEJM 2008;358:1160-74

# Integrated experimental platforms



# Genetic alterations of the EGFR signalling pathway predict response to cetuximab

Moroni *et al.*, *Lancet Oncology* 2005

Benvenuti *et al.*, *Cancer Research*. 2007

Di Nicolantonio *et al.*, *J Clin Oncol*. 2008

Sartore-Bianchi A *et al.*, *Cancer Res* 2009

Siena, Di Nicolantonio and Bardelli *JNCI* 2009

Bardelli and Siena *J Clin Oncol* 2010

De Roock, Martini *et al* *Lancet Oncology* 2010

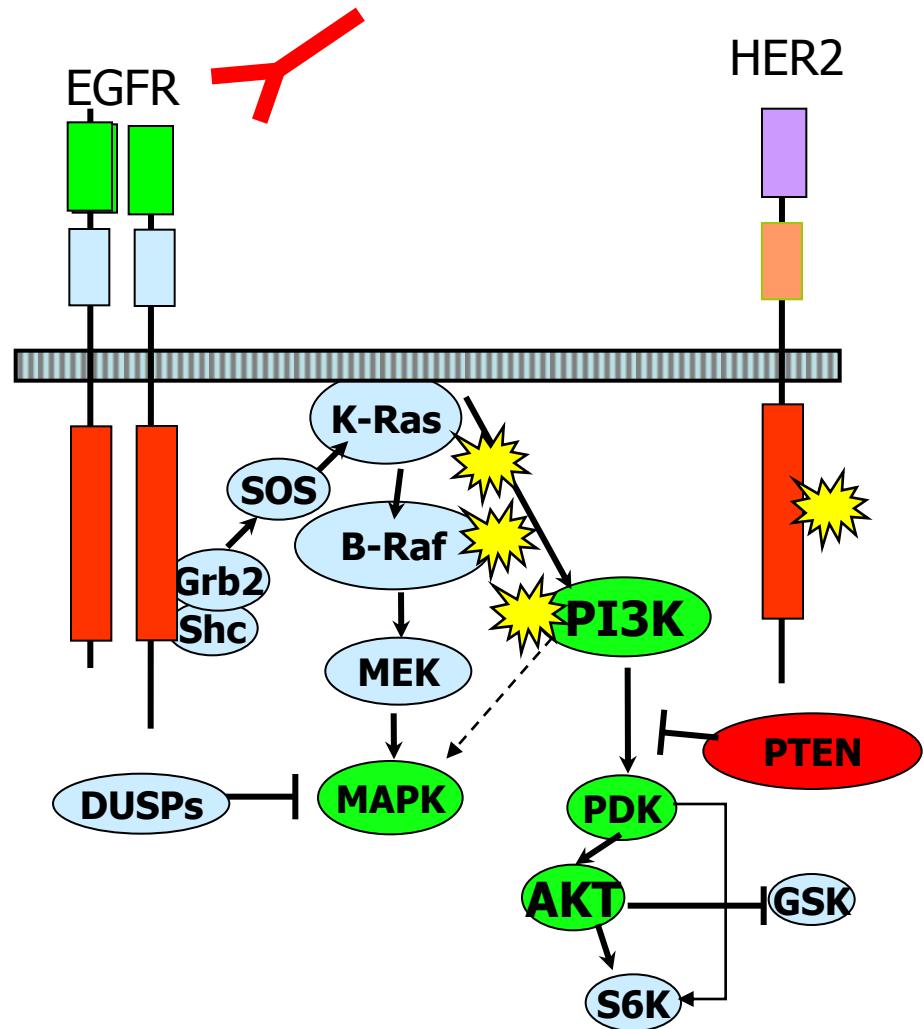
Di Nicolantonio, Arena *et al.*, *JCI* 2011

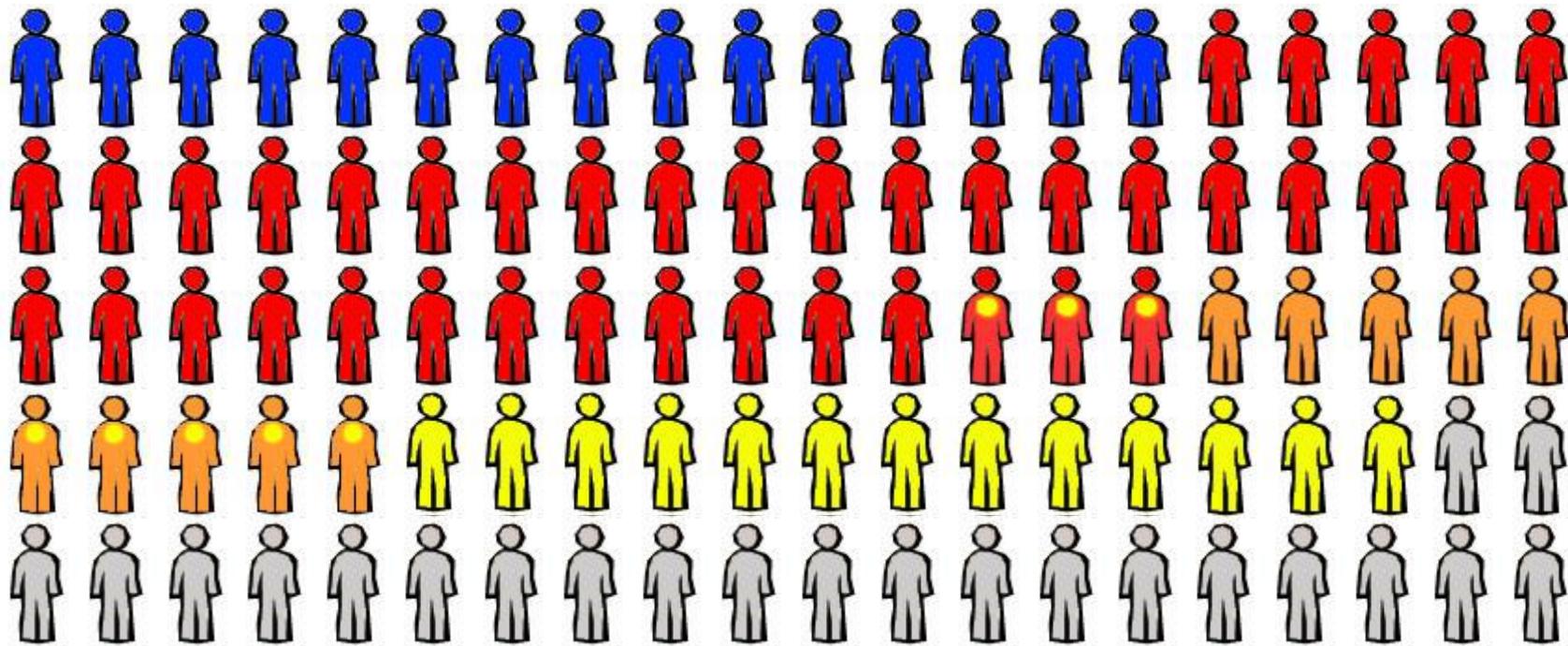
De Roock, Di Nicolantonio *et al*, *JAMA* 2011

Bertotti *et al.*, *Cancer Discovery* 2011

Prahallad *et al.*, *Nature* 2012

Misale *et al.*, *Nature In press*





Responder (15%)



KRAS-NRAS mutated (35-45%)



BRAF mutated (8%)



PIK3CA mutated and/or  
PTEN loss (15-20%)



