DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

Druggable Targets in Colorectal Cancer

Federica Di Nicolantonio
University of Torino, Department of Oncology
Candiolo Cancer Institute IRCCS - Italy

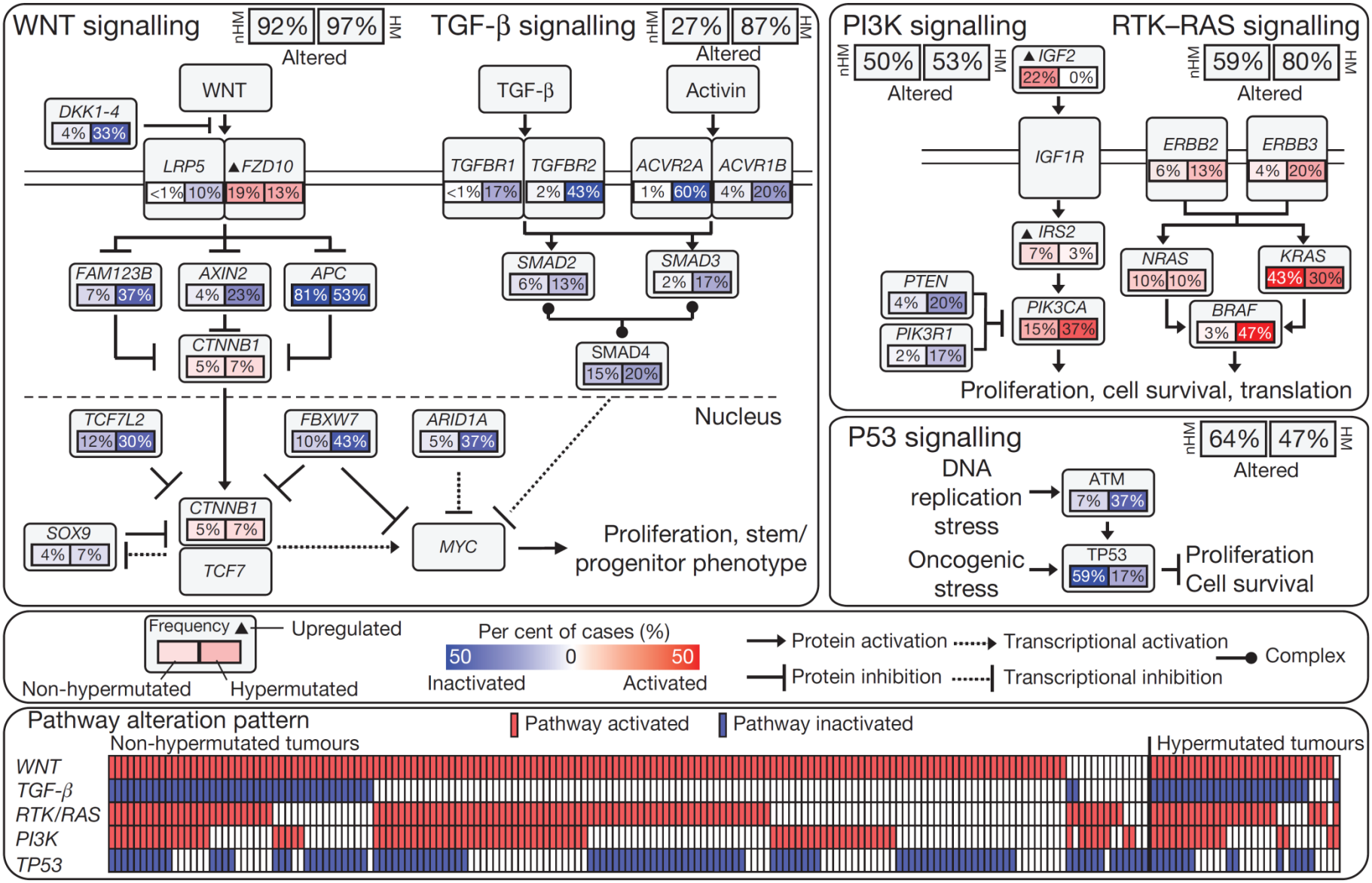
Disclosures

- No relevant relationships to disclose

Outline

- Genomic alterations in CRC signalling pathways
- Emerging molecular determinants of resistance to EGFR targeted therapies in mCRC
- Validation of these molecular alterations as alternative ‘drivers’ of CRC tumorigenesis and progression
- Challenging molecular alterations as actionable therapeutic targets within the context of CRC molecular landscape

Deregulation of signalling pathways in CRC



The Cancer Genome Atlas Network, Nature **487**, 330-337 (2012)

Colorectal cancer progression

A genetic model for colorectal tumorigenesis.
Fearon ER, Vogelstein B.
Cell. 1990 Jun 1;61(5):759-67

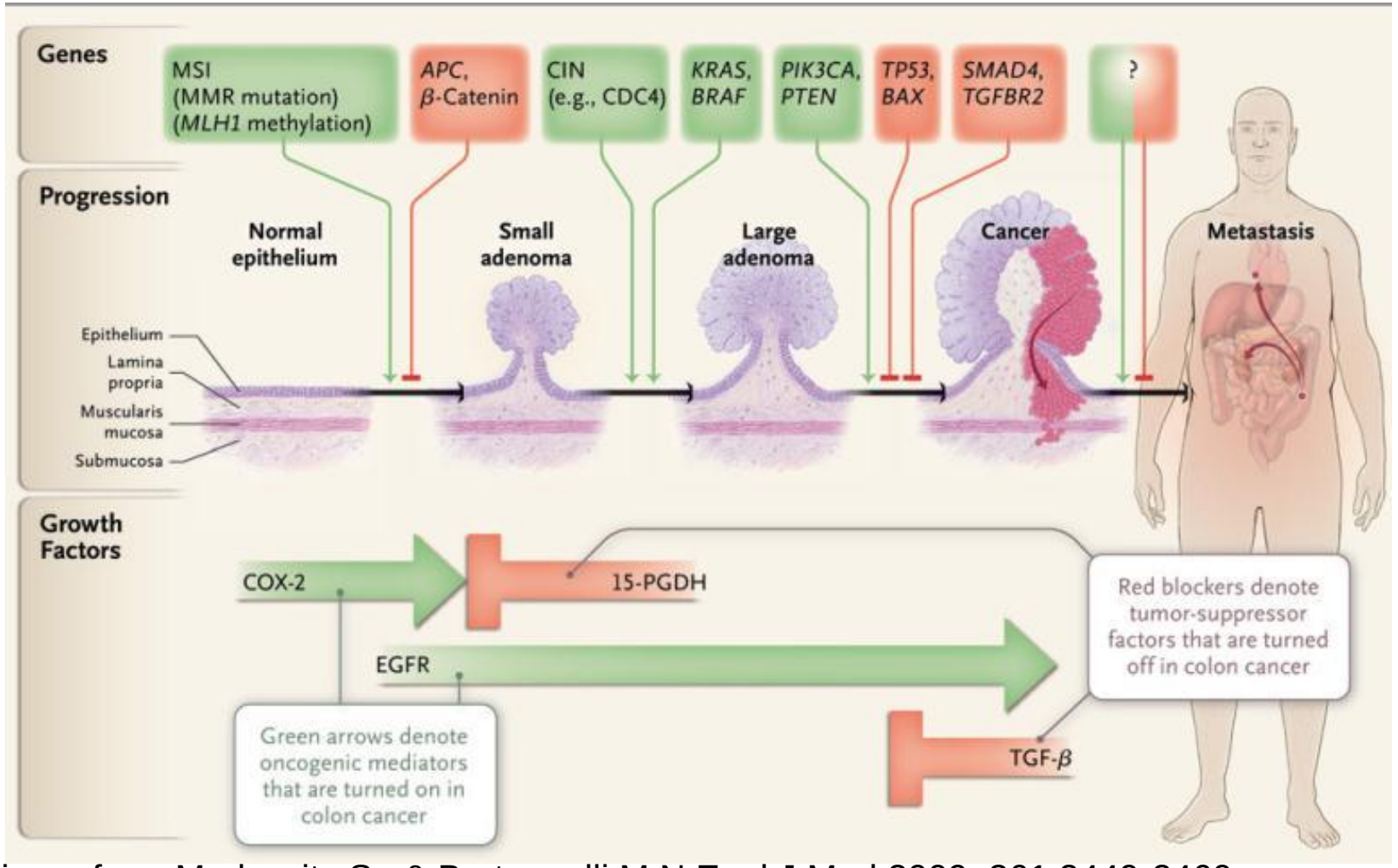


Figure from Markowitz S., & Bertagnolli M N Engl J Med 2009; 361:2449-2460

What we have learnt on CRC genomics

The Cancer Genome Atlas Network, Nature **487**, 330-337 (2012)

- Several hundred molecular aberrations (not only mutations)
- Co-existence of genetic, epigenetic and transcriptional drivers of tumour progression

What we have not learnt so far

- Which are drivers?
- Co-existence of multiple drivers within the same tumour?

Outline

- Genomic alterations in CRC signalling pathways
- **Emerging molecular determinants of resistance to EGFR targeted therapies in mCRC**
- **Validation of these molecular alterations as alternative ‘drivers’ of CRC tumorigenesis and progression**
- **Challenging molecular alterations as actionable therapeutic targets within the context of CRC molecular landscape**

Colorectal cancer preclinical models

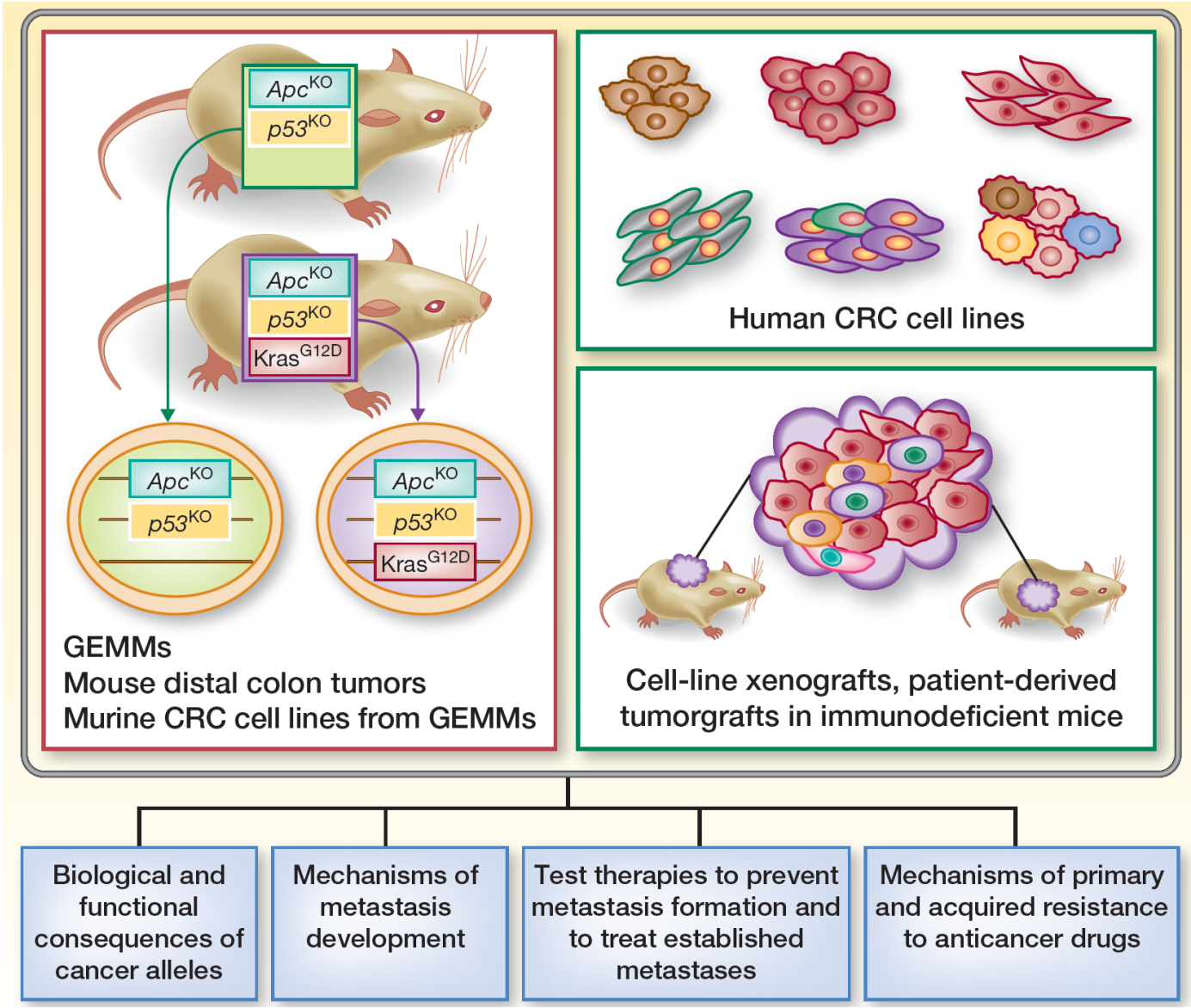


FIGURE 1. Di Nicolantonio F. Clin Cancer Res. 2013 Apr 23.
Mouse models of Kras mutant colorectal cancer: valuable GEMMs for drug testing?

