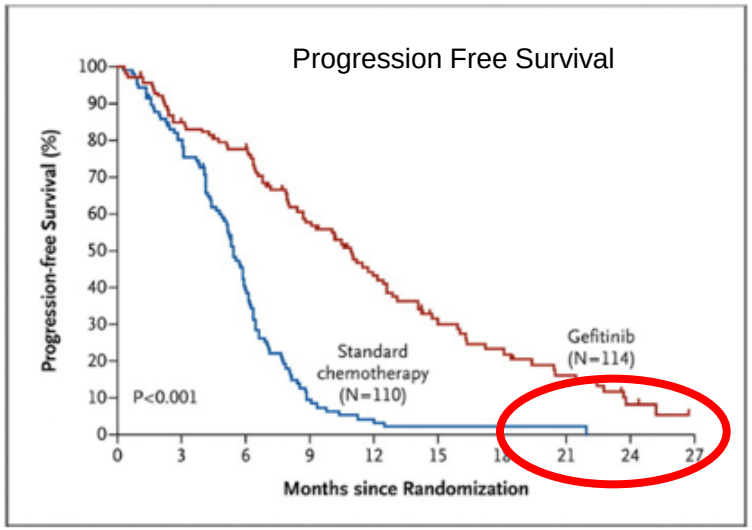
Rational drug combinations: Concepts and pre-clinical proof of principle

René Bernards

The Netherlands Cancer Institute
Amsterdam
The Netherlands

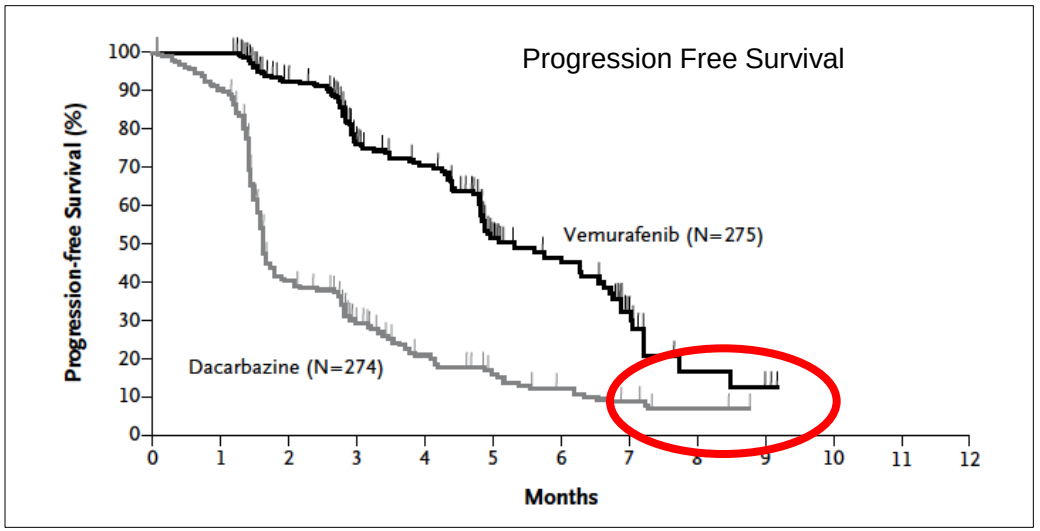
Targeted agents: dramatic, but short-lived responses