KRAS/PIK3CA mutated

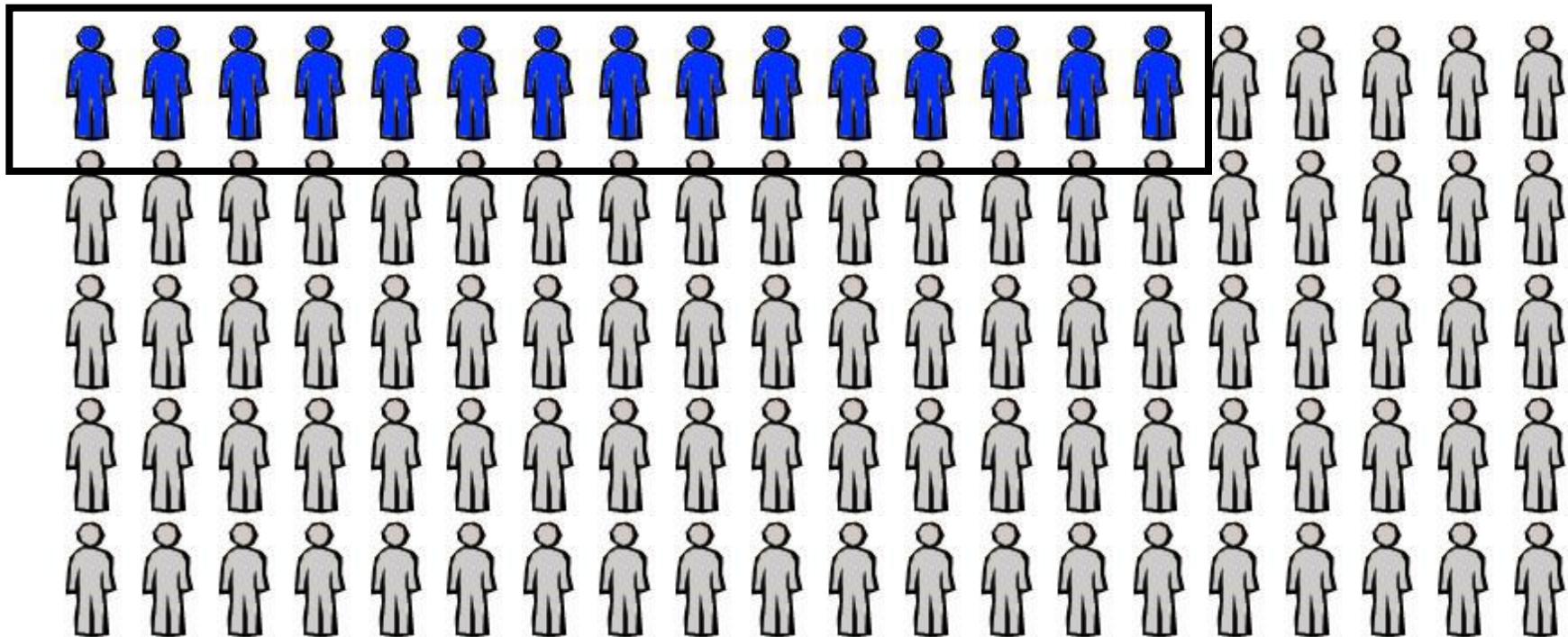


BRAF/PIK3CA mutated



20-25% ? (quadruple negative)