Colorectal cancer preclinical models

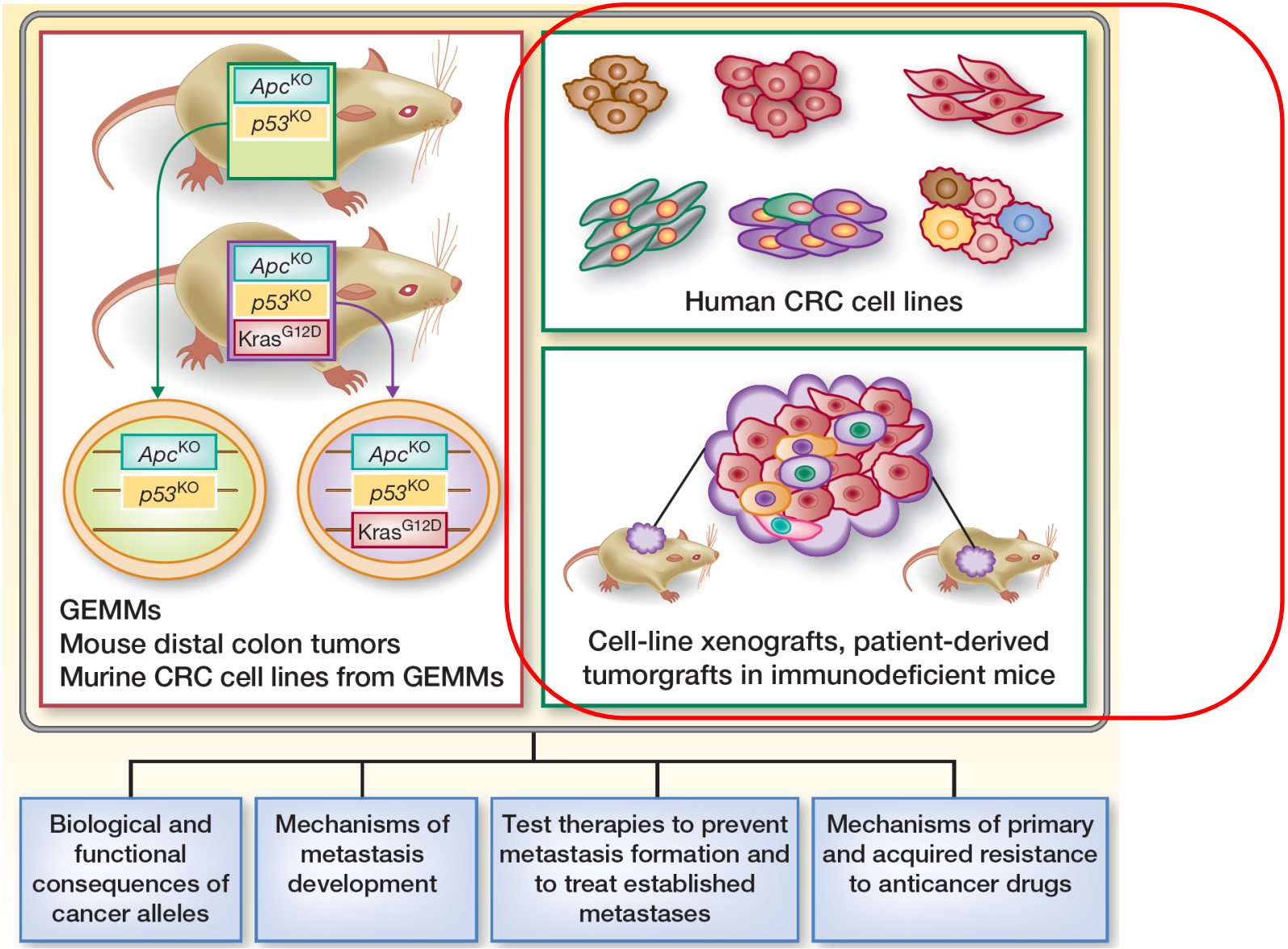
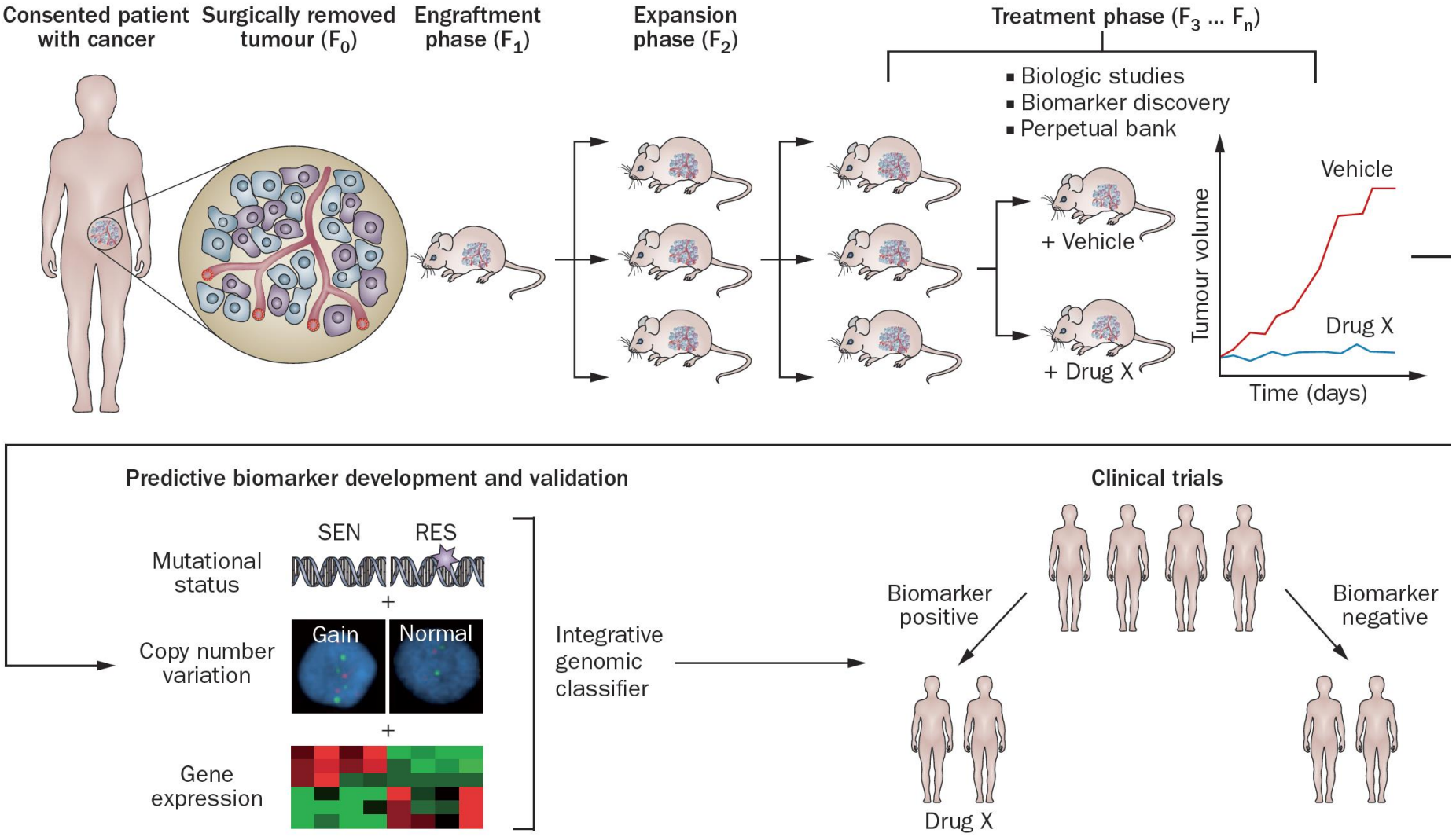


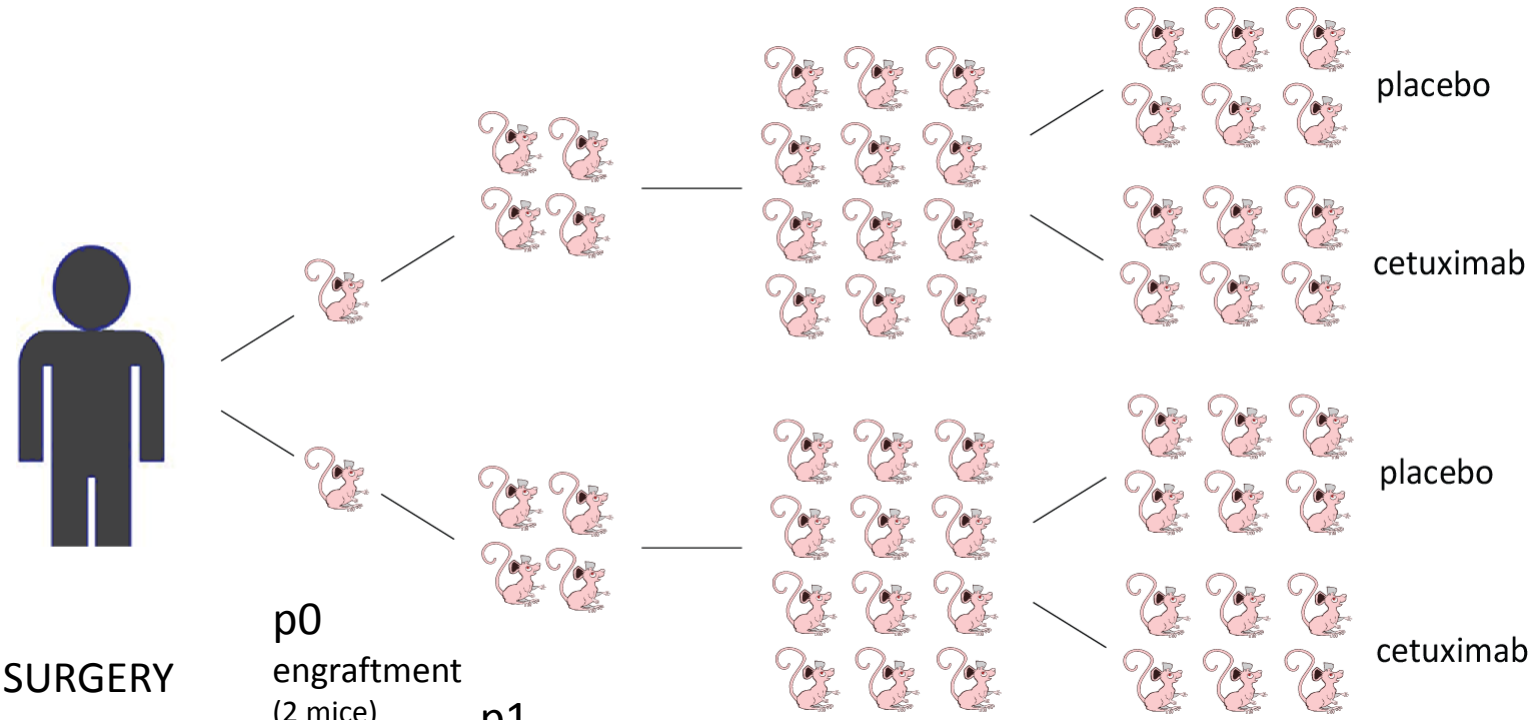
FIGURE 1. Di Nicolantonio F. Clin Cancer Res. 2013 Apr 23.
Mouse models of Kras mutant colorectal cancer: valuable GEMMs for drug testing?

Patient derived xenografts



From Tentler J et al., Nature Reviews Clinical Oncology 9, 338-350 (June 2012)