Lung cancer/Gefitinib

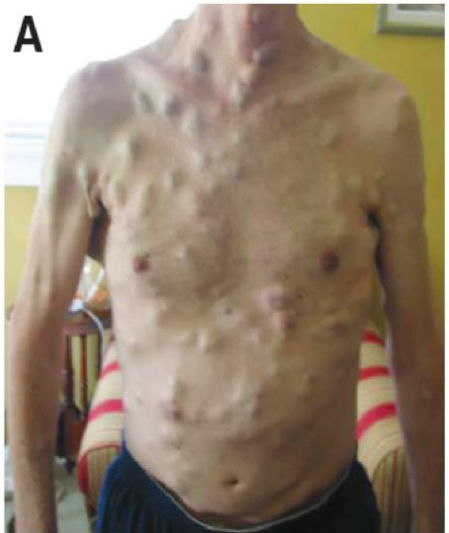


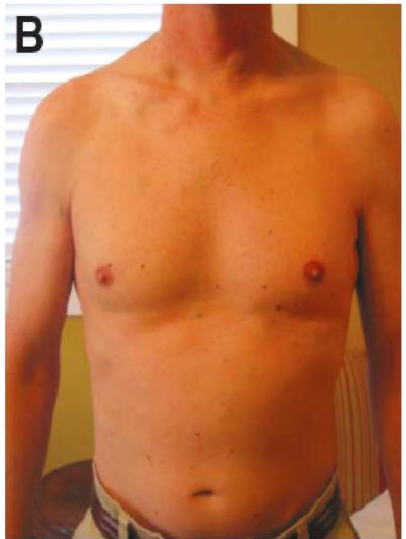
Maemondo et al., N Engl J Med 2010

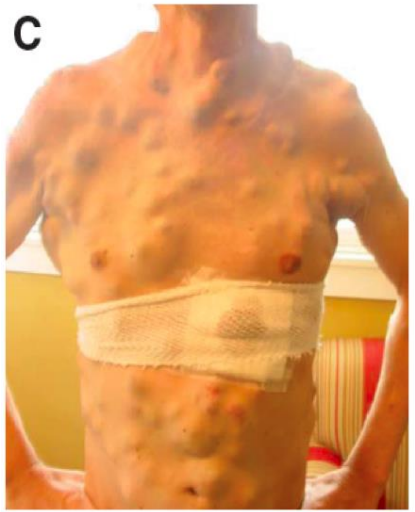
Melanoma /Vemurafenib



Chapman et al., N Engl J Med 2011







Endless two-way combinations of cancer drugs

PharmaTimes ONLINE

News Magazine JobSearch Competitions Events/Meetings Reports

WORLD NEWS | UK NEWS | CLINICAL NEWS | FREE NEWS HEADLINES | FREE RSS FE

Where am I? > Article

Nearly 1,000 cancer drugs in development in USA

WORLD NEWS | JUNE 01, 2012

SHARE +1 0

KEVIN GROGAN

Tweet 0

As the doors open for the American Society of Clinical Oncology meeting in Chicago, a report reveals that drugmakers in the USA are testing 981 medicines and vaccines to fight the disease.

An analysis published by the Pharmaceutical Research and Manufacturers of America notes that these therapies, which are either in clinical trials or under review by the US Food and Drug Administration, include 121 for lung cancer, 117 for lymphoma and 111 for breast cancer. The report notes the "steady improvements in cancer survivorship rates in the USA and quotes figures from the American Cancer Society which show that the death rate fell 22% for men and 14% for women between 1990 and 2007; this translates to 898,000 fewer deaths.

$$\frac{1{,}000 \times 1{,}000}{2} - 1000 = 499{,}000 \text{ combinations}$$

Test each combination in 1,000 patients:

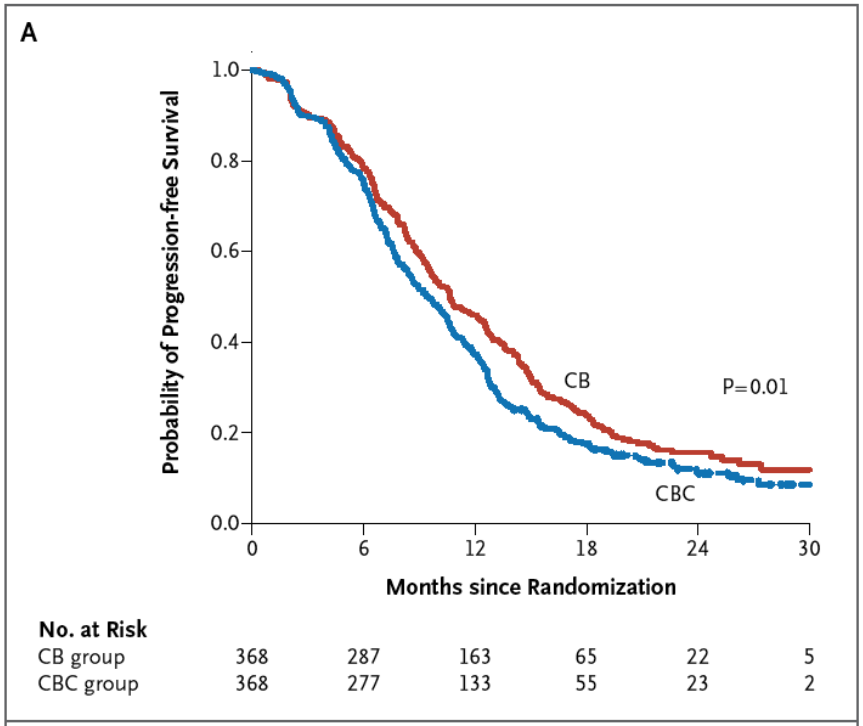
499,000,000 patients needed

“Fool around and hope to get lucky” trials

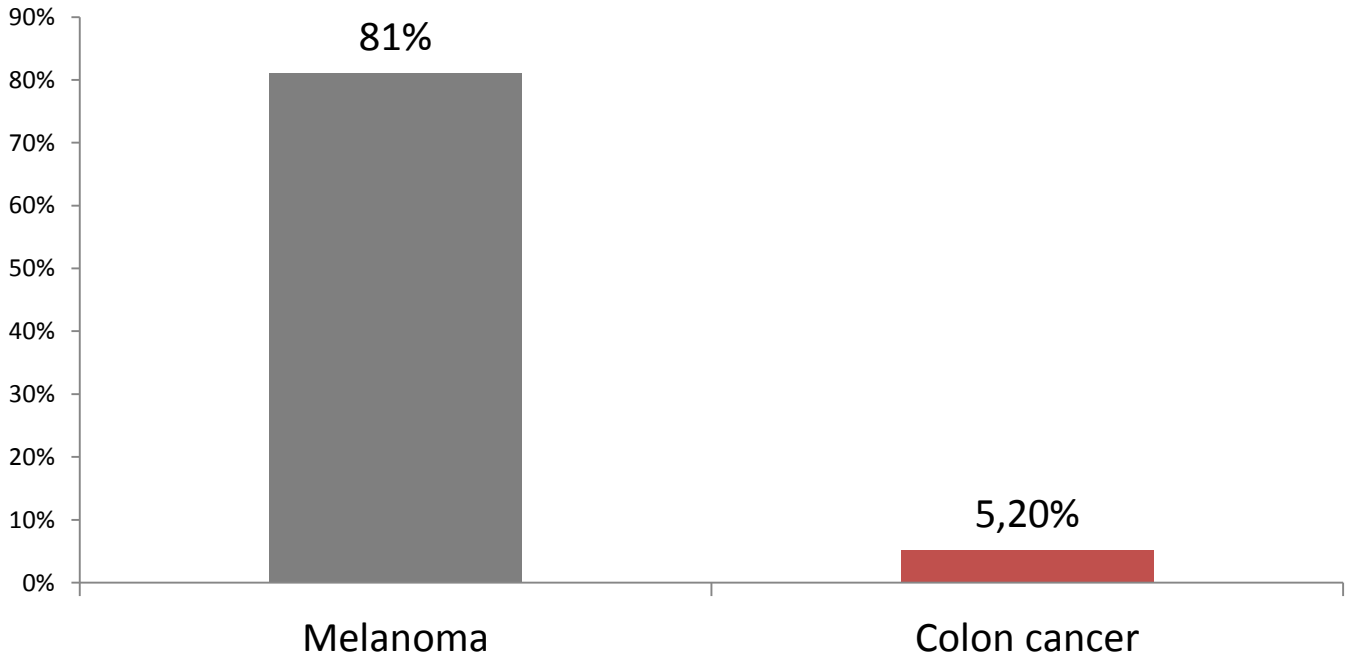
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 5, 2009 VOL. 360 NO. 6