# Secondary resistance to EGFR targeted therapies

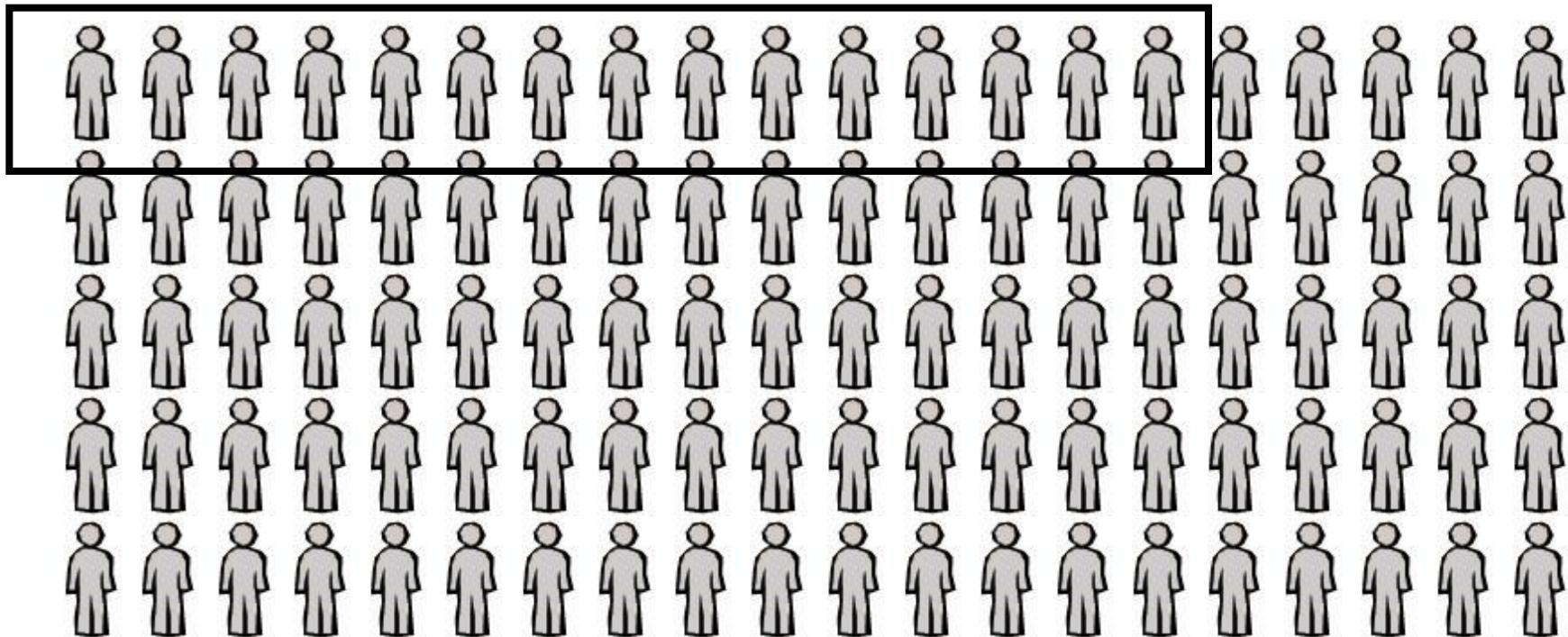


**Responders (15-20%)**



**Non-Responders**

# Secondary resistance to EGFR targeted therapies



**Responders (15-20%)**



**Non-Responders**

**6-12 months later**

RESISTANCE- RESISTANCE

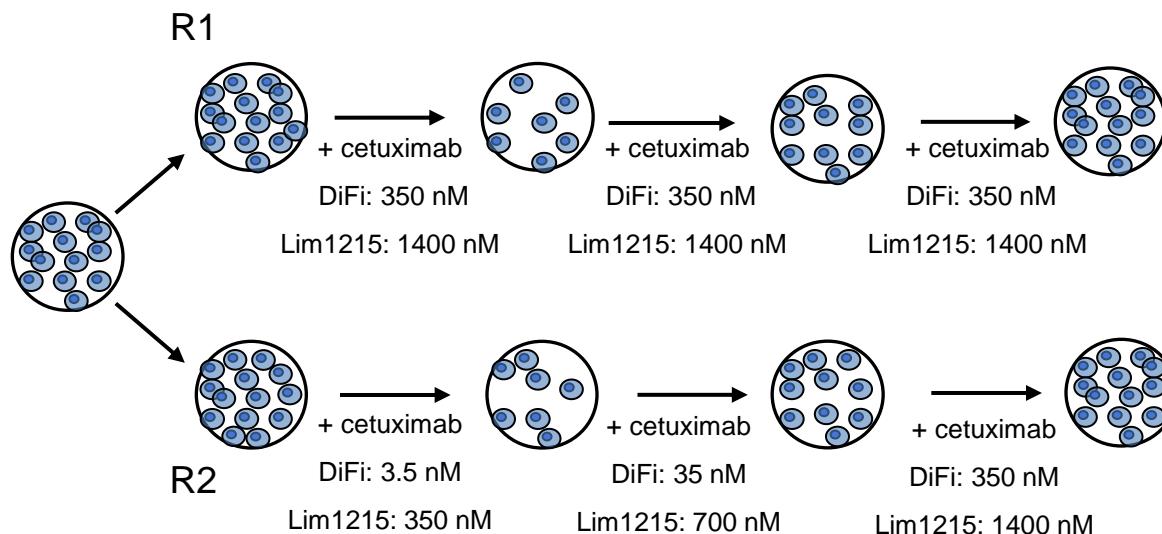
RESISTANCE- RESISTANCE

RESISTANCE- RESISTANCE

RESISTANCE- RESISTANCE

# Emergence of KRAS mutations and acquired resistance to anti EGFR therapy in colorectal cancer

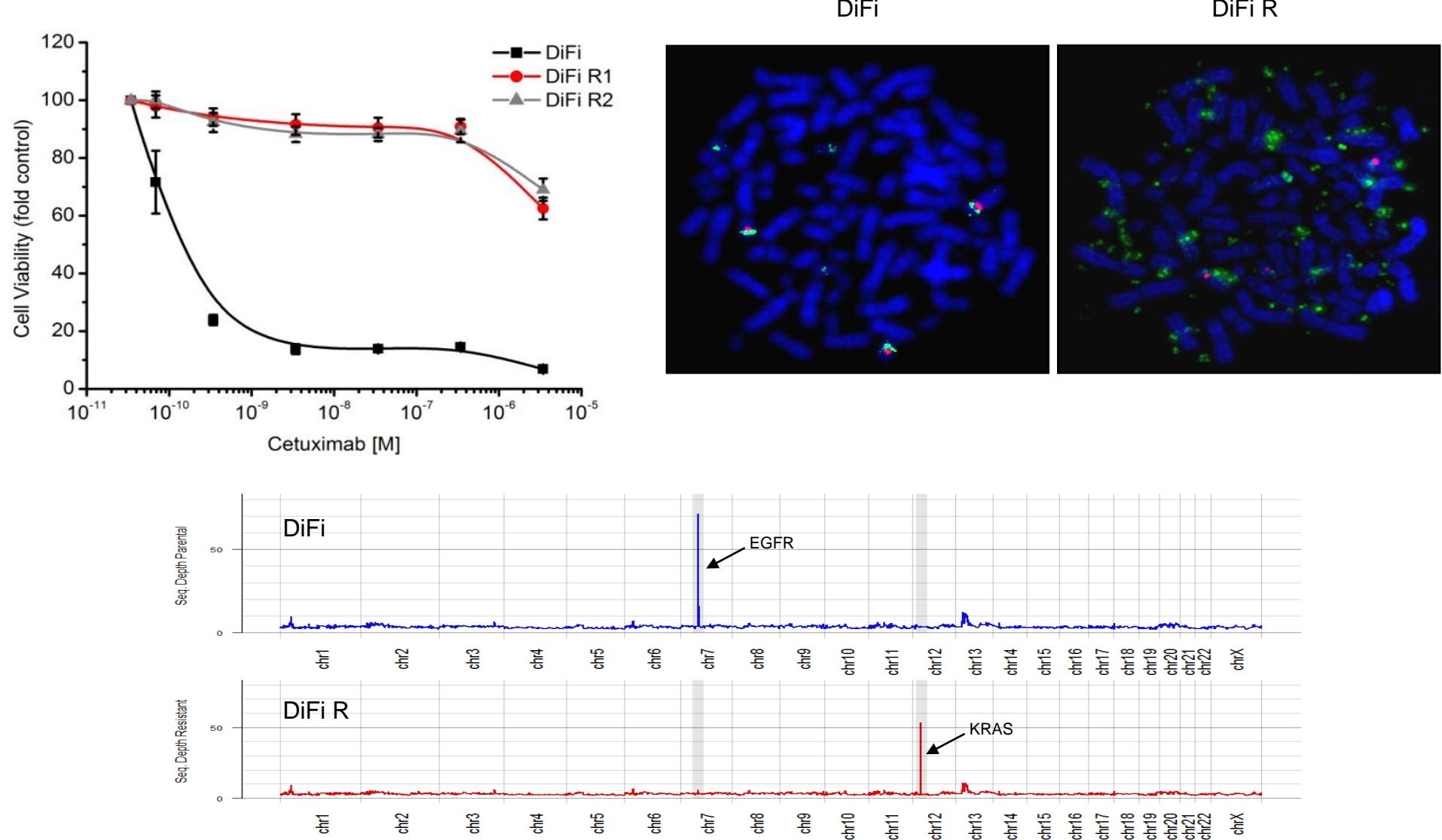
Sandra Misale, Sebastijan Hobor



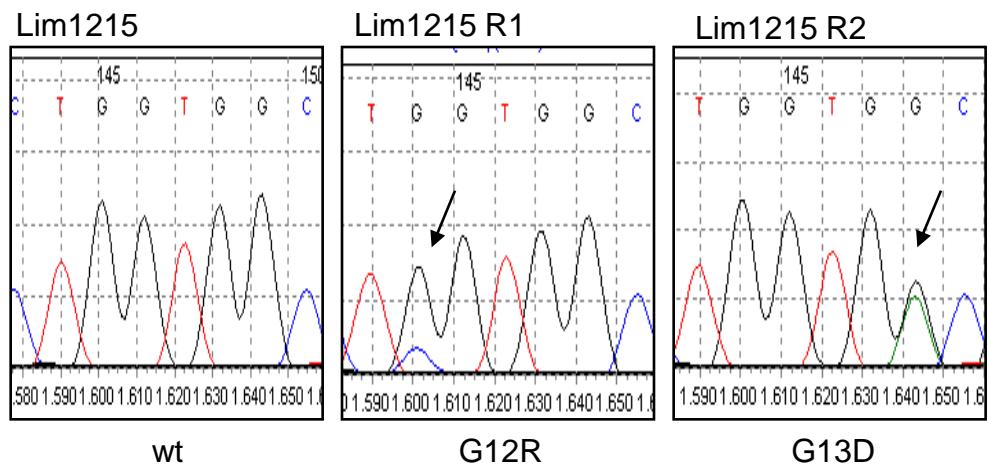
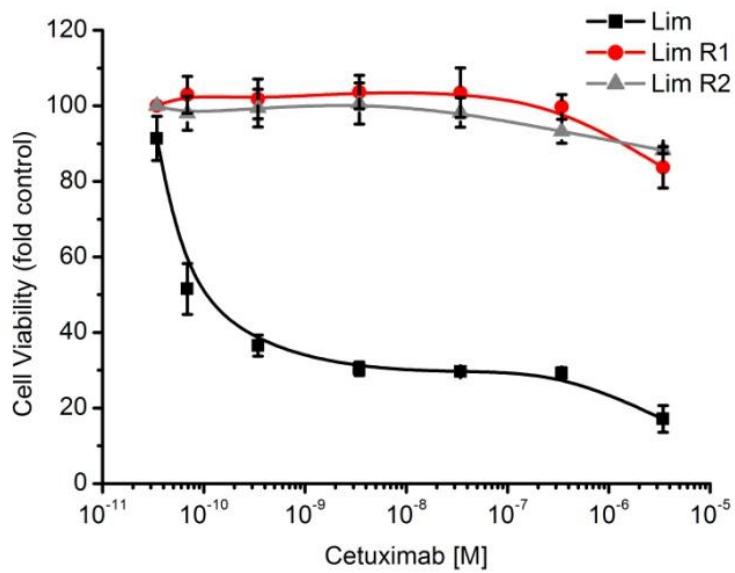
R1: Constant dosage

R2: Incremental dosage

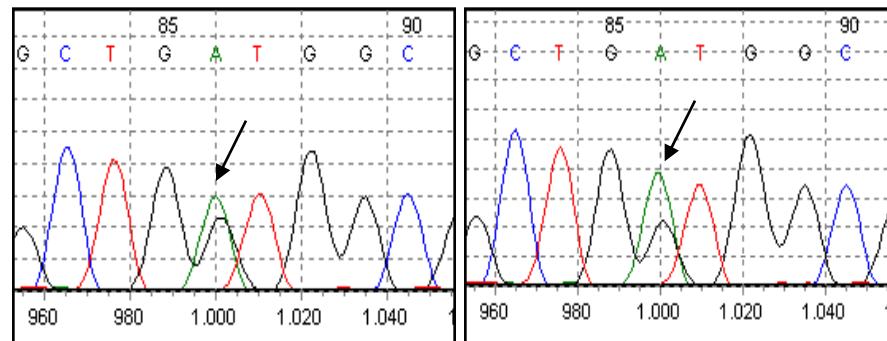
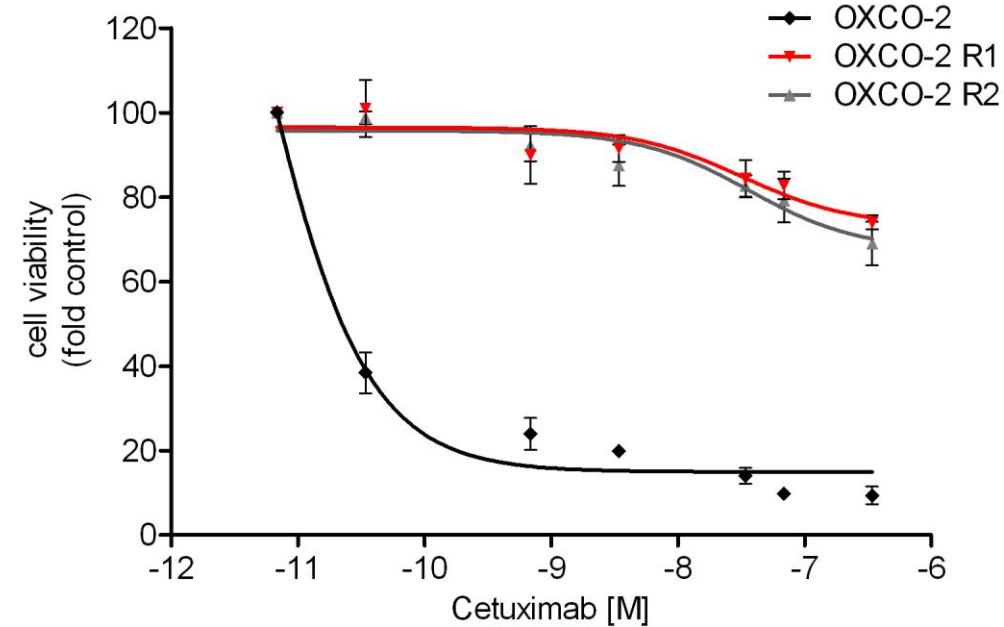
# KRAS amplification and acquired resistance to cetuximab in DiFi cells