Cetuximab monotherapy mouse clinical trial in PDXs



NUMBER OF INITIAL SAMPLES

150 ⟶ >85% ⟶ 85

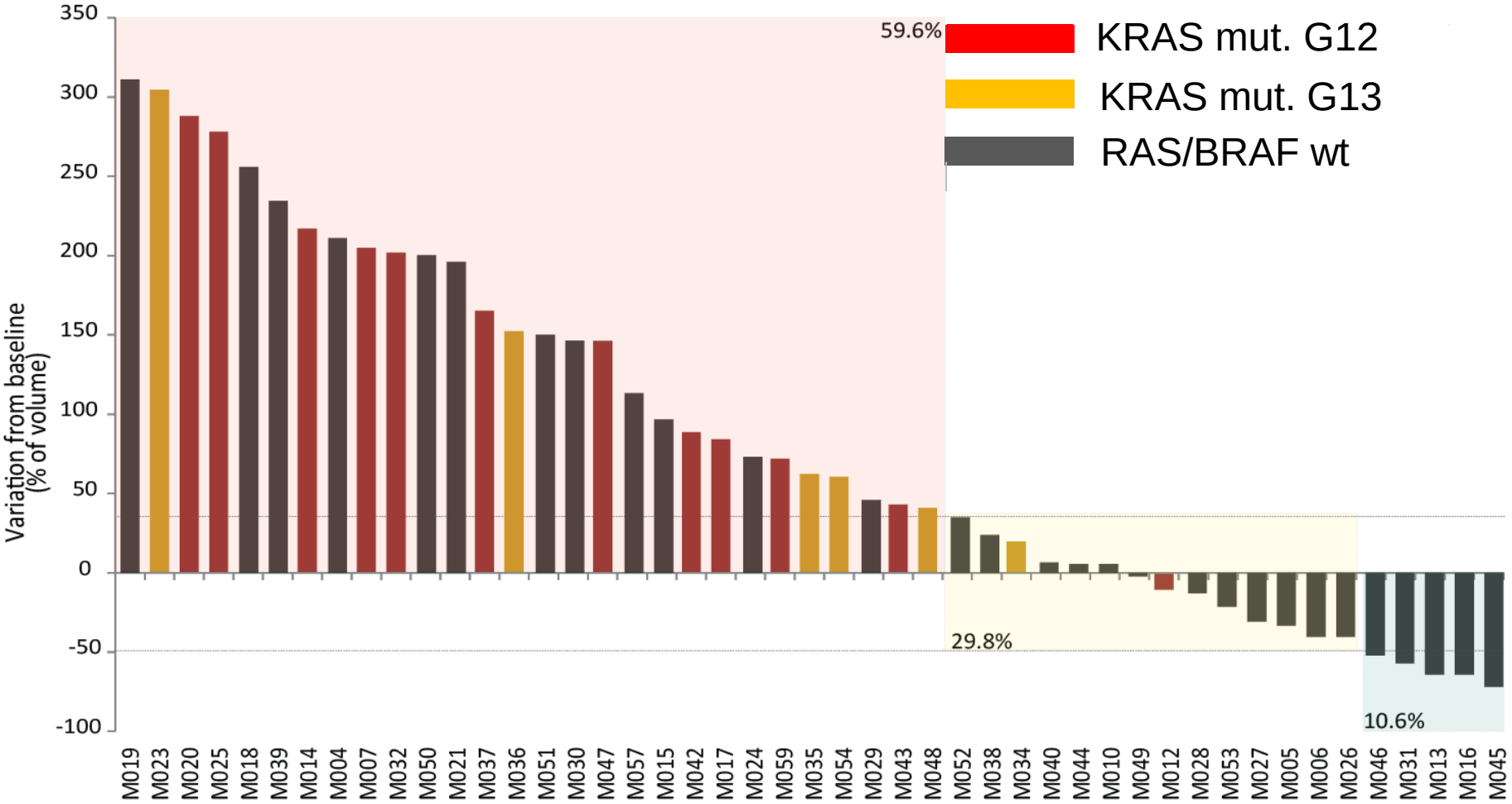
Biobank Archive

RNA extraction

Genomic DNA extraction

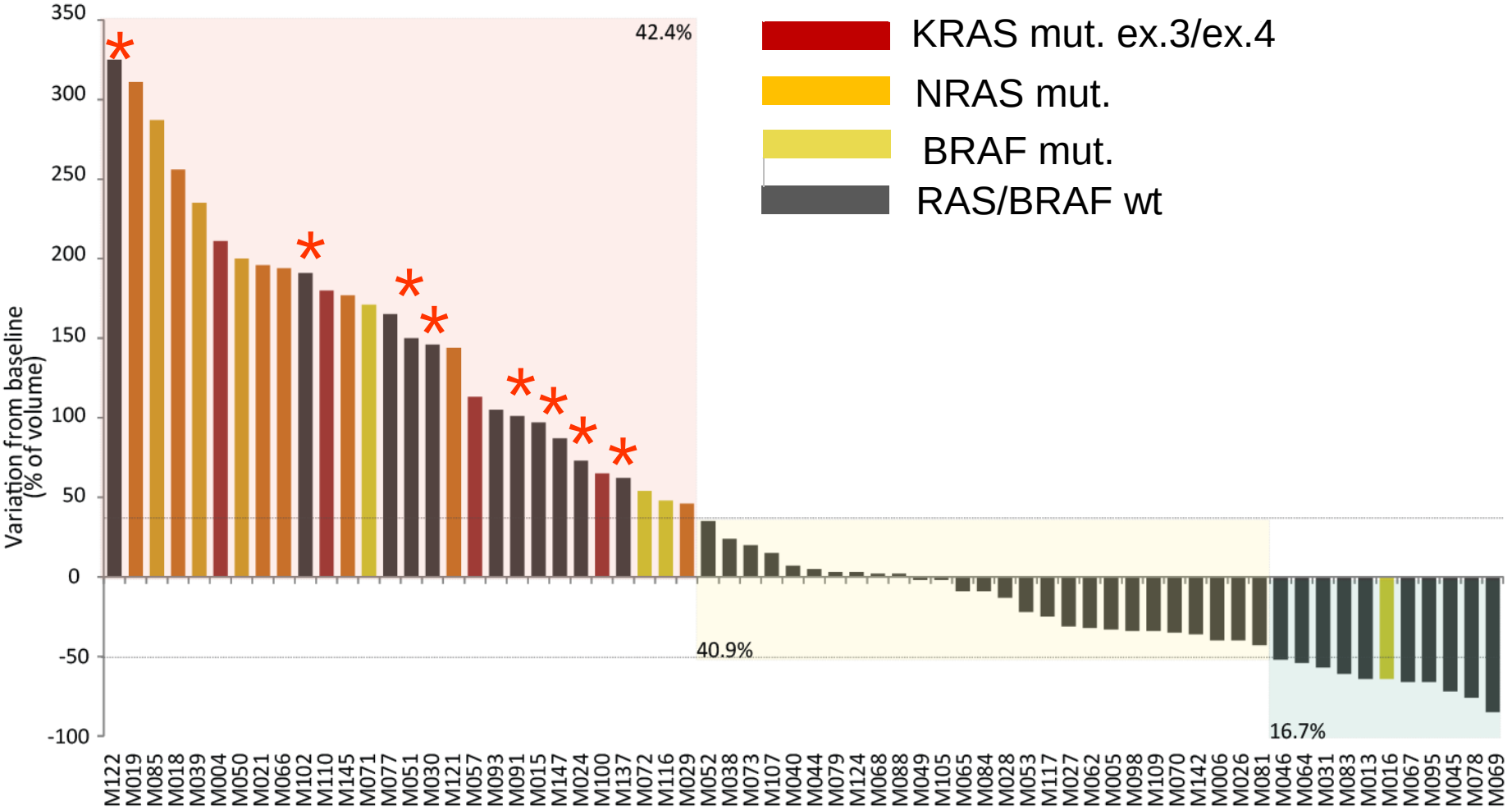
Bertotti & L. Trusolino, Molecular Pharmacology, IRCCS - Candiolo

Response to EGFR signalling inhibition in mCRC PDXs



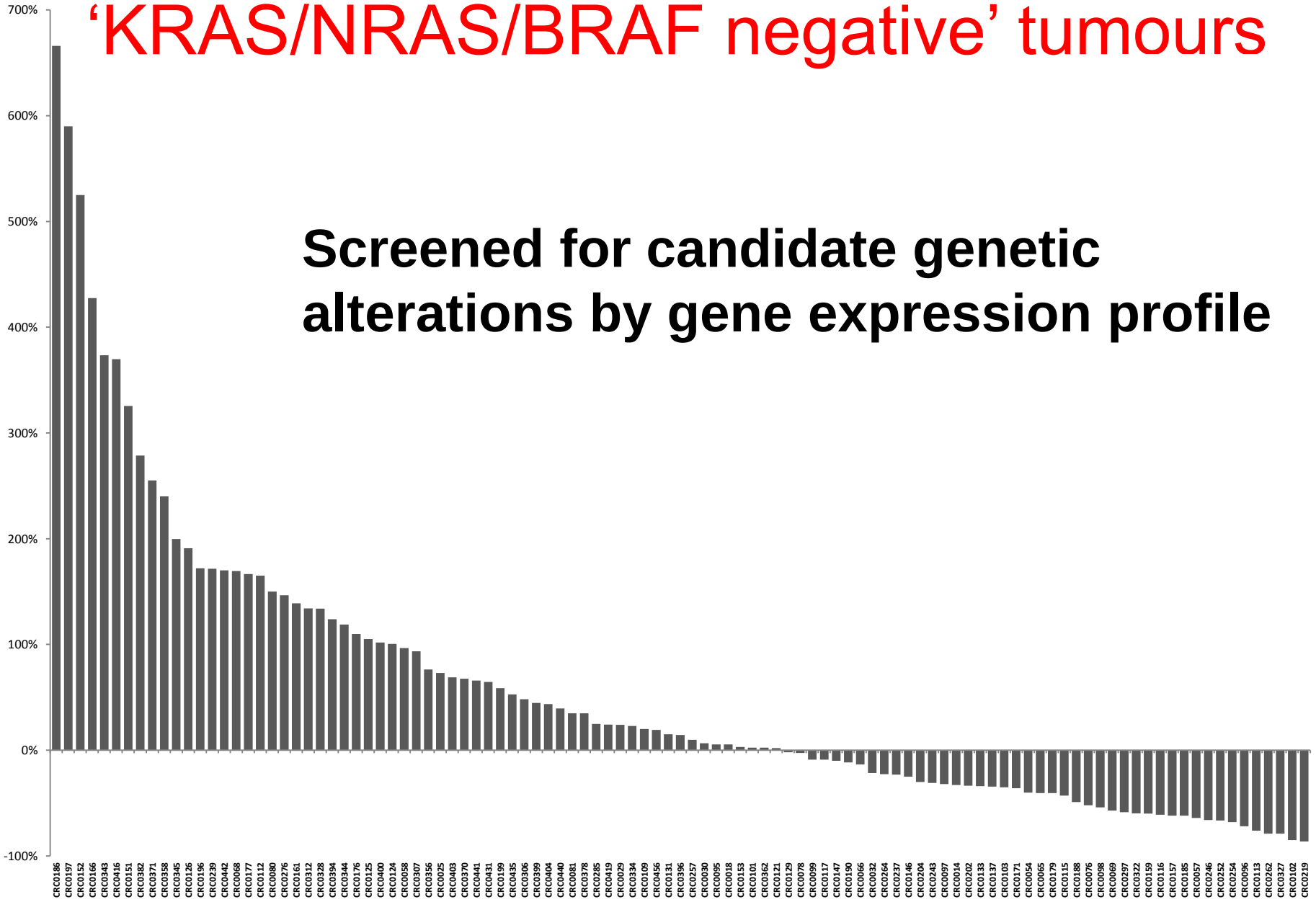
Bertotti A. et al., Cancer Discov. 2011 Nov;1(6):508-23.

KRAS ex.3/ex.4, NRAS, BRAF mutations are associated resistance to cetuximab in KRAS ex.2 wt PDXs



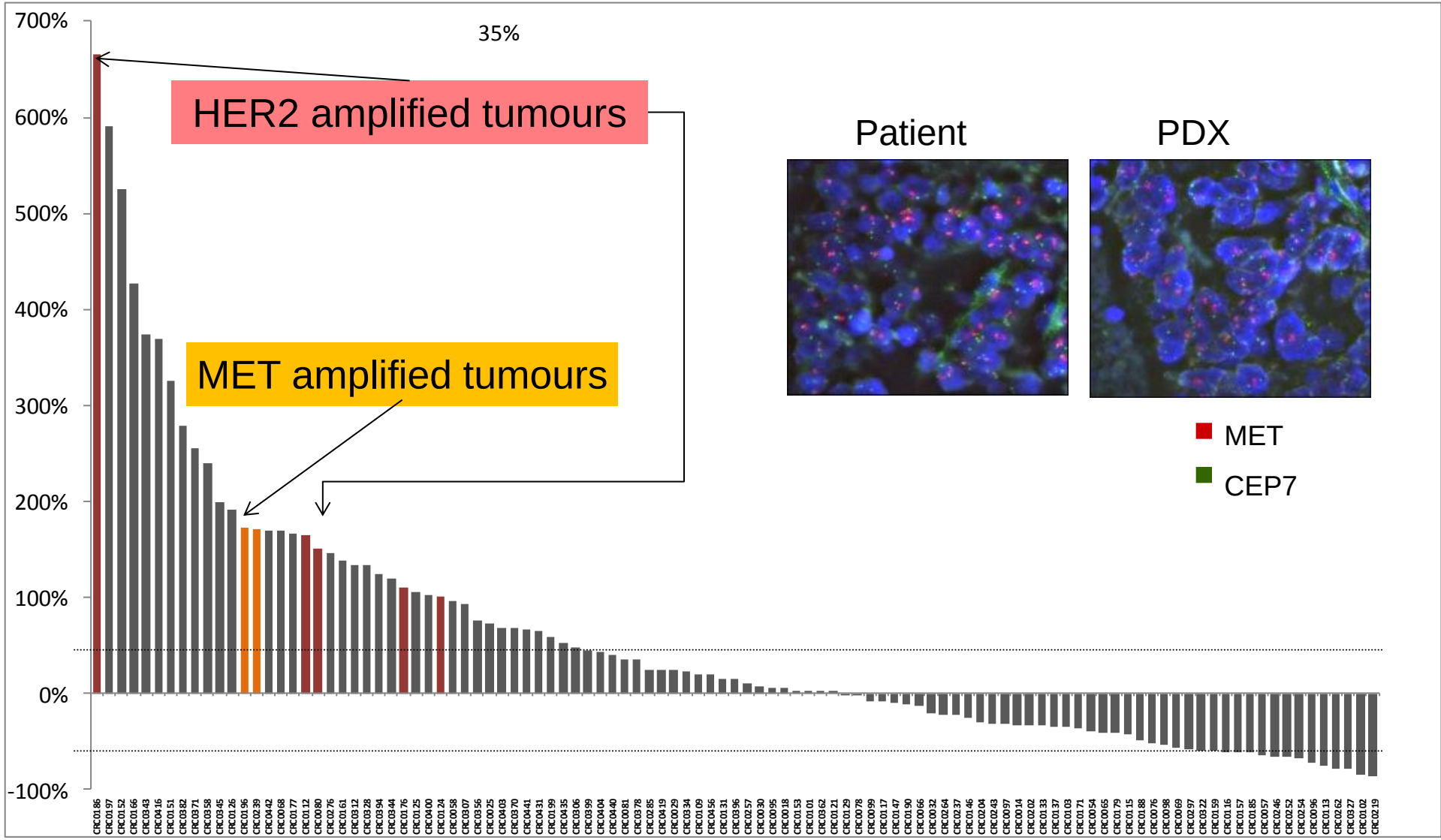
* Quadruple negative (unexplained) non responders

‘KRAS/NRAS/BRAF negative’ tumours



Screened for candidate genetic alterations by gene expression profile

HER2 and MET are actionable biomarkers that correlate with resistance to EGFR therapies in CRC

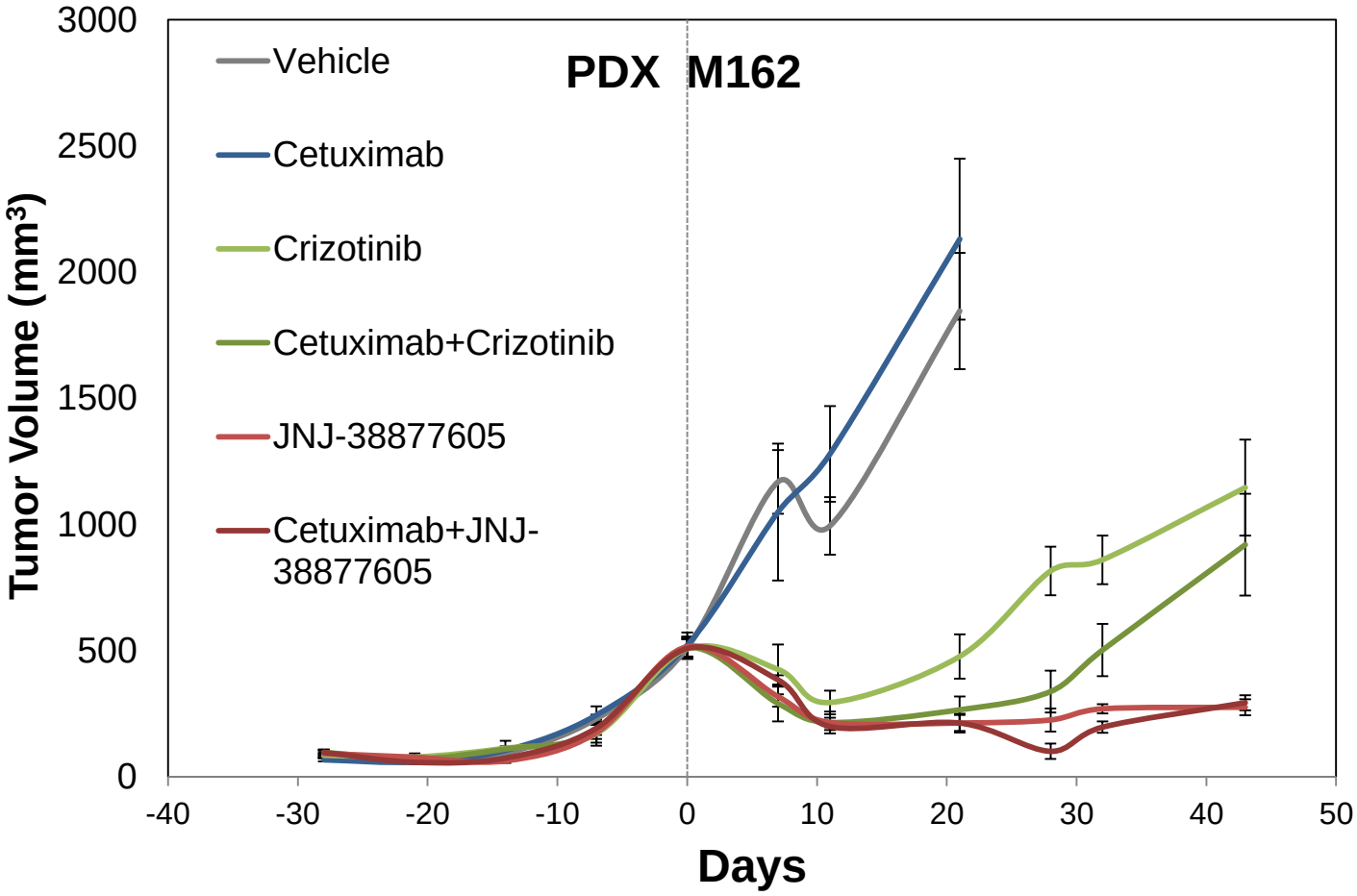


Bertotti A et al., Cancer Discov. 2011 Nov;1(6):508-23.
Bardelli A et al., Cancer Discov. 2013 Jun;3(6):658-73.