Chemotherapy, Bevacizumab, and Cetuximab in Metastatic Colorectal Cancer

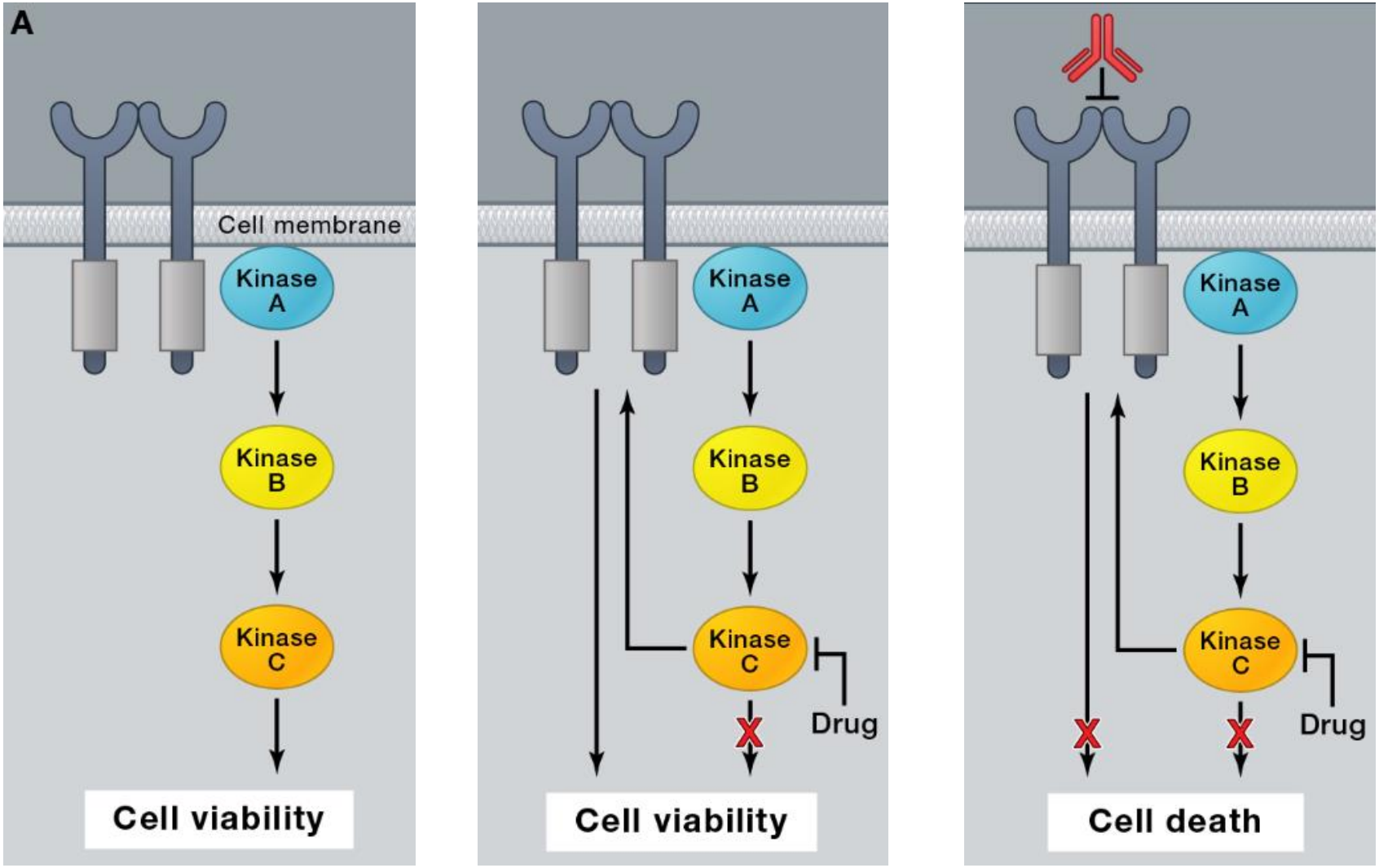


Differential response of BRAF inhibition in *BRAF* mutant melanoma versus colon cancer