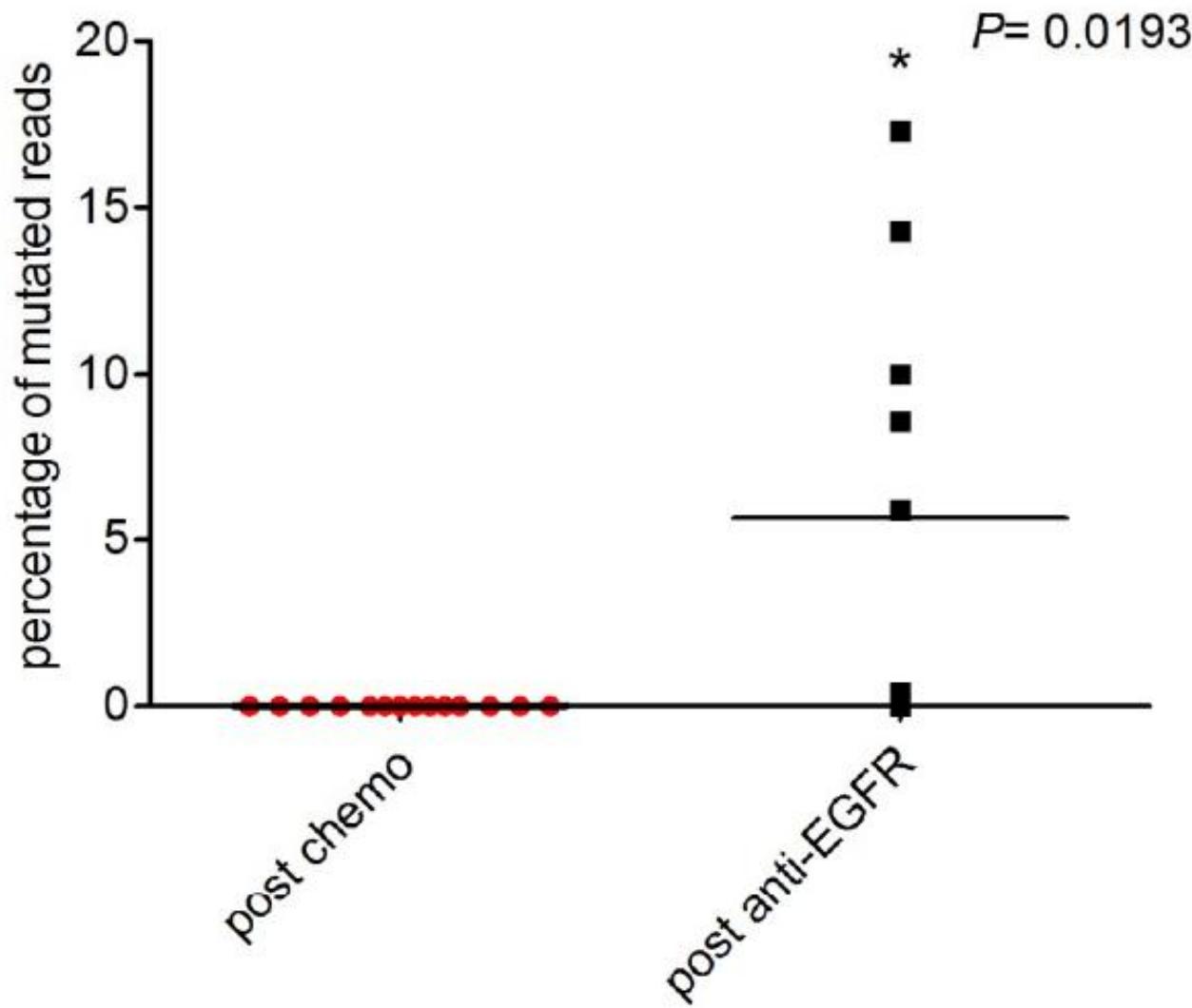
# KRAS mutations and acquired resistance to cetuximab in Lim1215 cells