Outline

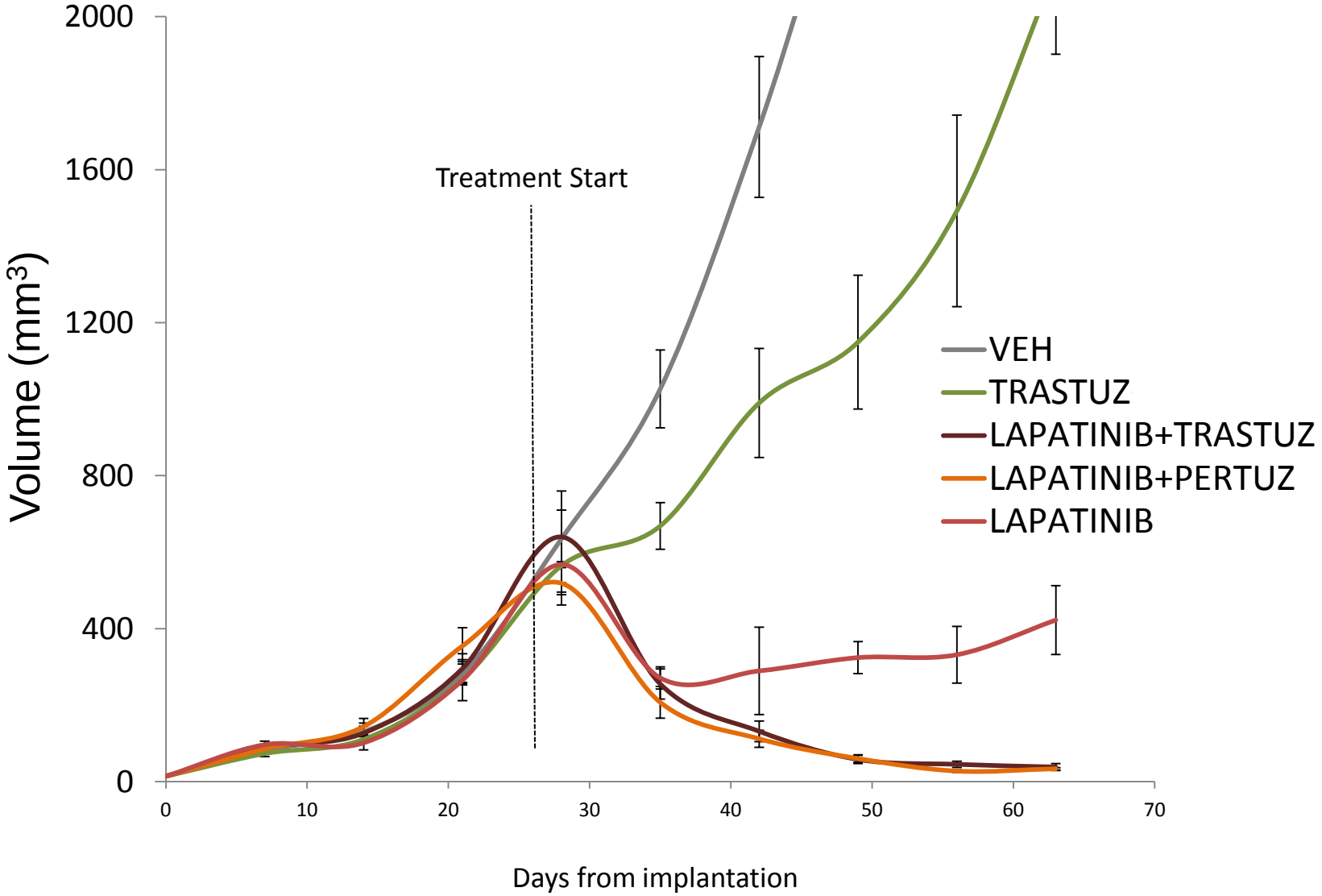
- Genomic alterations in CRC signalling pathways
- Emerging molecular determinants of resistance to EGFR targeted therapies in mCRC
- **Validation of these molecular alterations as alternative ‘drivers’ of CRC tumorigenesis and progression**
- **Challenging molecular alterations as actionable therapeutic targets within the context of CRC molecular landscape**

Is MET a target in MET amplified CRC?



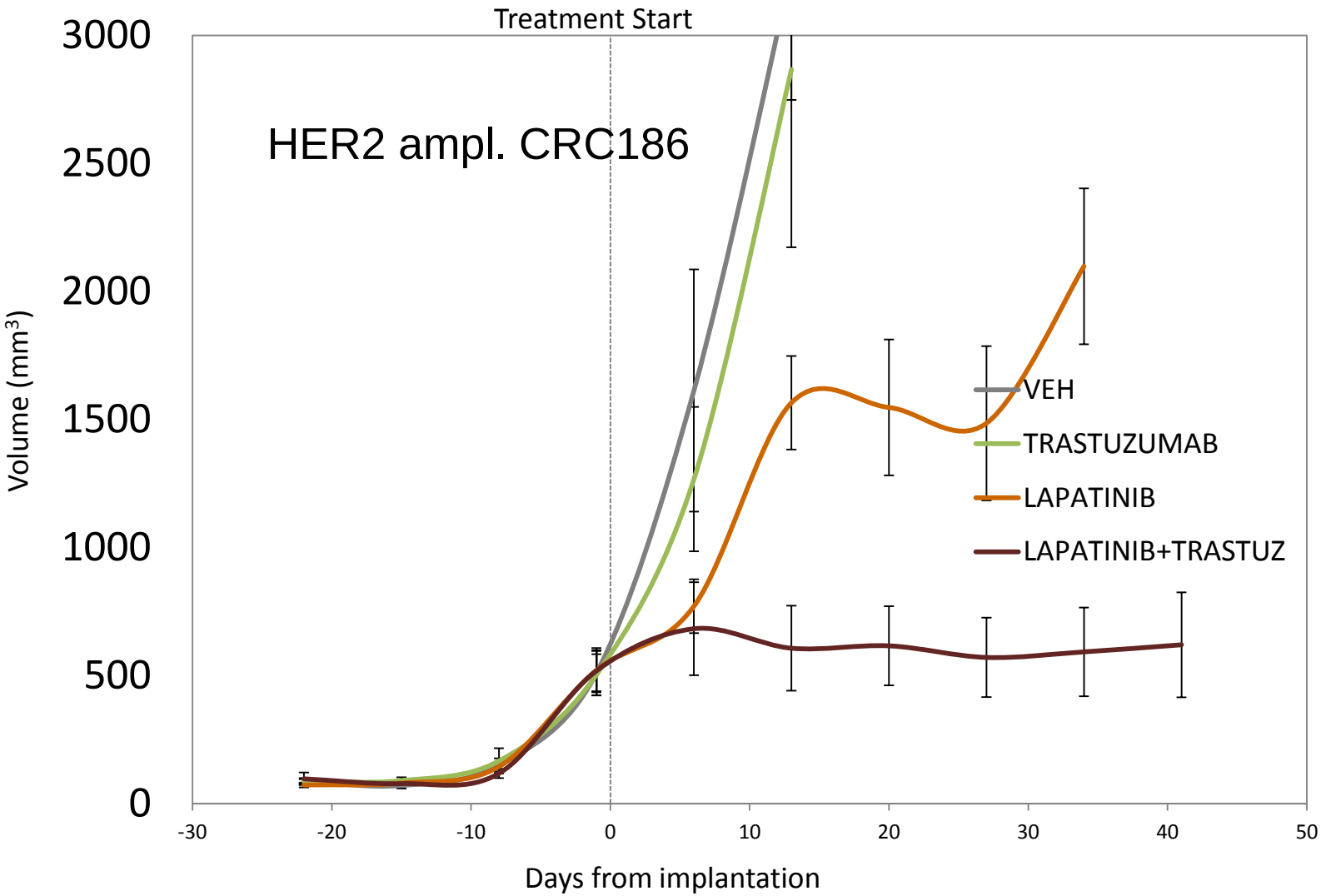
Bardelli A et al., Cancer Discov. 2013 Jun;3(6):658-73.

Is HER2 a target in CRC? Only a small molecule-antibody combination of anti-HER2 therapies has preclinical efficacy



Bertotti A et al., Cancer Discov. 2011 Nov;1(6):508-23.

… But efficacy is variable



Heracles Studies

HER2 Amplification for Colo-rectaL Cancer Enhanced Stratification

Heracles Companion Diagnostic

A retrospective study to establish a HER2 scoring system for CRC to identify suitable patients for enrollment in trial of trastuzumab and lapatinib in advanced metastatic colorectal cancer.

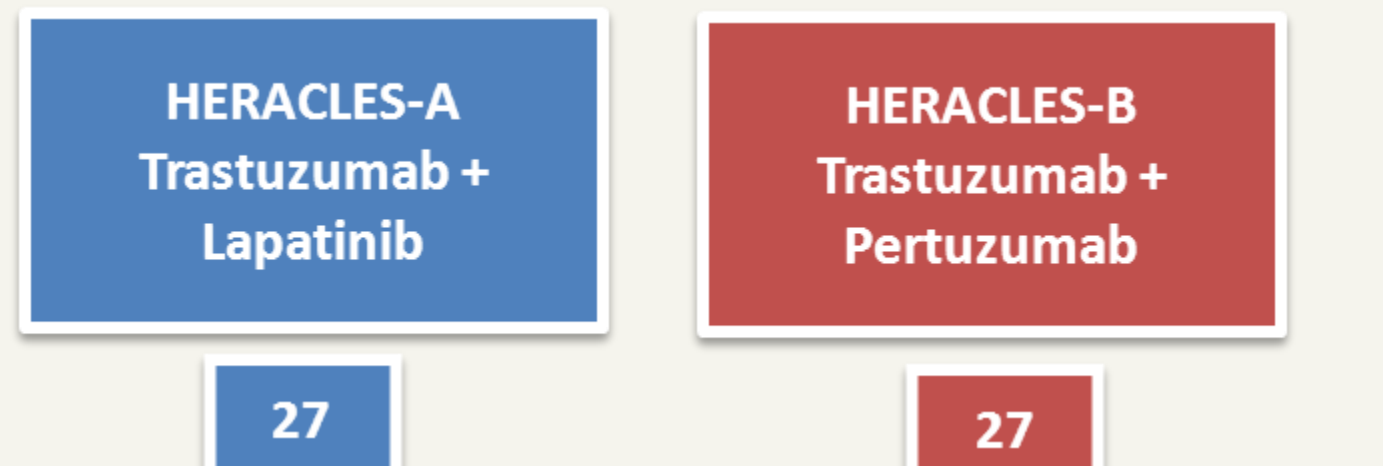
Heracles Therapeutic Trial

A single arm, Phase II, multi-center, trial designed to assess the objective response rate in an HER2 amplification-enriched population of mCRC patients receiving trastuzumab + lapatinib

The HERACLES Trial

The HERACLES trial

- **HERACLES *(HER2 Amplification for Colo-rectaL Cancer Enhanced Stratification)***
- HER-2 amplified chemorefractory mCRC patients (Chair: Salvatore Siena, Niguarda Hospital, Milan, Italy)