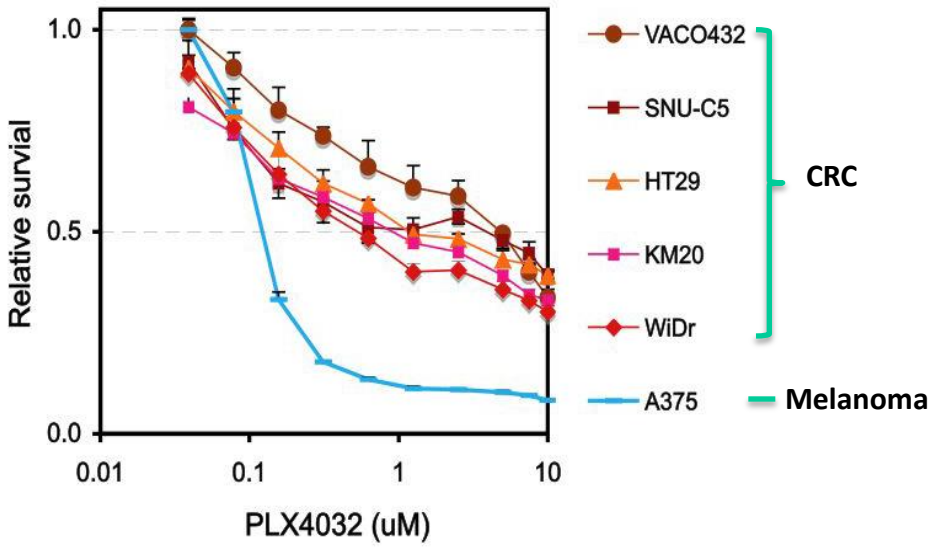
N Engl J Med. 2010 363:809-19
Kopetz et al., ASCO 2010

Is feedback regulation responsible for the resistance of CRC cells to BRAF inhibitors?

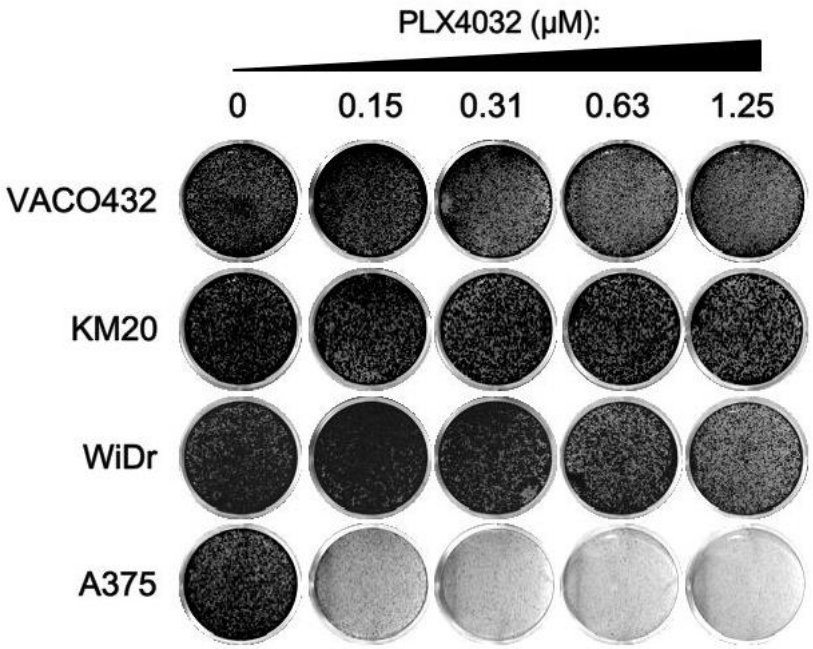


BRAF^{V600E} mutant CRC cell lines are also less responsive to PLX4032 than melanomas having the same mutation