# KRAS mutations and acquired resistance to cetuximab in OXCO-2 cells

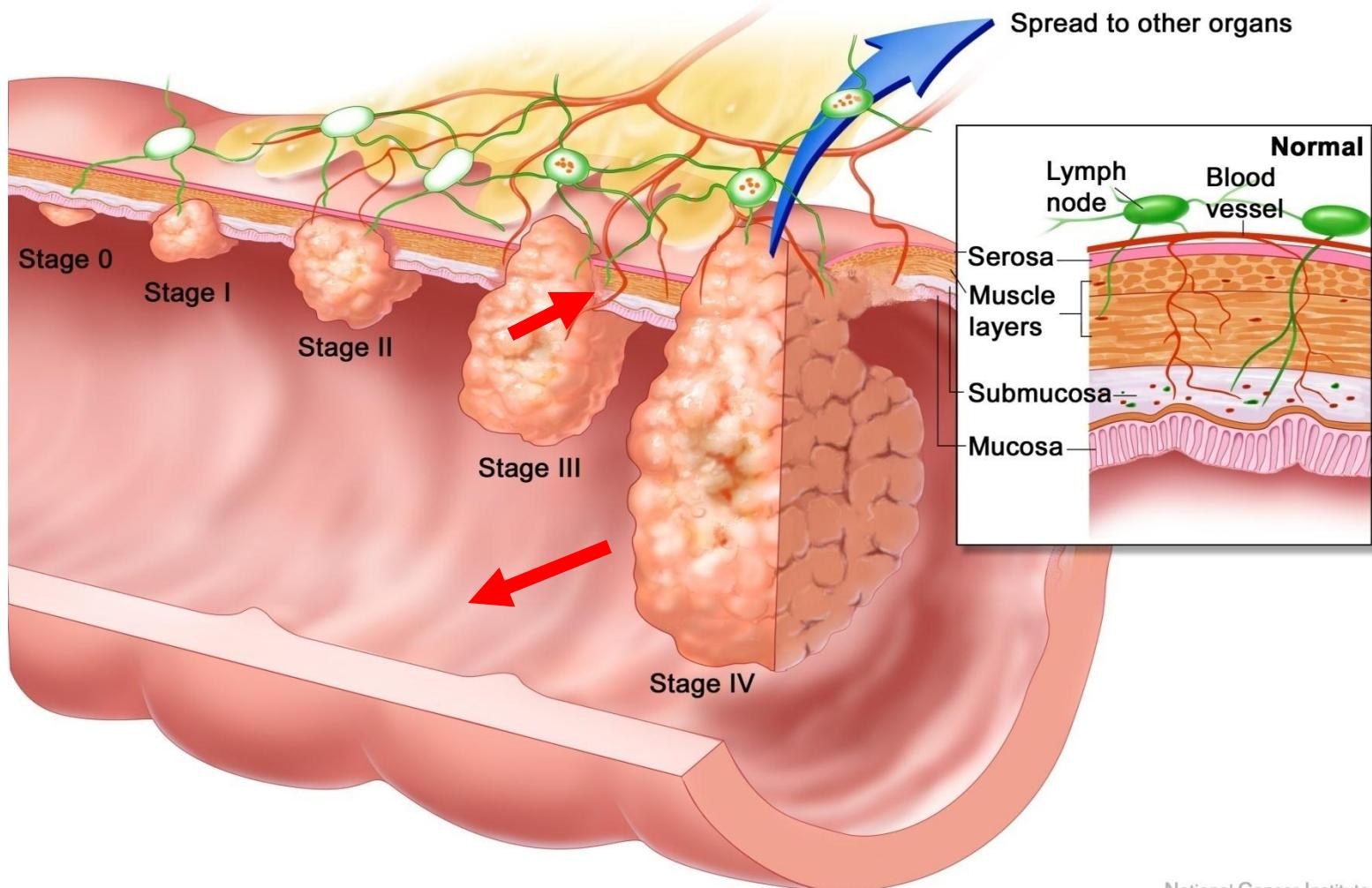


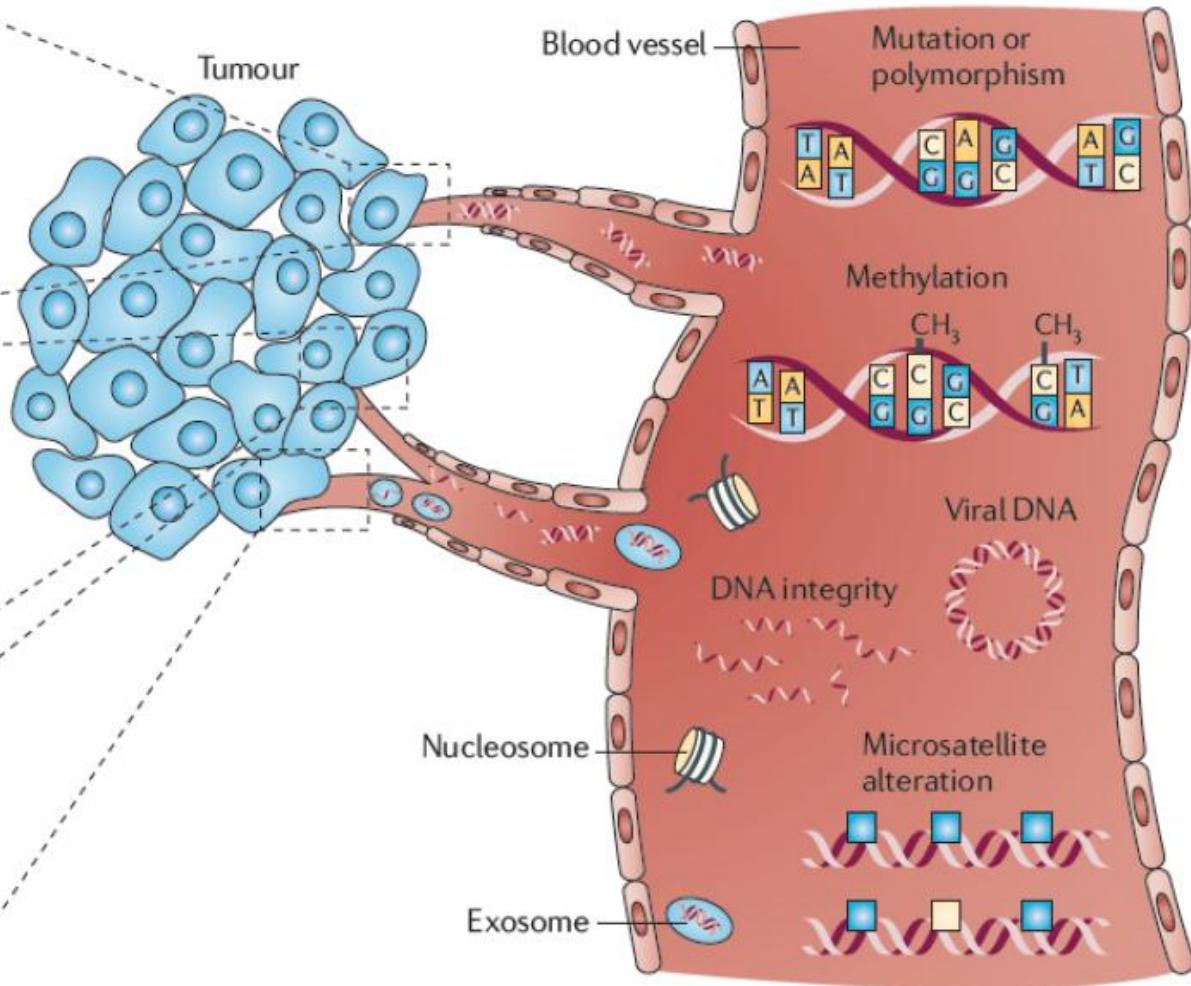
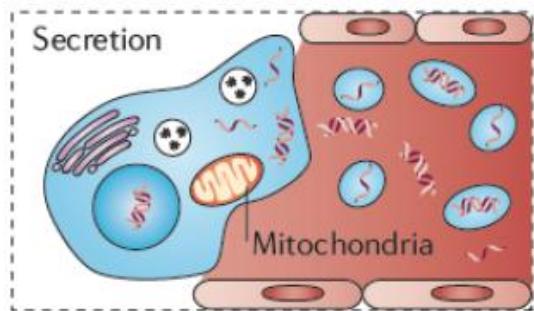
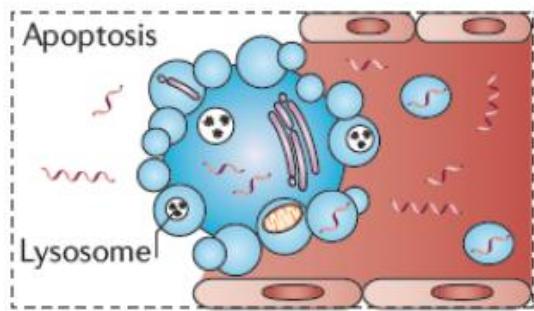
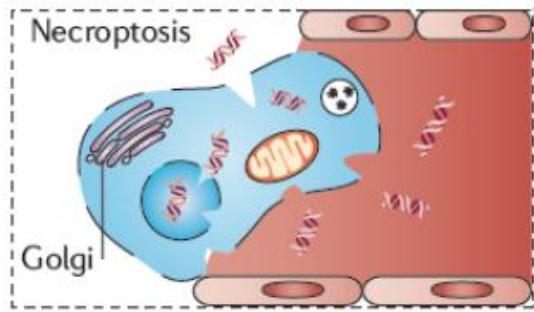
# KRAS mutations and acquired resistance to anti EGFR targeted therapies in CRC patients



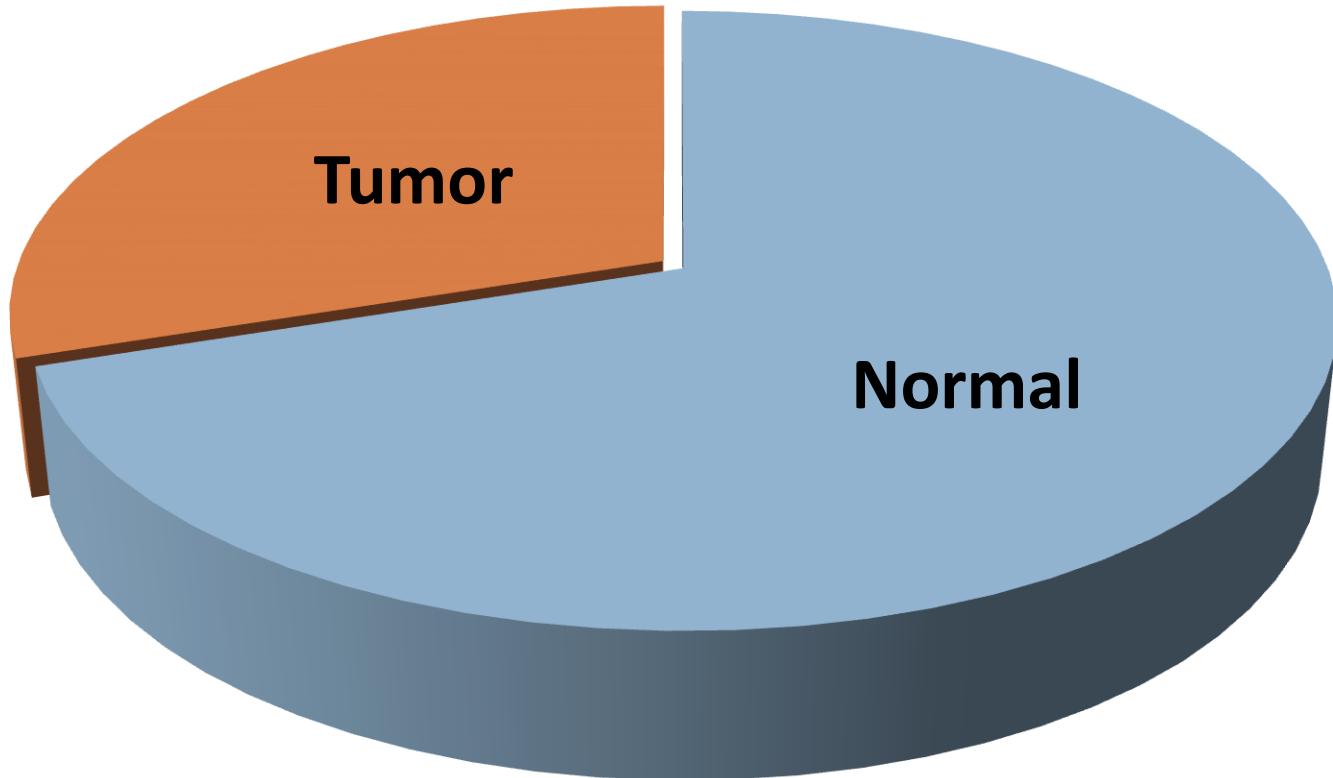
Monitoring the emergence of resistance  
in the blood of cancer patients