Colorectal cancer preclinical models

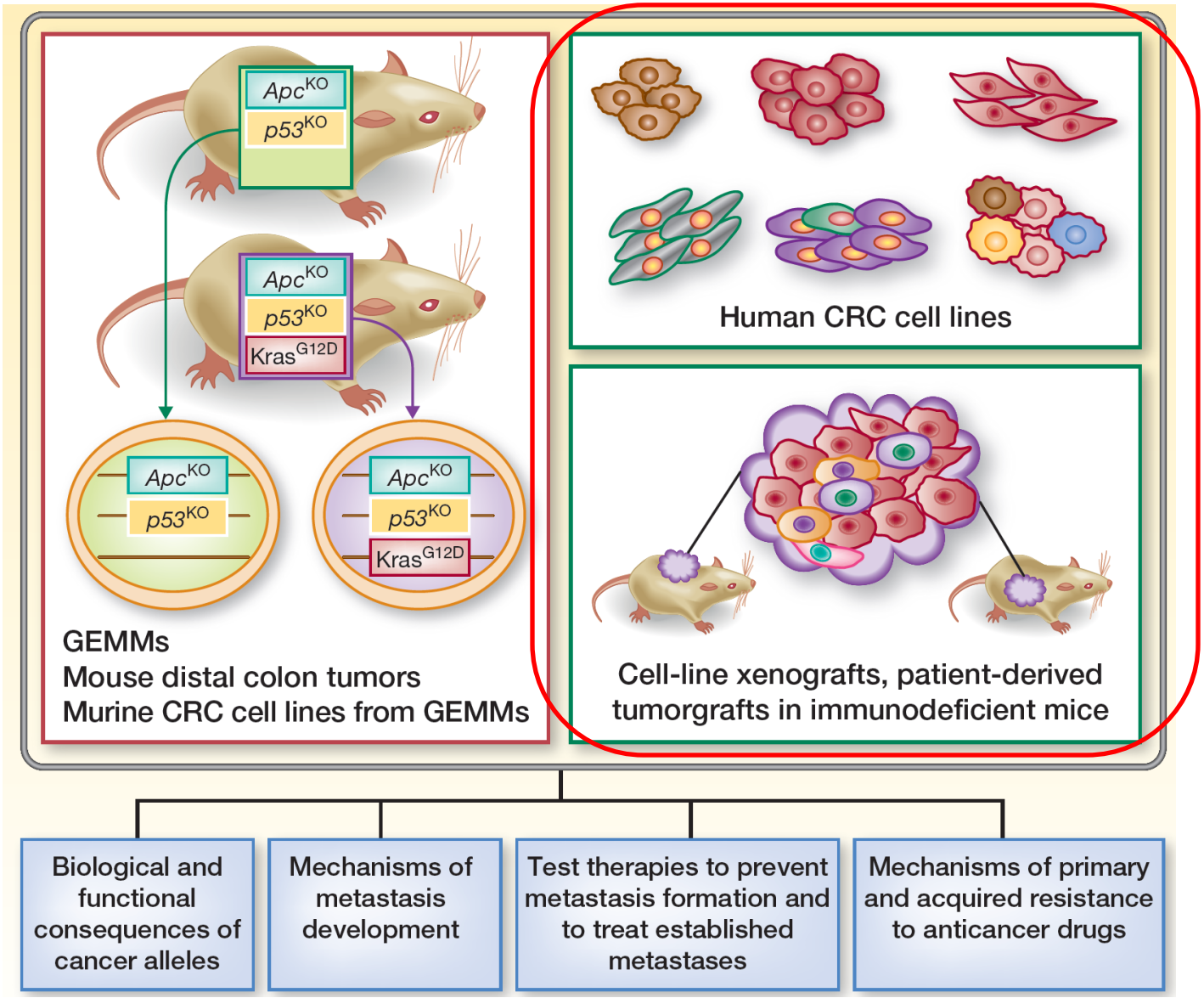
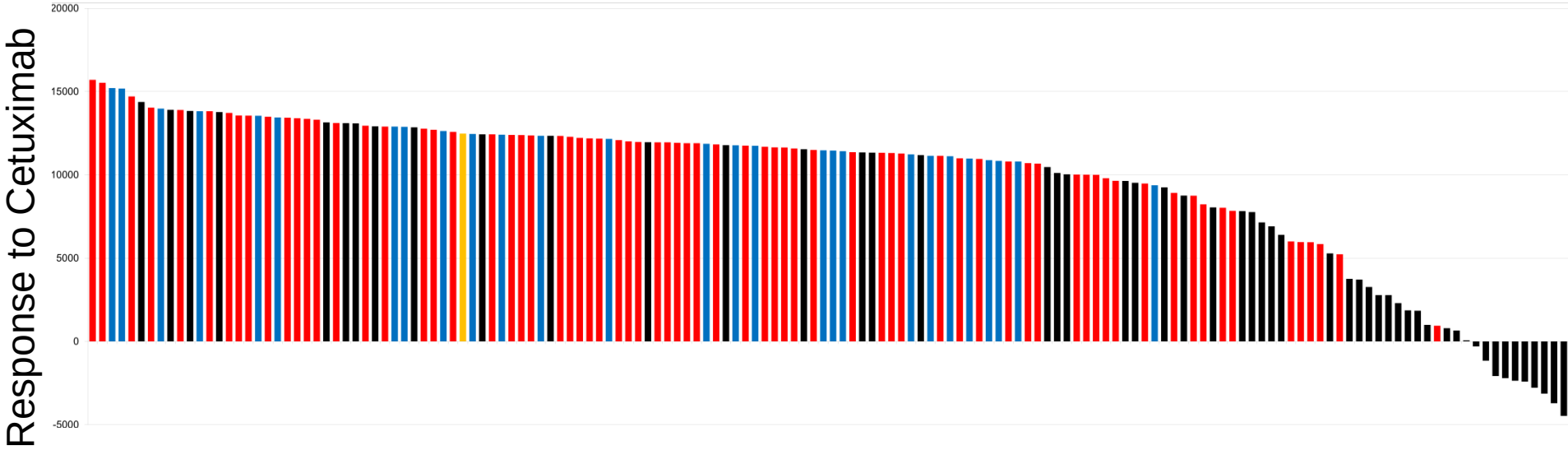


FIGURE 1. Di Nicolantonio F. Clin Cancer Res. 2013 Apr 23.
Mouse models of Kras mutant colorectal cancer: valuable GEMMs for drug testing?

Response to EGFR signaling inhibition in CRC cell lines

Resistance **Sensitivity**



KRAS mutations/ampl.

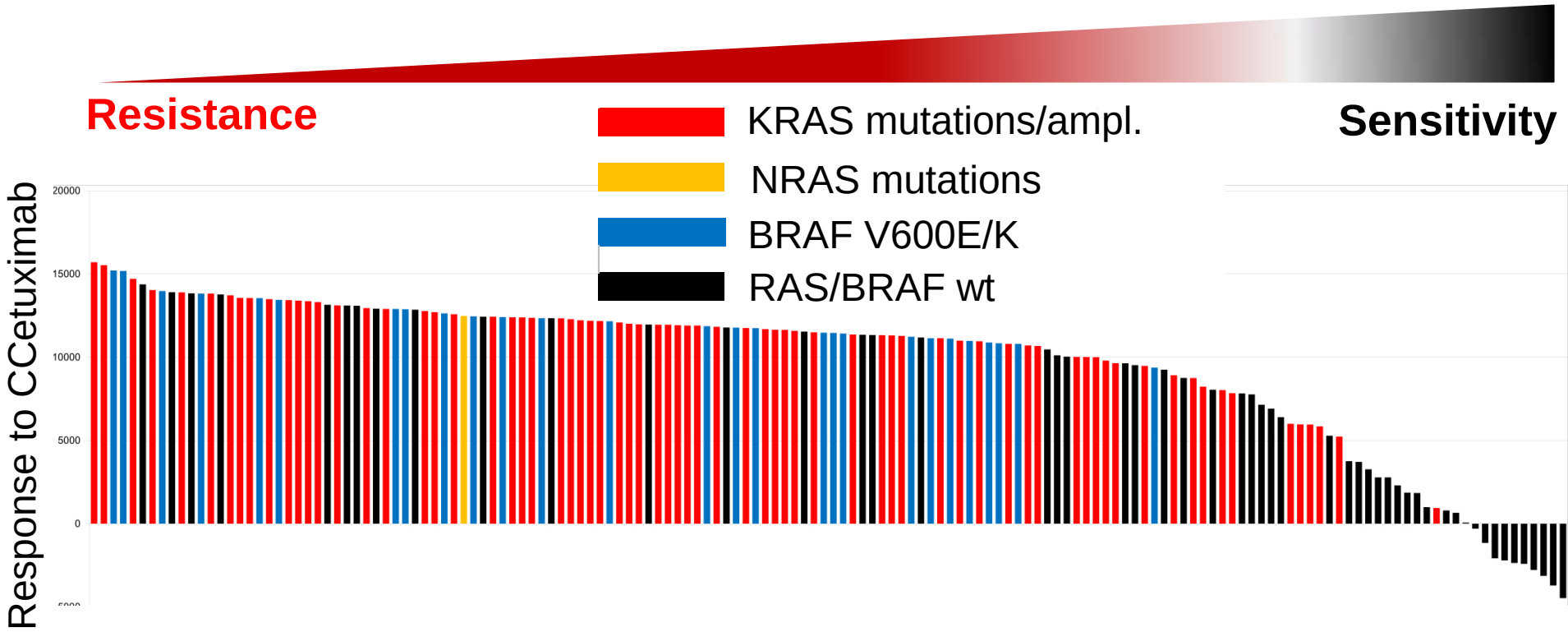
NRAS mutations

BRAF V600E/K

RAS/BRAF wt

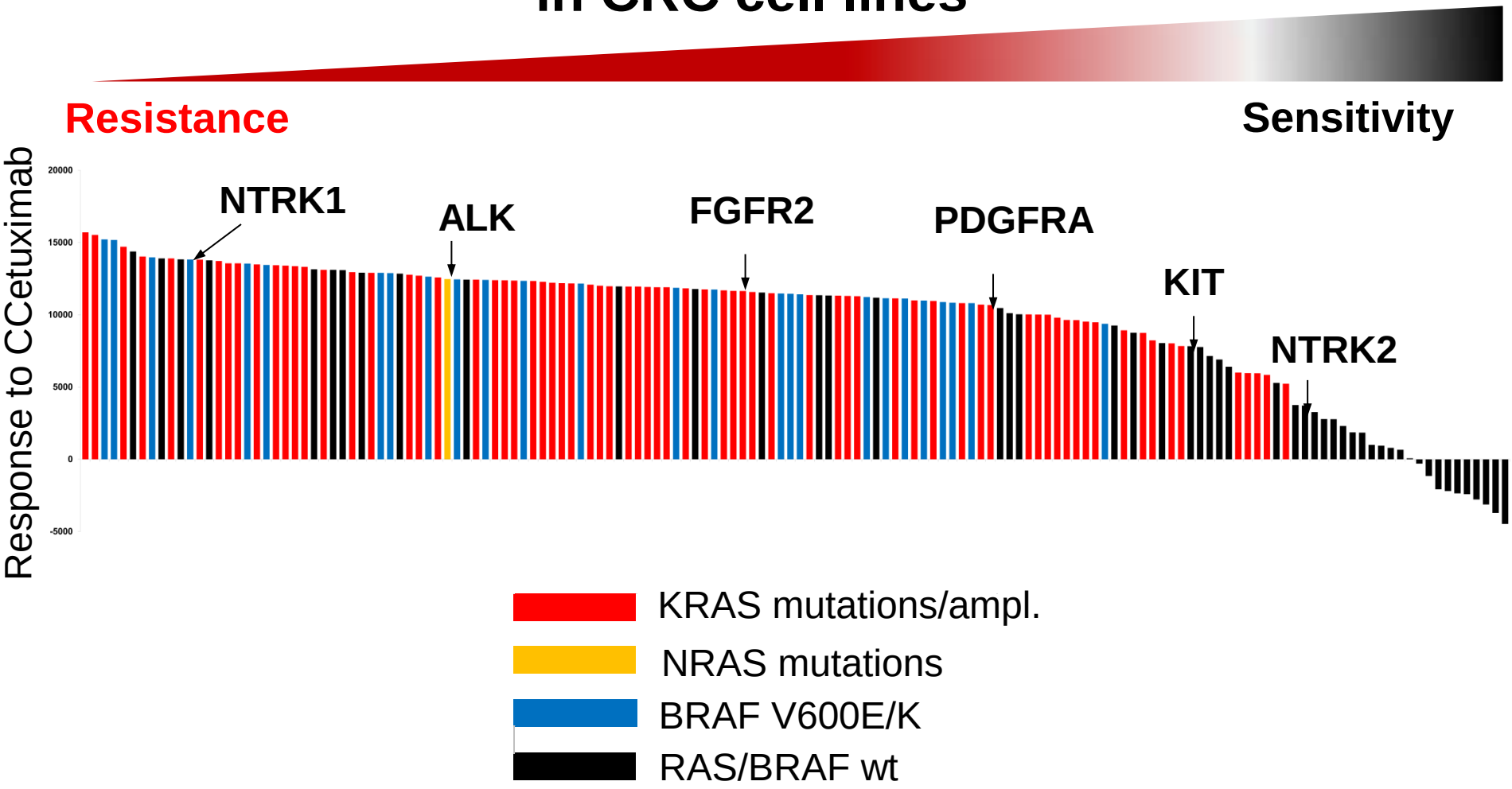
Unpublished data

Response to EGFR signaling inhibition in CRC cell lines



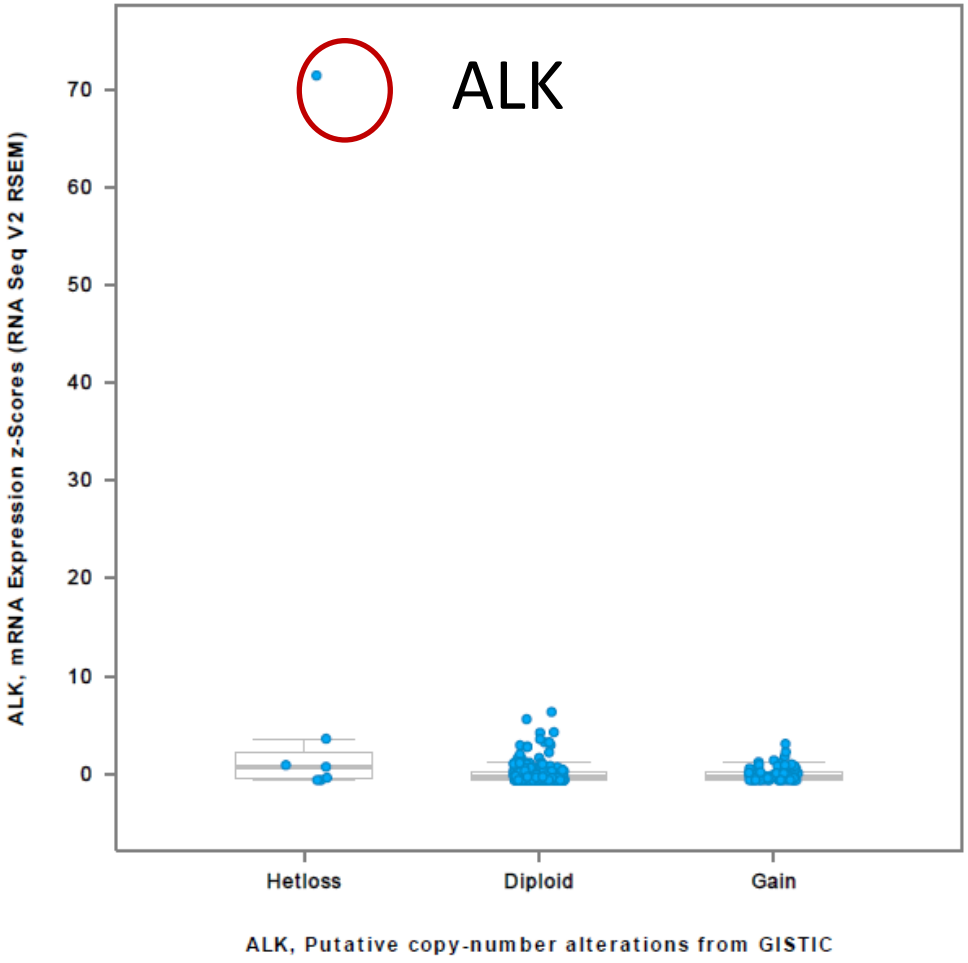
Screened for candidate genetic alterations responsible for cetuximab resistance in RAS/BRAF wt cells by gene expression profile