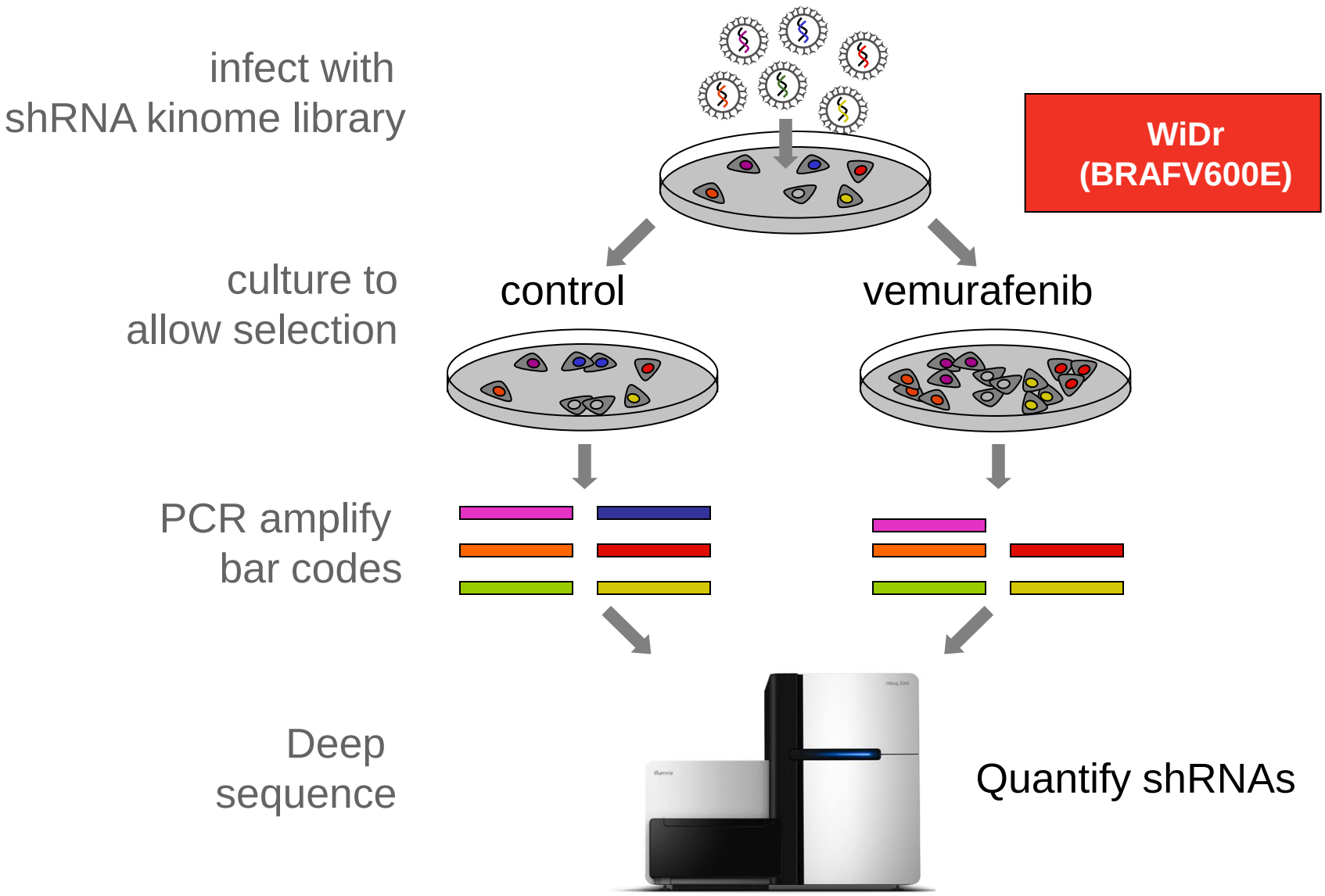
Short-term cell viability assay



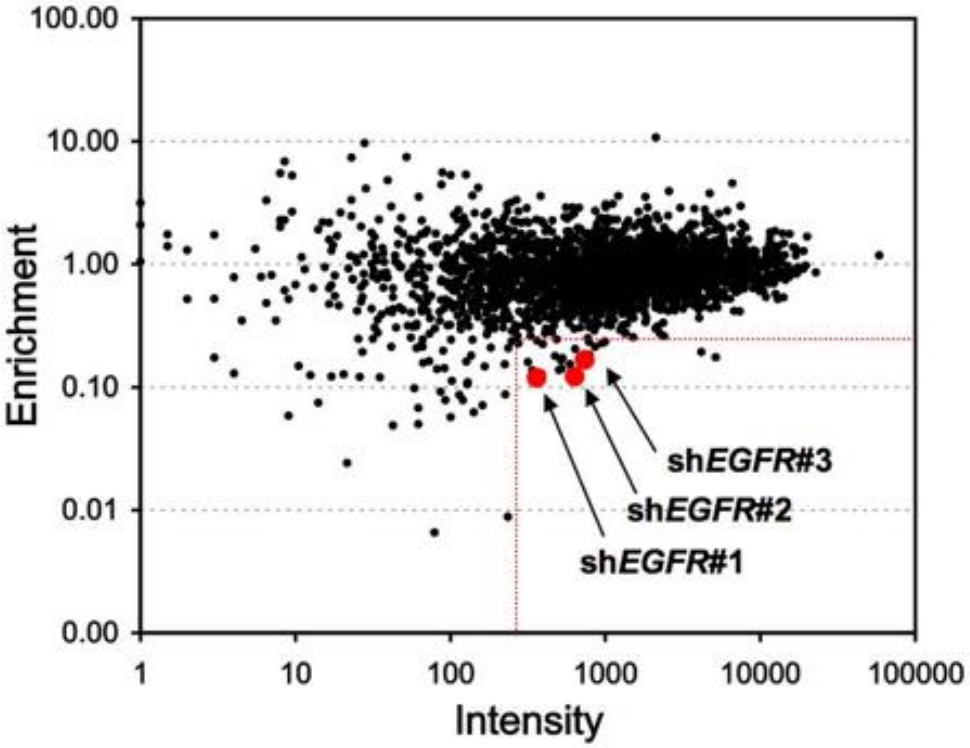
Long-term colony formation assay



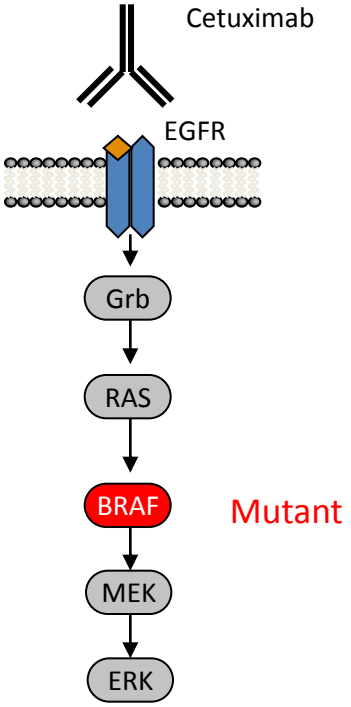
Synthetic lethal shRNA screen: Inhibition of which kinase synergizes with PLX in BRAF mutant CRC?