# Diagnostic approaches based on mutated DNA released from tumors

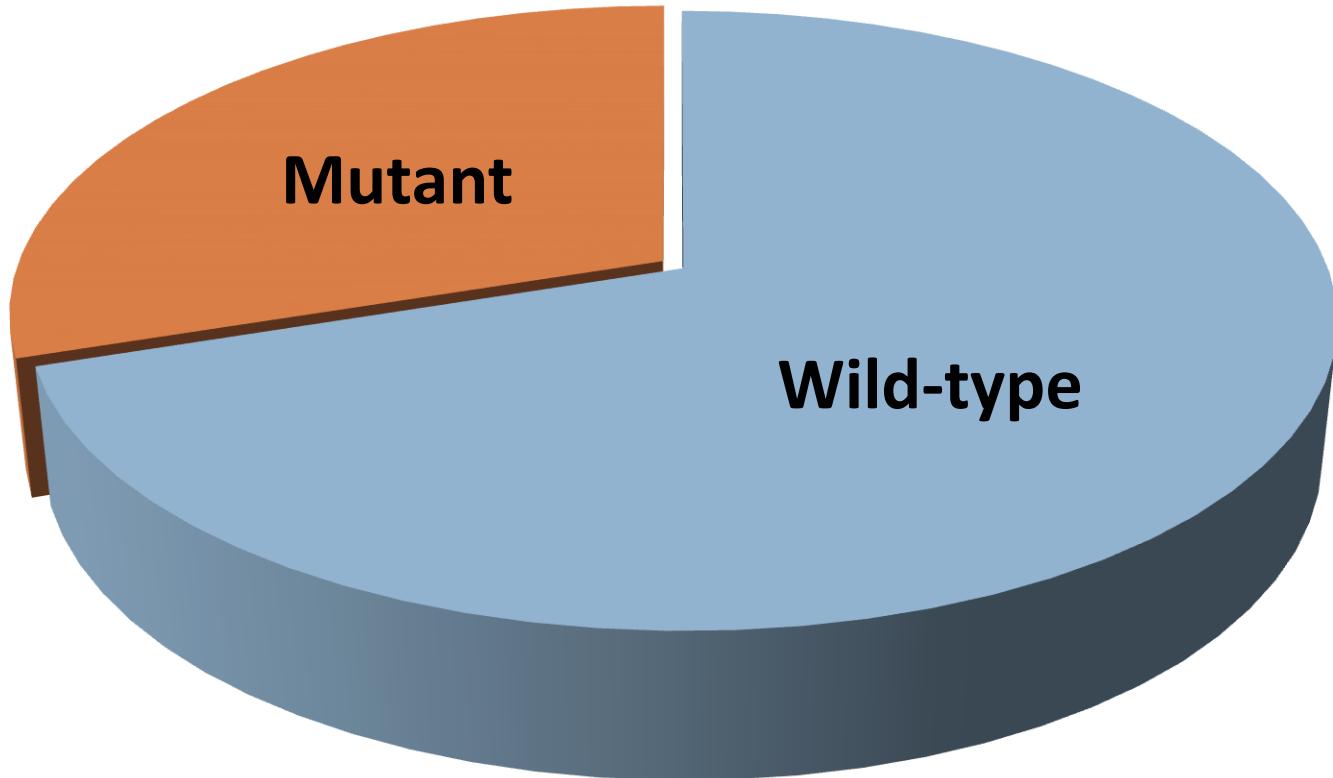




# Circulating DNA in a Cancer Patient



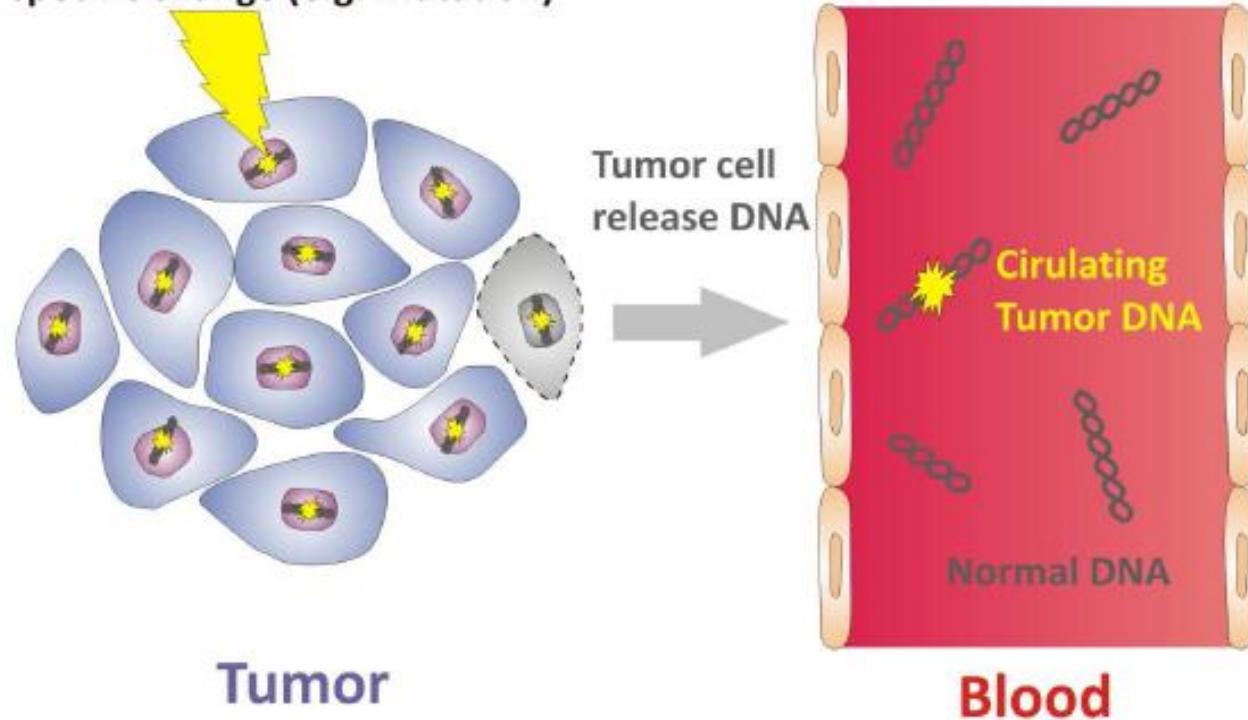
# Circulating DNA in a Cancer Patient



## Background:

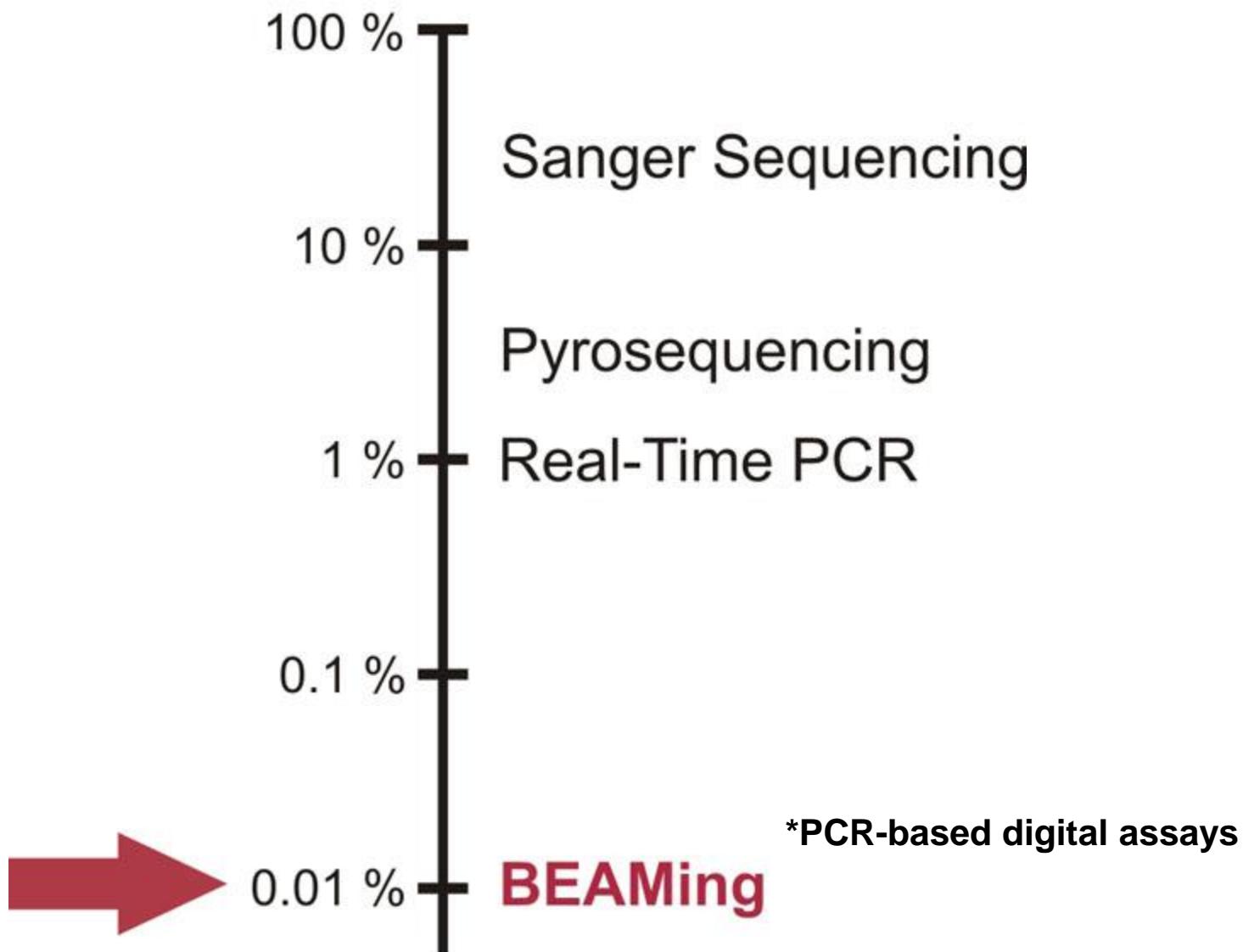
Mutant DNA detection in tumor tissue and blood

Tumor specific change (e.g. Mutation)