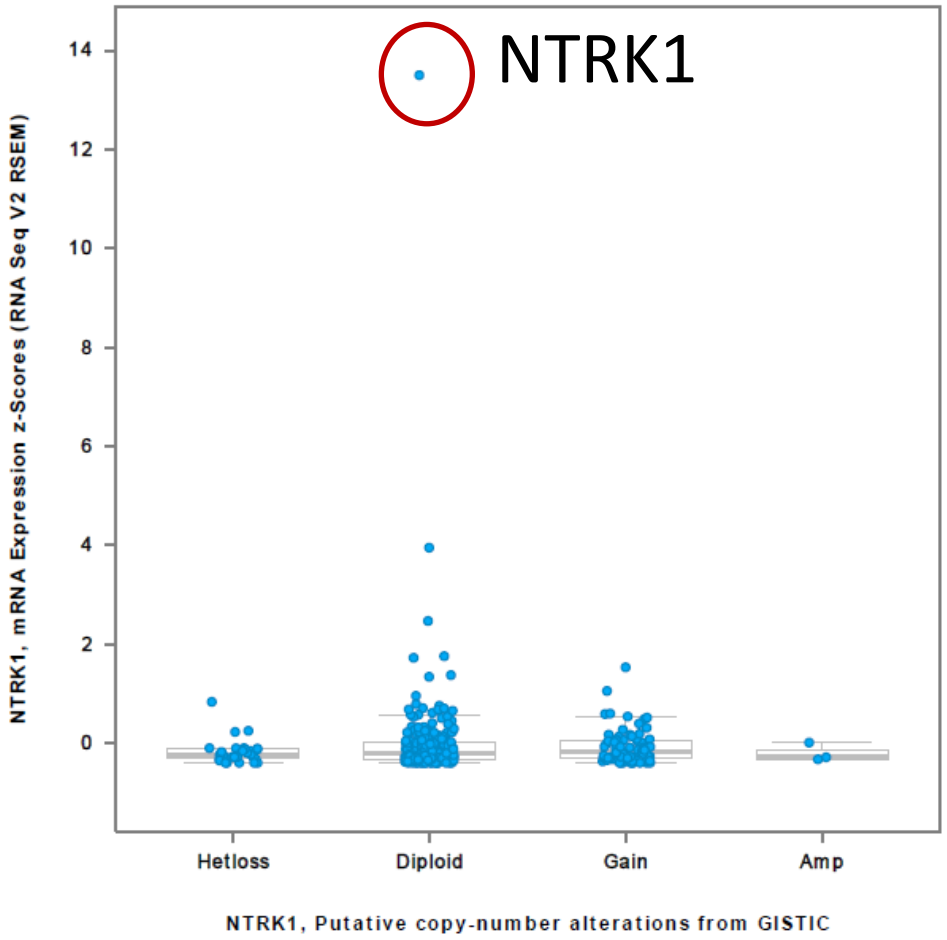
Outlier kinase expression predicts resistance to EGFRi in CRC cell lines



Prevalence of RTK overexpression in CRC specimens

Gene expression does not always correlate with gene amplification





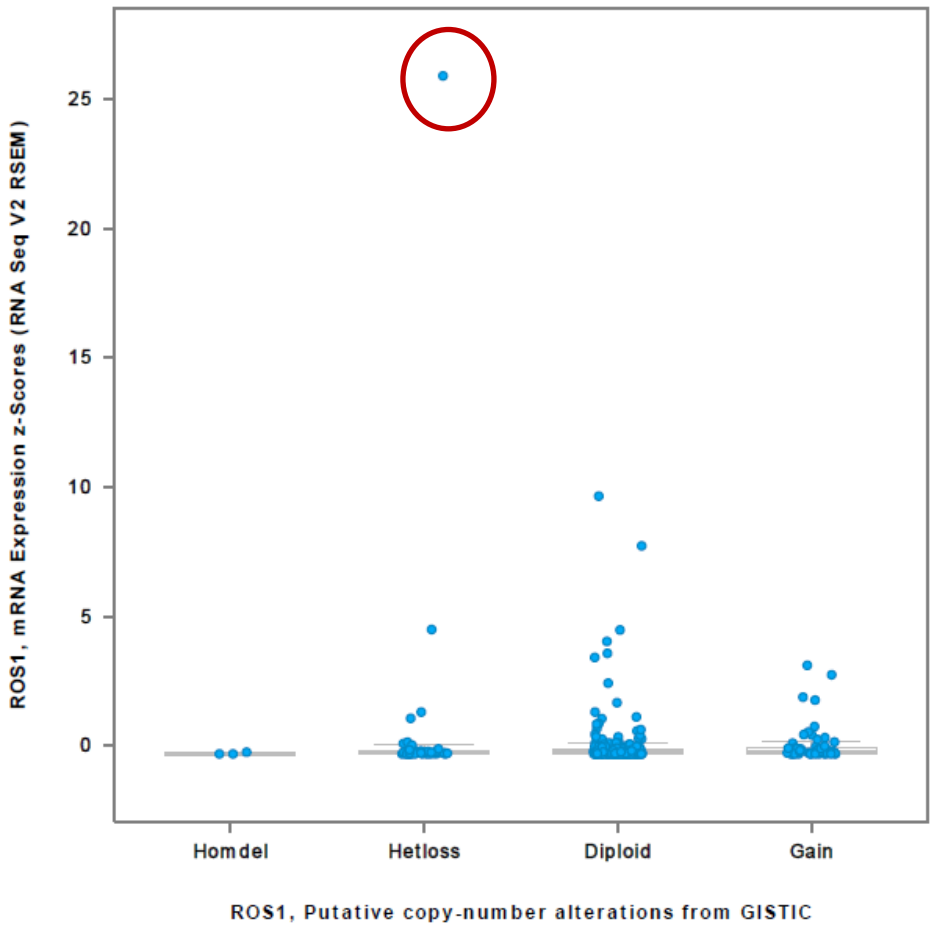
TCGA CRC dataset (195 complete tumors) interrogated through http://www.cbioportal.org/

Cerami E et al., Cancer Discov. 2012 May;2(5):401-4
Gao J et al., Sci Signal. 2013 Apr 2;6(269):pl1

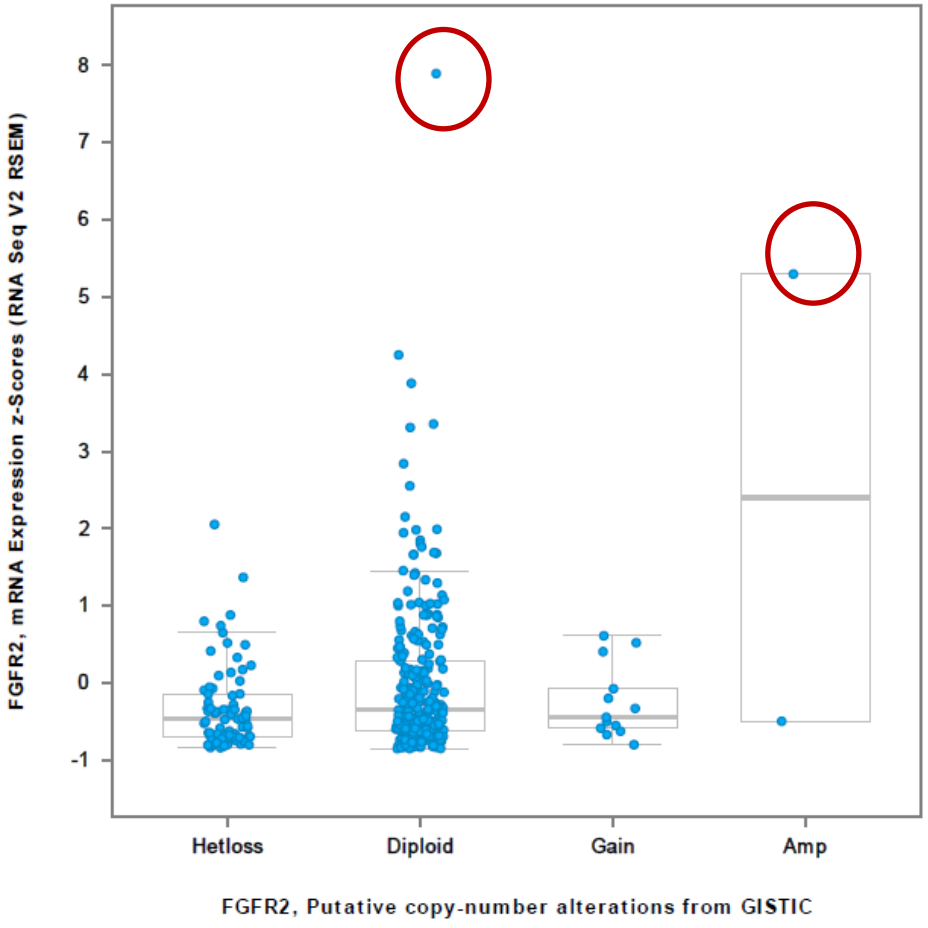
Prevalence of RTK overexpression in CRC specimens

Gene expression does not always correlate with gene amplification

ROS1



FGFR2



TCGA CRC dataset (195 complete tumors) interrogated through http://www.cbioportal.org/

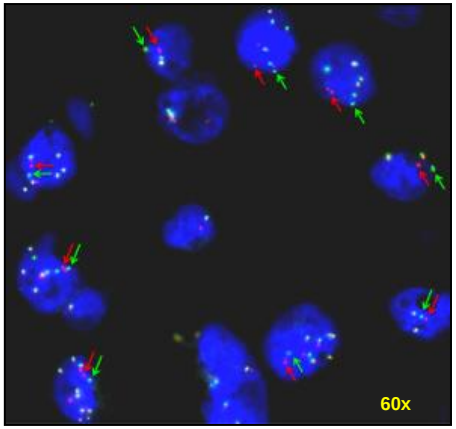
Cerami E et al., Cancer Discov. 2012 May;2(5):401-4

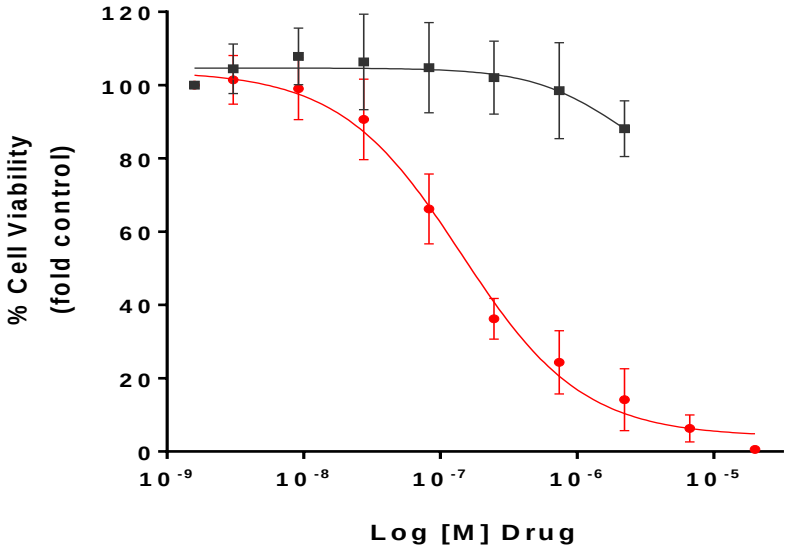
Gao J et al., Sci Signal. 2013 Apr 2;6(269):pl1

ALK translocation in CRC cells is associated with tumour sensitivity to ALK kinase inhibition

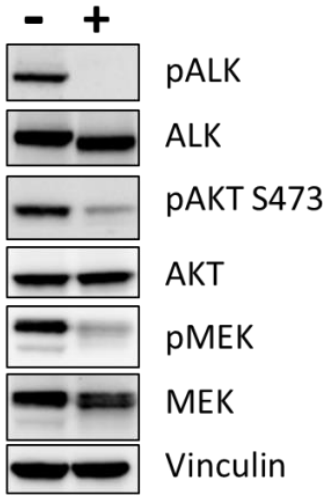
ALK gene fusions described in CRC – but lack of functional data.
(TCGA, 2012; Lipson D et al., Nat Med. 2012 2;18:382-4; Aisner et al., Mol Cancer Res. 2014;12:111-8)

CRC cells (*EML4-ALK*)