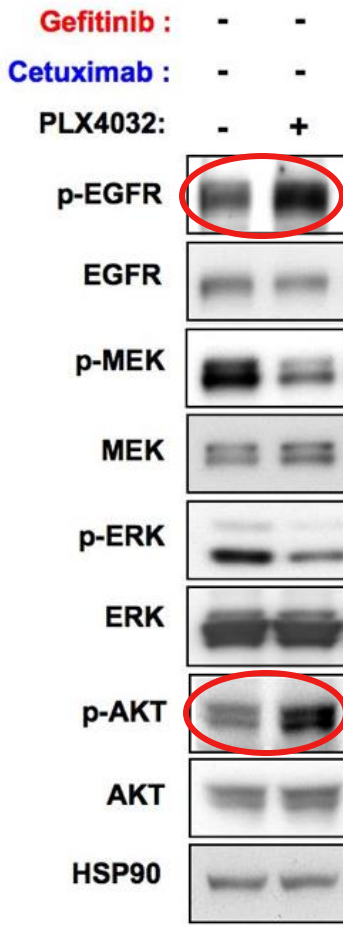
Inhibition of EGFR makes BRAF mutant CRC cells vulnerable to BRAF inhibition



Cutoff:
> 300 reads (untreated)
> 5 fold negatively enriched



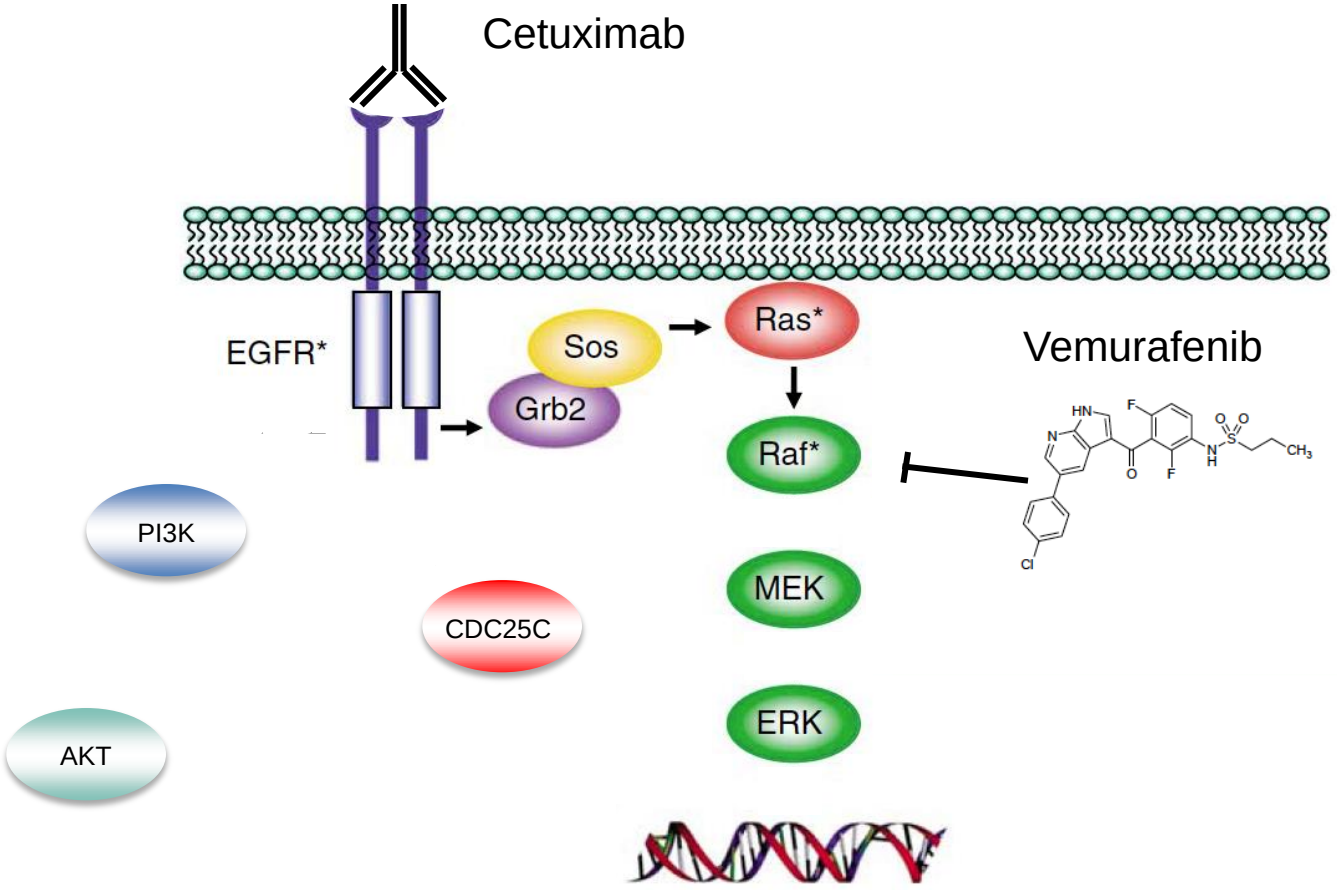
$BRAF^{V600E}$ inhibition causes feedback activation of EGFR