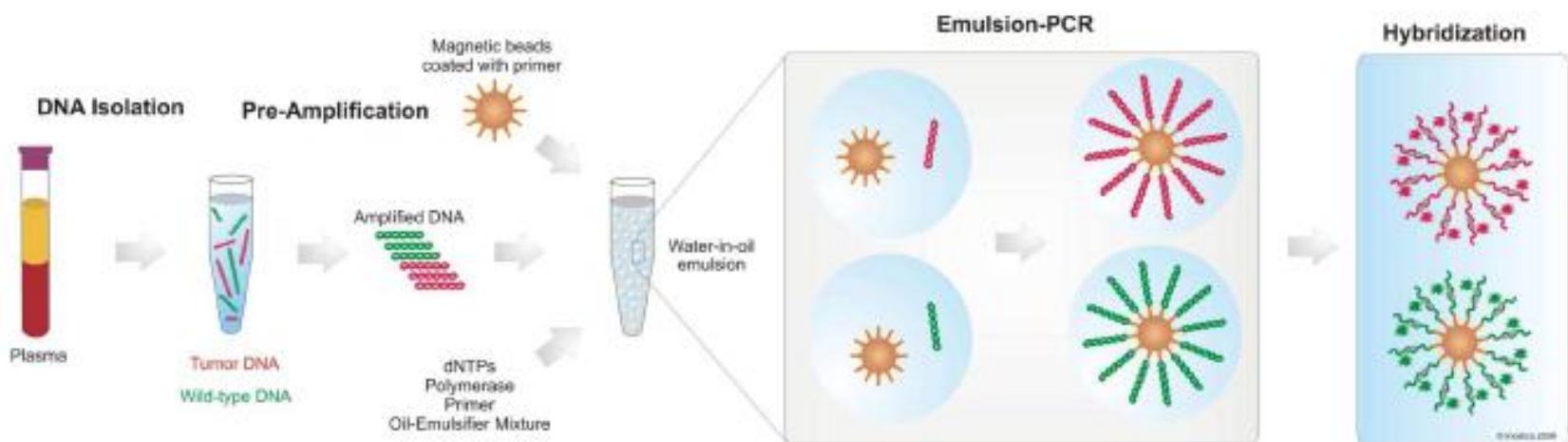


# Detection Capability

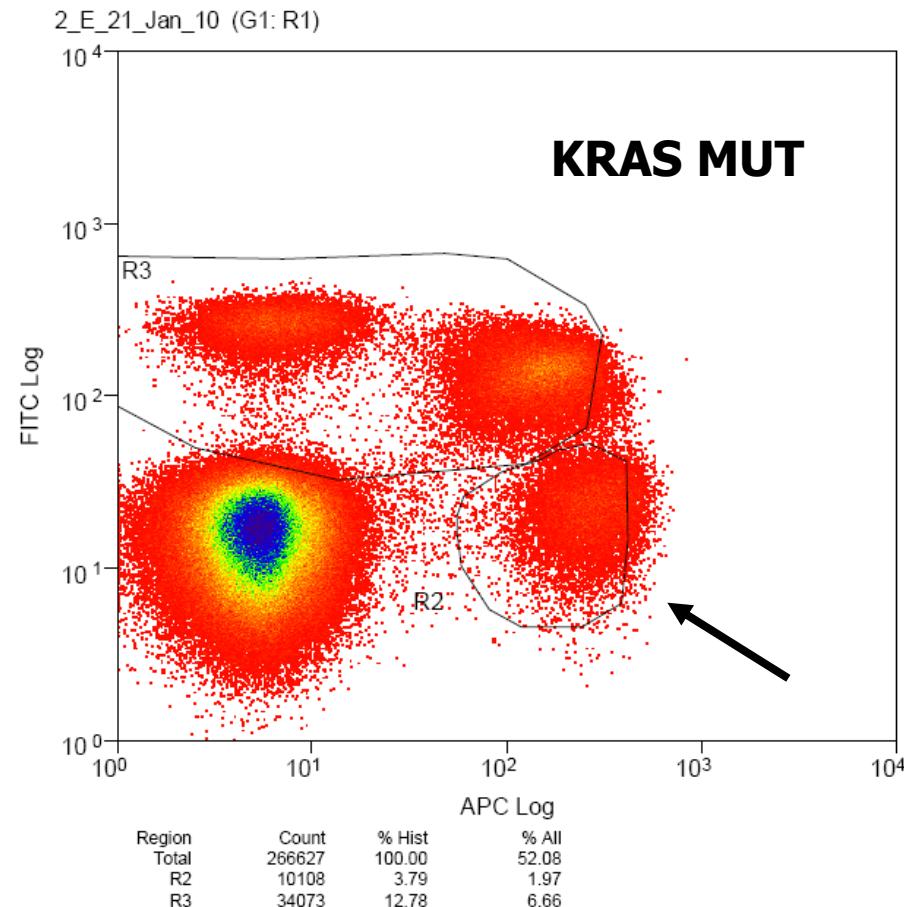
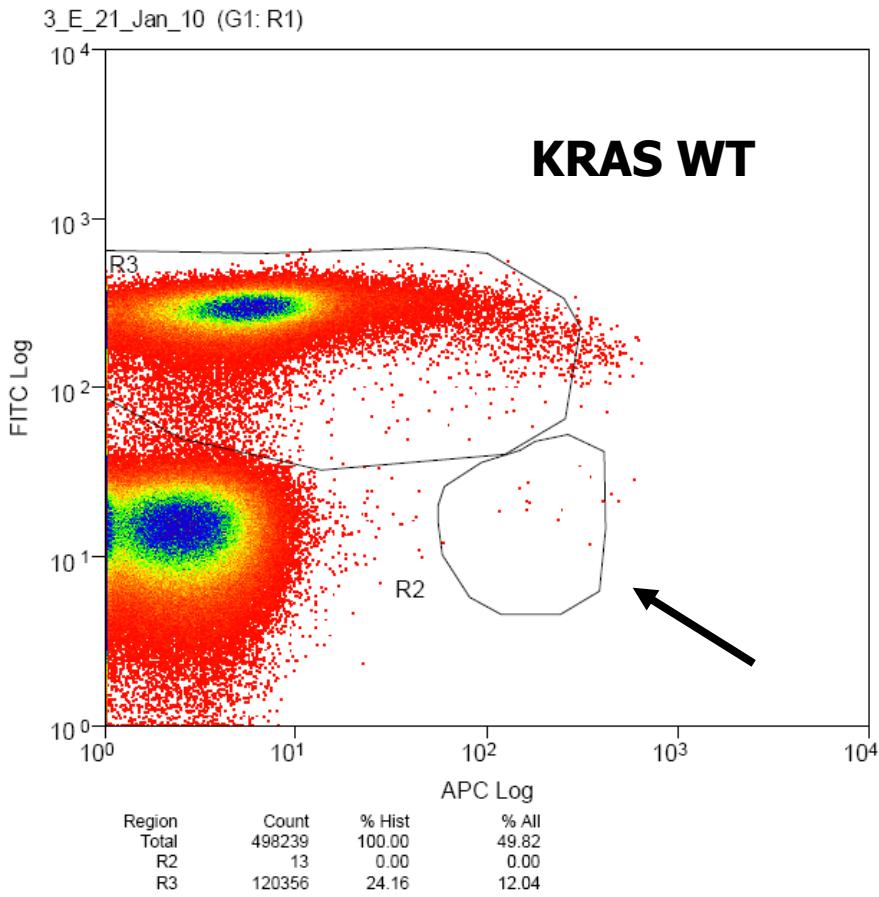
(mutant DNA / total DNA)