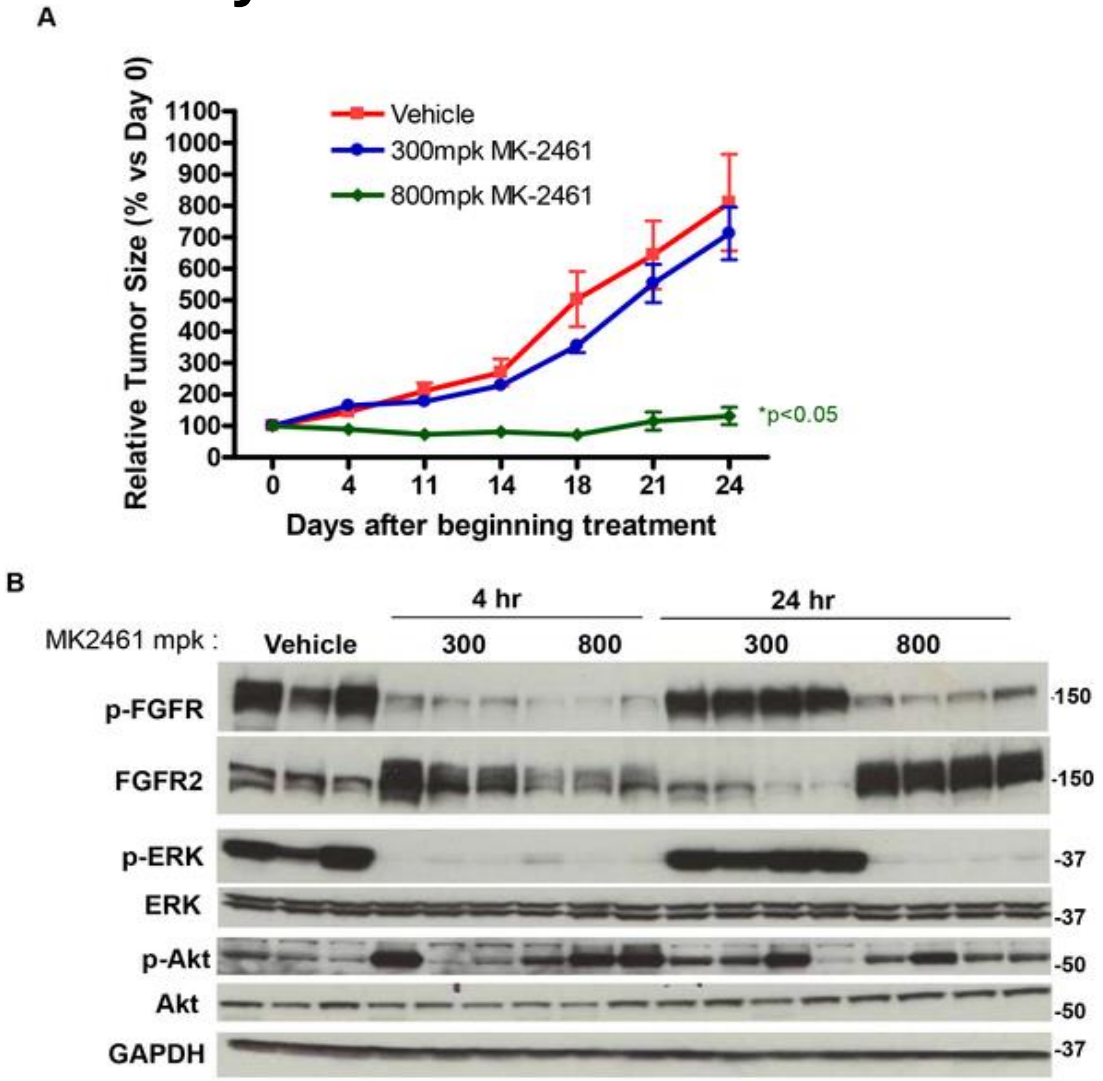


Crizotinib



Unpublished data

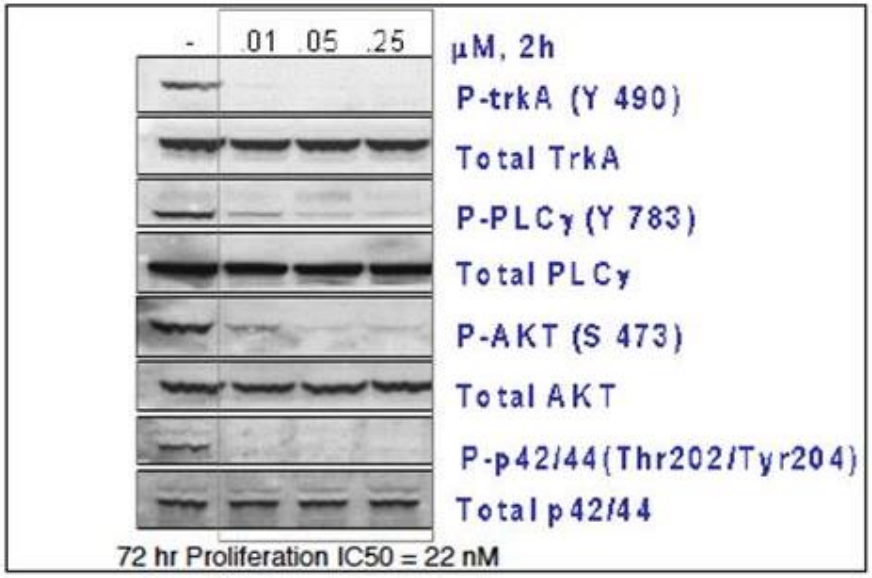
FGFR2 amplification in CRC cells is associated with tumour sensitivity to FGFR kinase inhibition

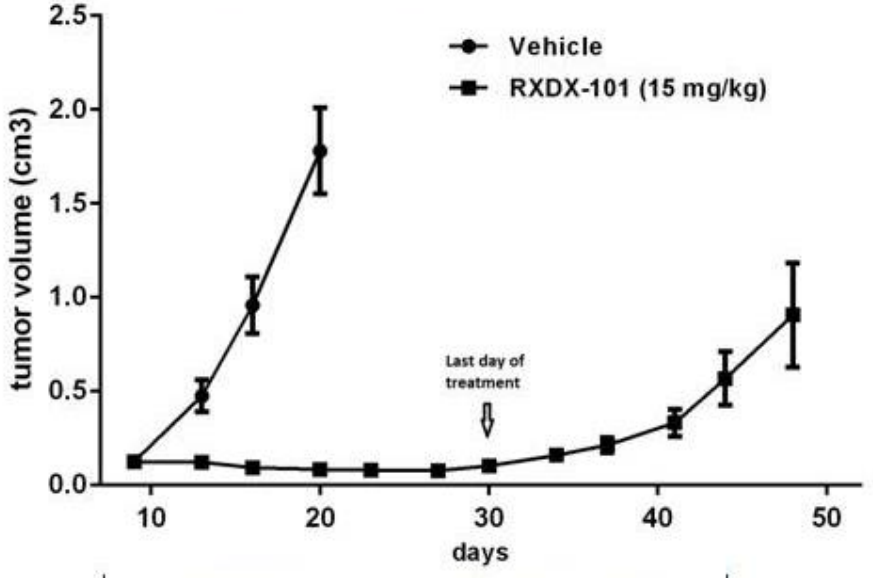


Mathur A, Ware C, Davis L, Gazdar A, et al. (2014) FGFR2 Is Amplified in the NCI-H716 Colorectal Cancer Cell Line and Is Required for Growth and Survival. PLoS ONE 9(6): e98515. doi:10.1371/journal.pone.0098515

NTRK1 rearrangements in CRC cells are associated with tumour sensitivity to TRKA kinase inhibition

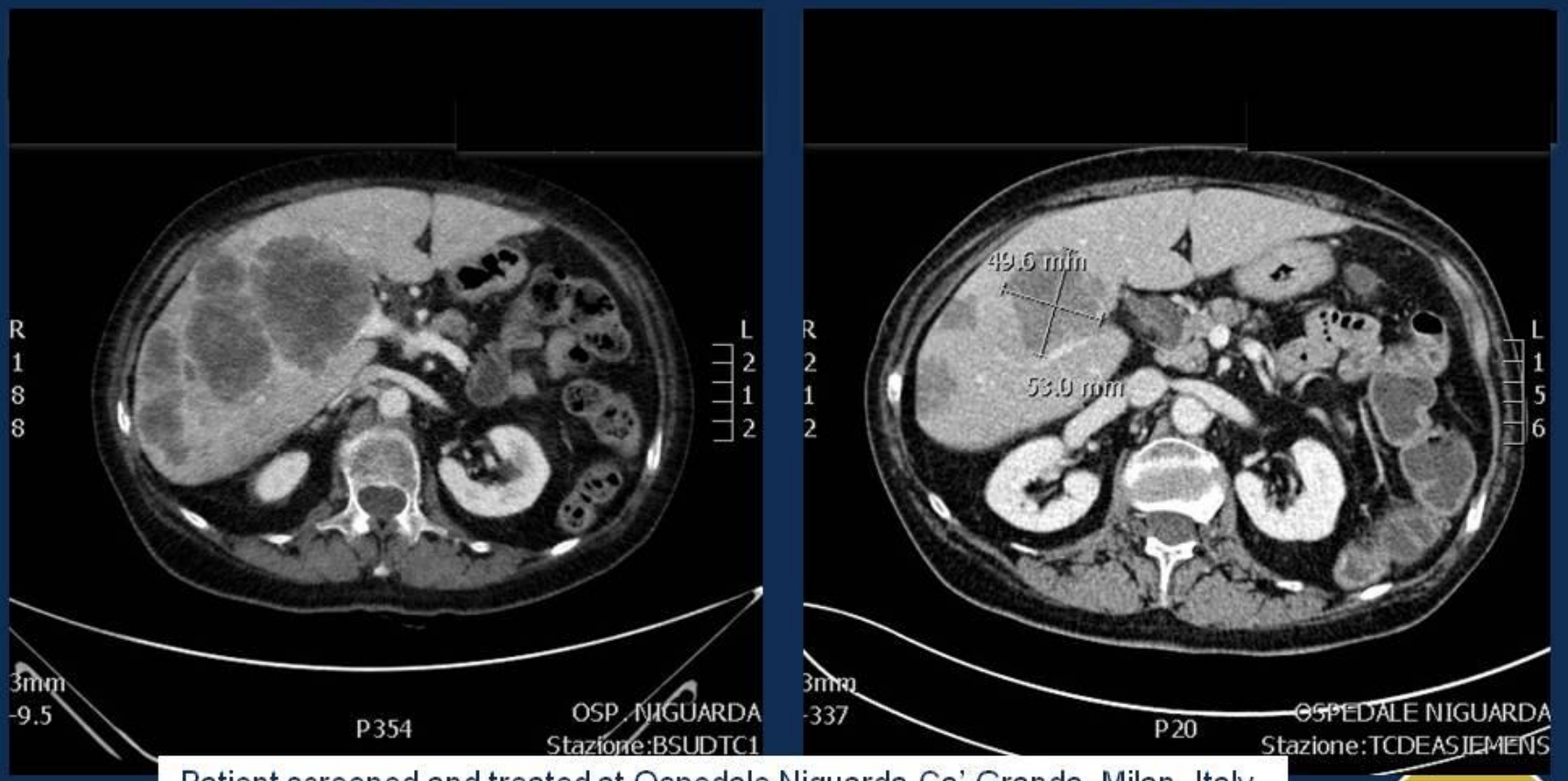
- *NTRK1*, *NTRK2* and *NTRK3* genes encode for TRKA, TRKB and TRKC receptors
- Cell line found to have TPM3-NTRK1 translocation
- TRK inhibition by RXDX-101 shows activity *in vitro* and *in vivo* in NTRK1 rearranged CRC cells





From: Ardini E., et al., Mol Oncol. 2014 Jun 12. pii: S1574-7891(14)00125-2. doi: 10.1016/j.molonc.2014.06.001

Partial Response in Patient with TrkA Rearranged Colorectal Cancer



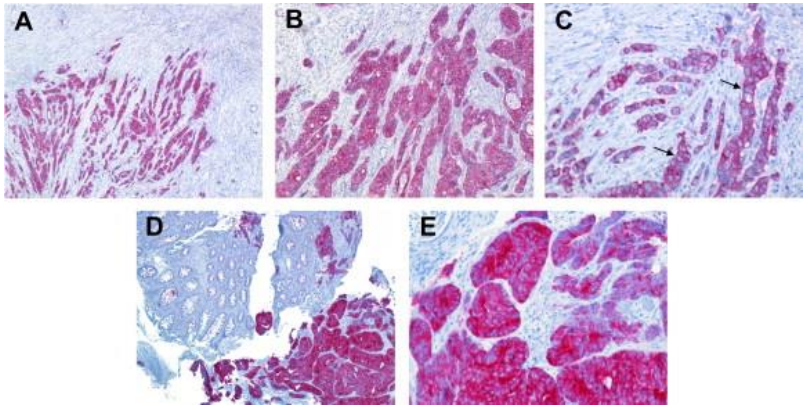
Patient screened and treated at Ospedale Niguarda Ca' Granda, Milan, Italy

ASCO

De Braud F et al., 2014 ASCO Annual Meeting, J Clin Oncol 32:5s, 2014 (suppl; abstr 2502)

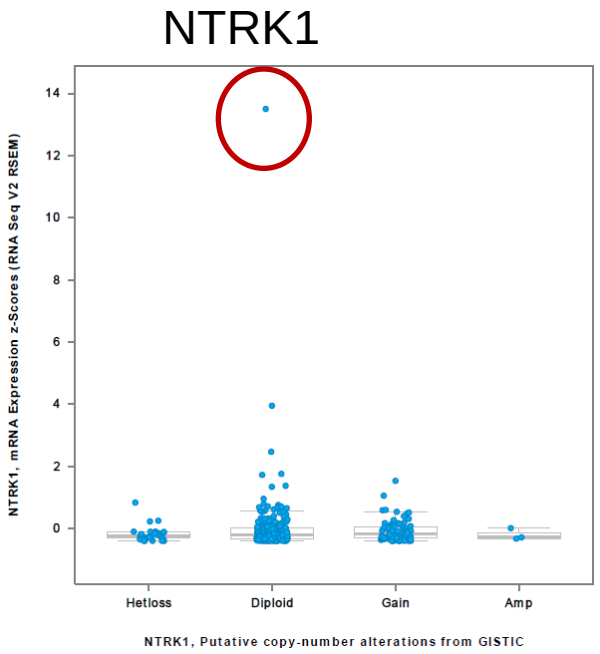
Prevalence of NTRK1 overexpression in CRC

1/66 (1.5%) CRC specimens (by RNA expression and IHC, re-arrangment confirmed by FISH)