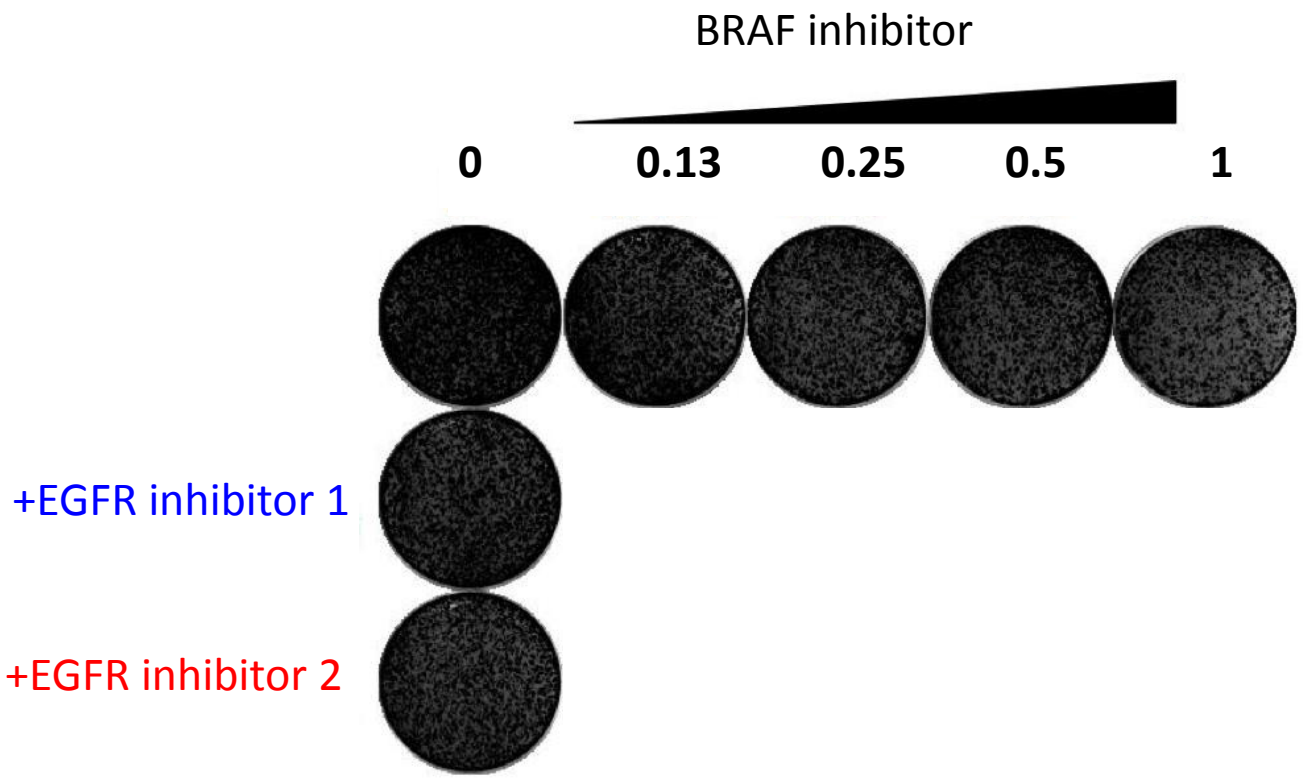
VACO (*$BRAF^{V600E}$*)

Also seen in WiDr and KM20 (*$BRAF^{V600E}$*)

Feedback regulation of EGFR by BRAF inhibition



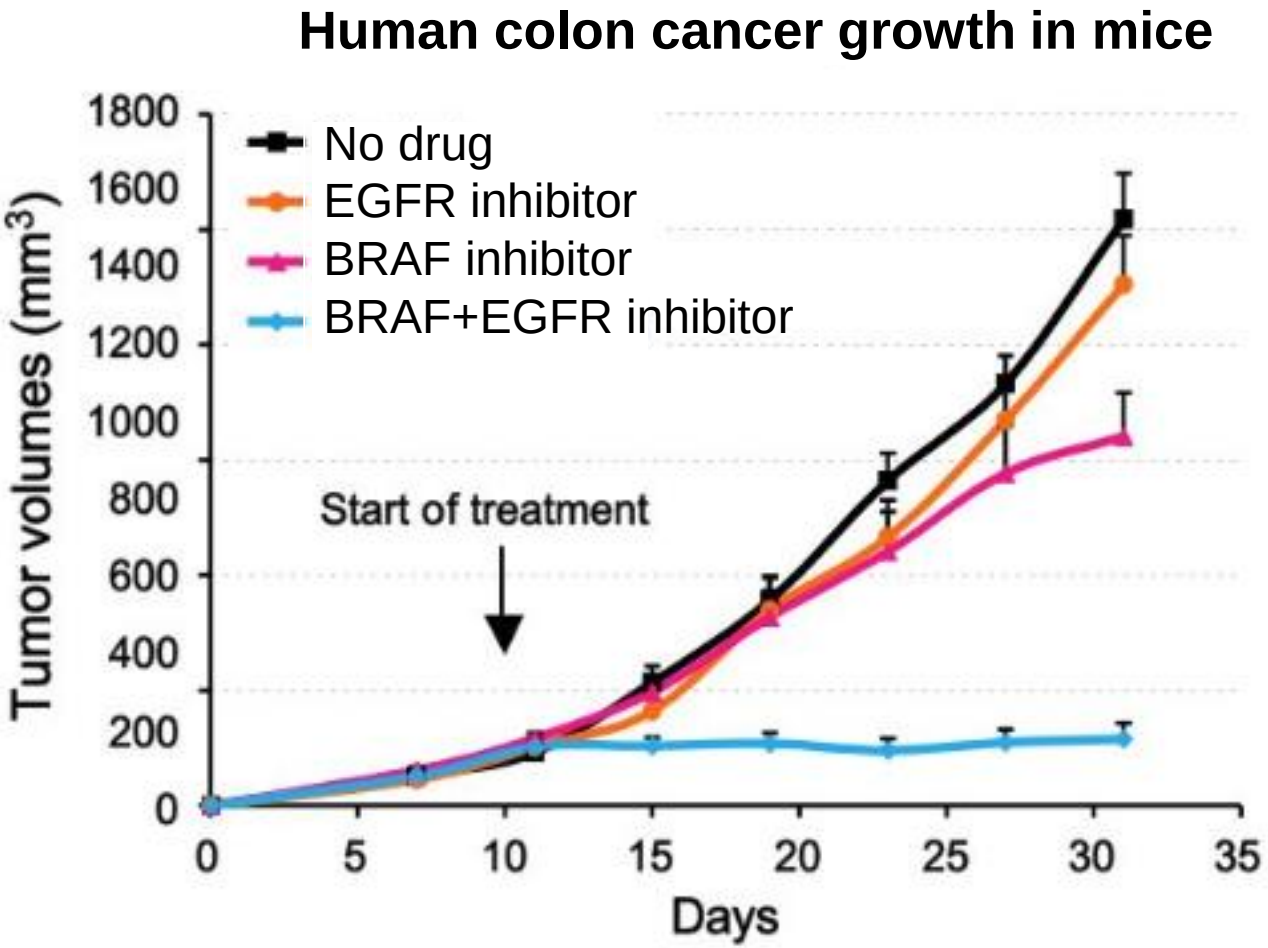
Synergistic response of *BRAF*^{V600E} colon cancer to EGFR and BRAF inhibition