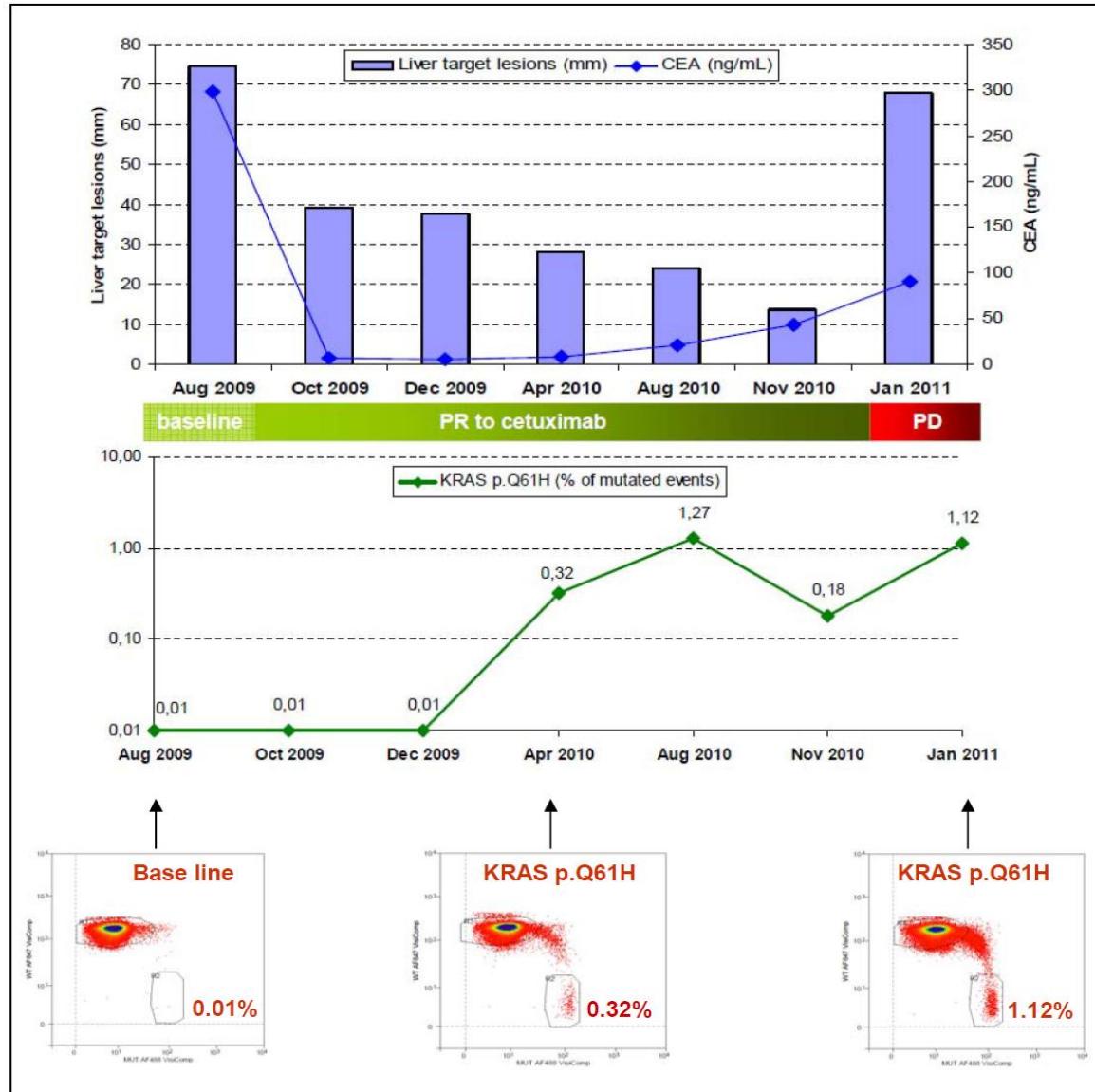


# BEAMing-Plasmatest: Single-Molecule Amplification on Beads in Water-in-Oil Emulsions



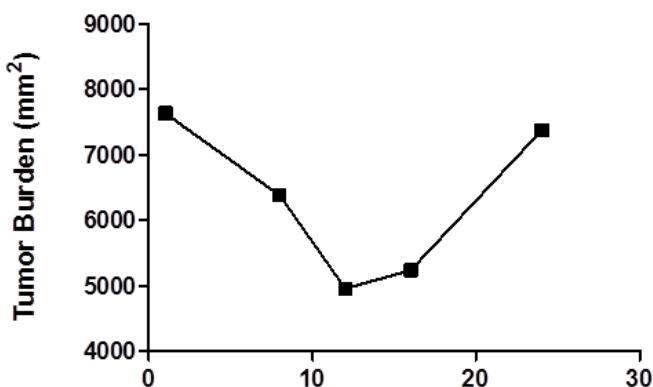
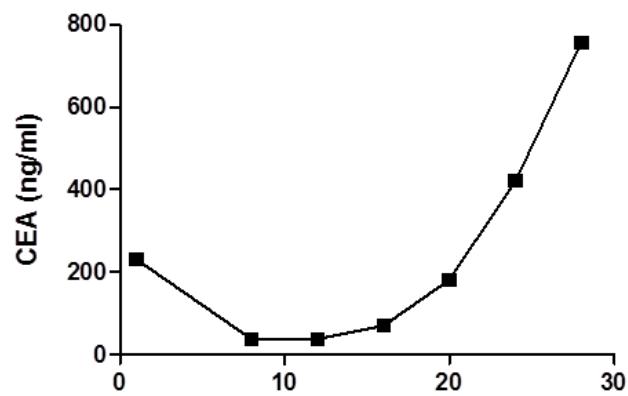
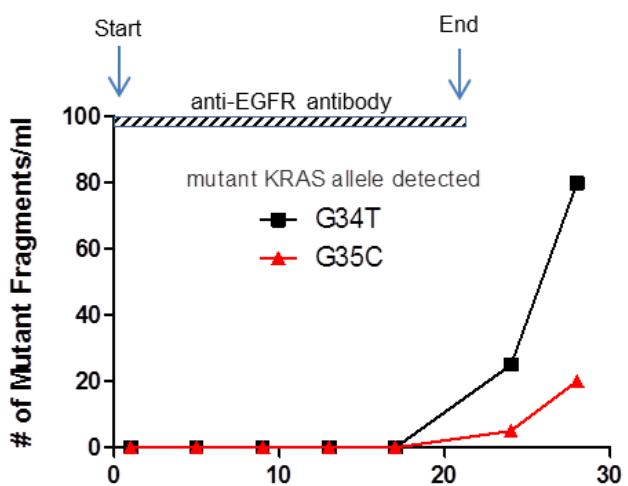
# Detection of KRAS mutations in plasma of mCRC patients



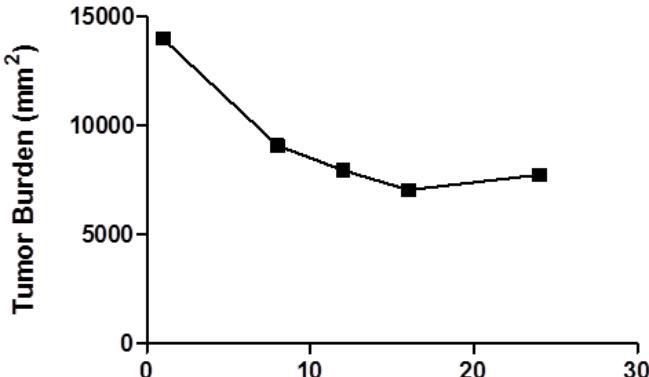
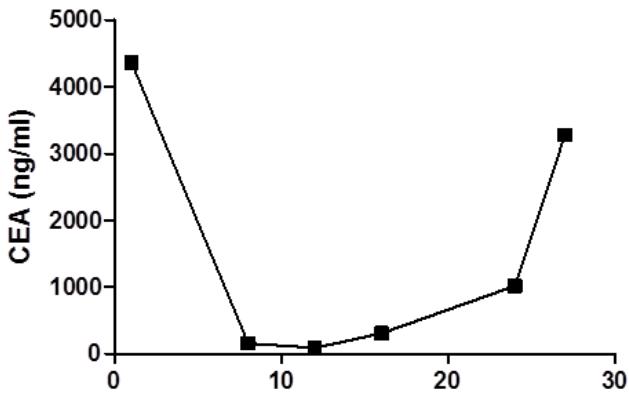
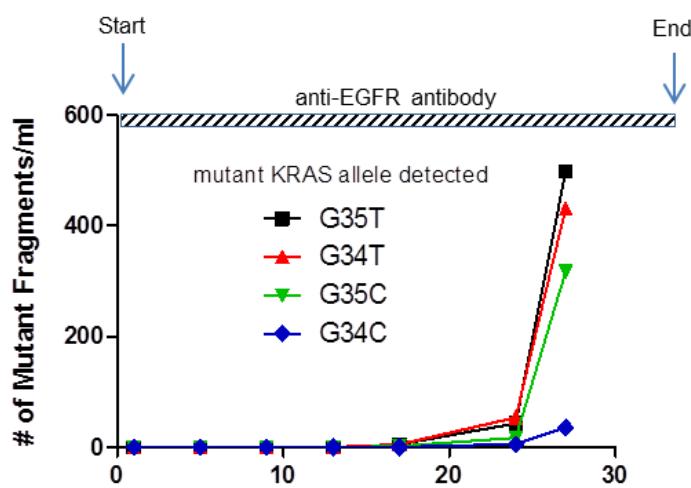


Tumor

Misale et al., Nature 2012



Luis Diaz  
Bert Vogelstein



Luis Diaz  
Bert Vogelstein

# The doctor's perspective



Royal Mail Stamp Issue 25 February 2003

# The patient's perspective



**"Here's my  
sequence..."**

# Molecular Genetics Lab



Federica Di Nicolantonio

Sabrina Arena

Miriam Martini

Emily Crowley

Elisa Scala

Carlotta Cancelliere

Sebastijan Hobor

Davide Zecchin

Simona Lamba

Michela Buscarino

Mariangela Russo

Sandra Misale

Livio Trusolino

Andrea Bertotti

David Solit

Renè bernard  
Josep Tabernero  
Sabine Tejpar

Salvatore Siena

Andrea Sartore Bianchi  
Marcello Gambacorta

alberto.bardelli@ircc.it