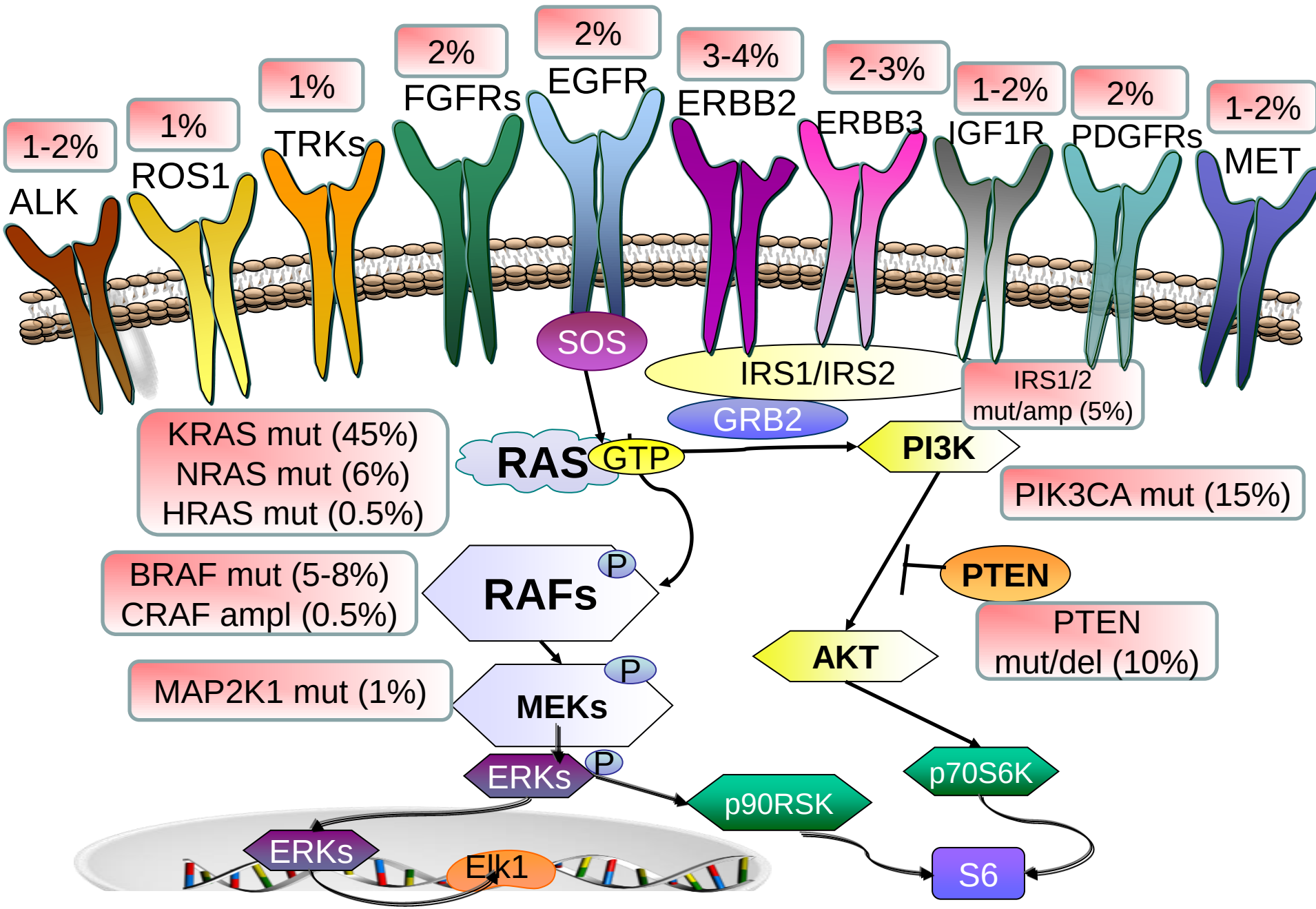
Ardini E., et al., Mol Oncol. 2014 Jun 12. pii: S1574-7891(14)00125-2. doi: 10.1016/j.molonc.2014.06.001

1/195 (0.5%) CRC specimens (by RNA Seq)

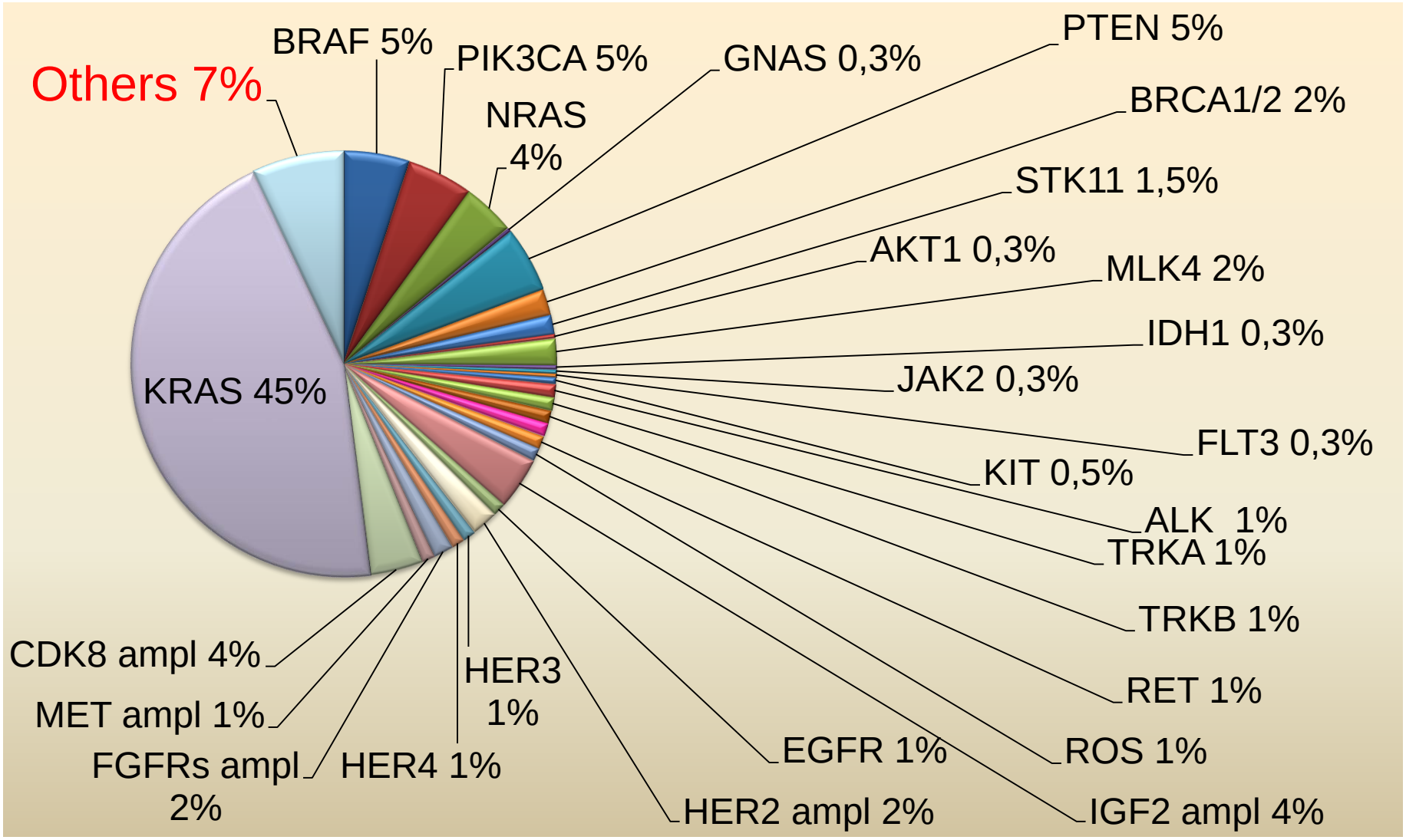


TCGA CRC dataset (195 complete tumors) interrogated through http://www.cbioportal.org/
Cerami E et al., Cancer Discov. 2012 May;2(5):401-4
Gao J et al., Sci Signal. 2013 Apr 2;6(269):pl1

Deregulation of RTK-RAS-PI3K signaling in CRC



Genomic classification of CRC: not there yet?



Challenging drivers as targets

- **Pinpointing exceptions in one tumour type needs big numbers:**
  - **Collect many cases and establish/find relevant preclinical models for functional validation (avoid mistake of translating from other tumour lineages)**

- **Identifying exceptions (and the contextual genetic milieu) needs integrated approaches with reliable outcomes:**
  - **Multi-dimensional genomic exploration of high-quality tumour material**

Defining clinically actionable targets

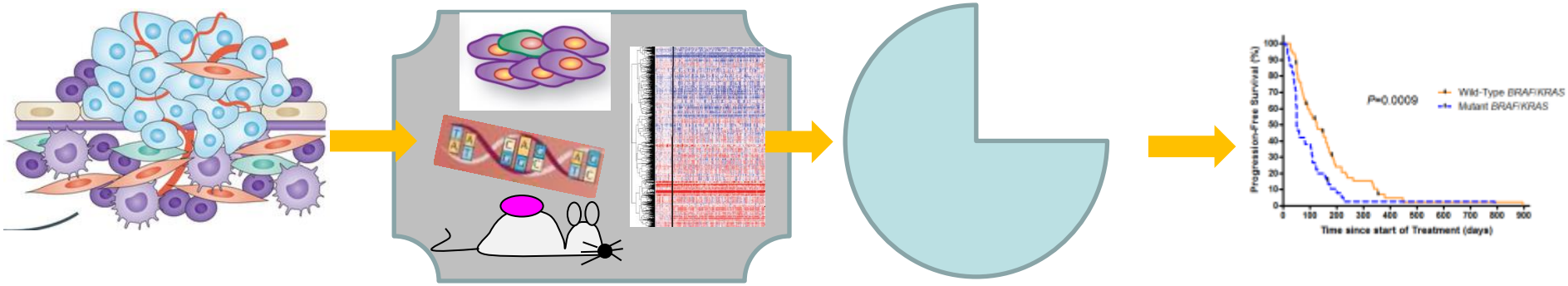
- Explore cancer genomics & study functional relevance in suitable preclinical models
- Find the biomarker(s) to best describe biologically distinct subtypes
- Design POC trial with the appropriate drug(s)

Tumour

Biology & ‘-omics’

Biomarkers

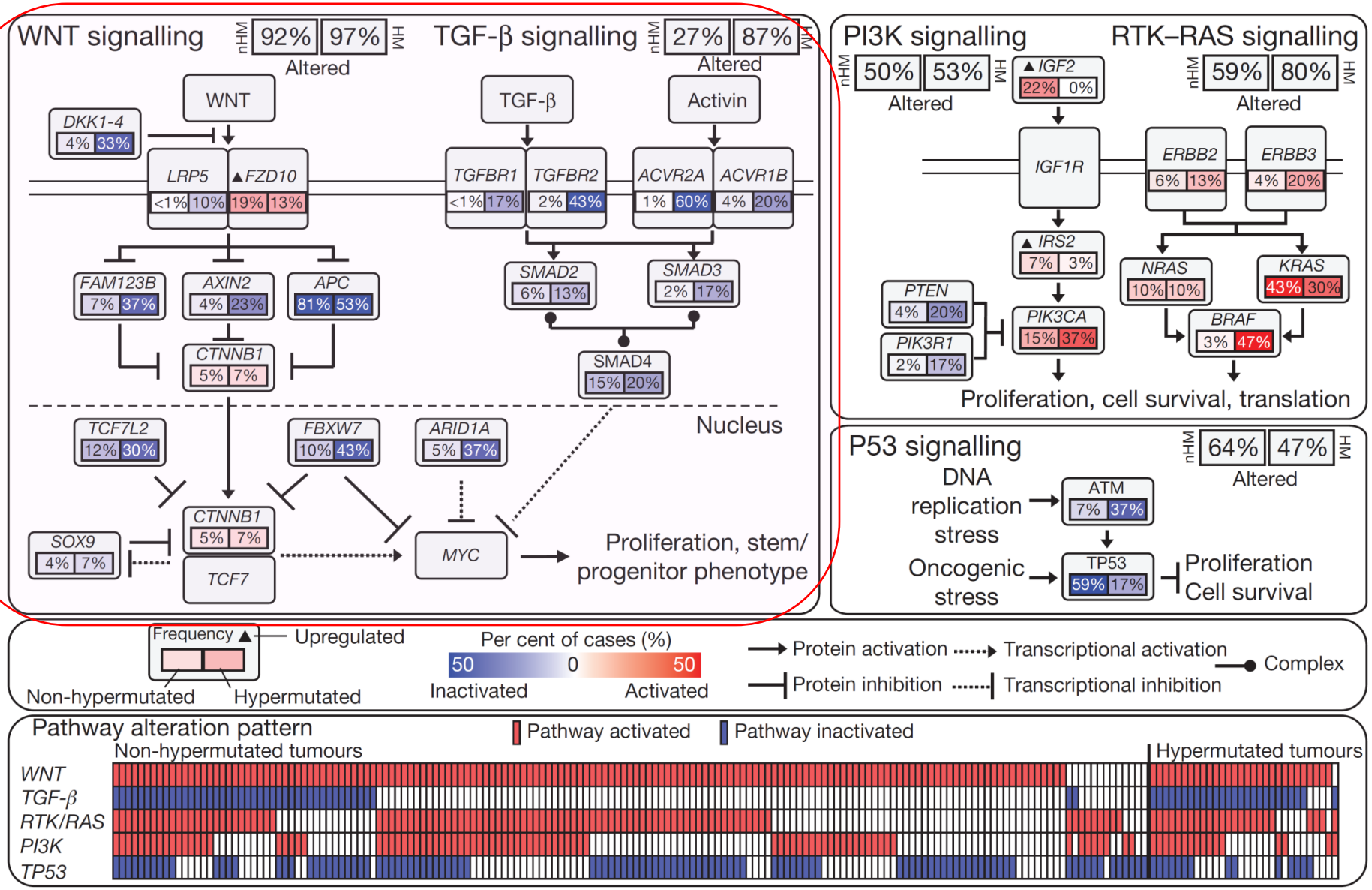
Trial



Outline

- Genomic alterations in CRC signalling pathways
- Emerging molecular determinants of resistance to EGFR targeted therapies in mCRC
- Validation of these molecular alterations as alternative ‘drivers’ of CRC tumorigenesis and progression
- **Challenging molecular alterations as actionable therapeutic targets within the context of CRC molecular landscape**

Deregulation of signalling pathways in CRC



The Cancer Genome Atlas Network, Nature **487**, 330-337 (2012)

Acknowledgments

- **IRCCS Candiolo –**
- **Experimental Clinical Molecular Oncology**
- Molecular Pharmacology (A. Bertotti & L. Trusolino)
- Molecular Genetics (A. Bardelli)
- Oncogenomics (E. Medico)
- Mariangela Russo
- Carlotta Cancelliere
- Gabriele Picco

Niguarda Hosp. Milan
Andrea Sartore Bianchi
Emanuele Valtorta
Salvatore Siena

AIRC
ASSOCIAZIONE ITALIANA PER LA RICERCA SUL CANCRO

FPRC Onlus

Netherlands Cancer Institute (NKI)
René Bernards
Chong Sun, Anirudh Prahallad

COLTHERES
colon therapy research consortium