BRAF mutant
Colon cancer cells

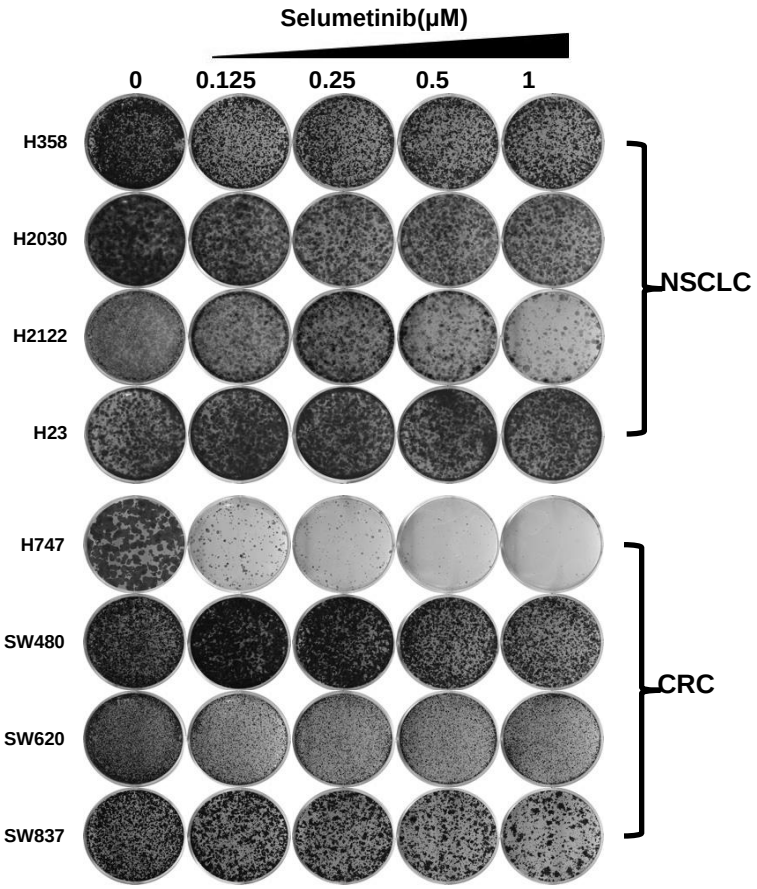
Cetuximab 1.25 μg/ml
Gefitinib 0.125 μM

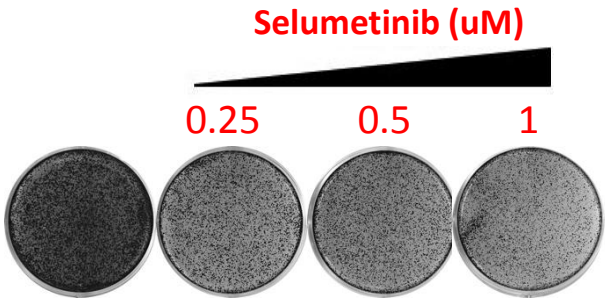
EGFR and BRAF inhibition synergize to suppress *BRAF* mutant colon cancer growth



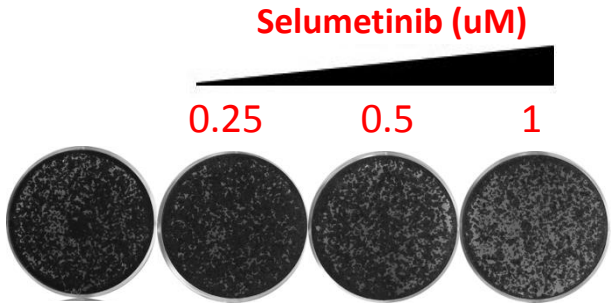
Prahallad et al, Nature 2012

Is the combination of MEK and EGFR inhibitors also effective in *KRAS* mutant cells?



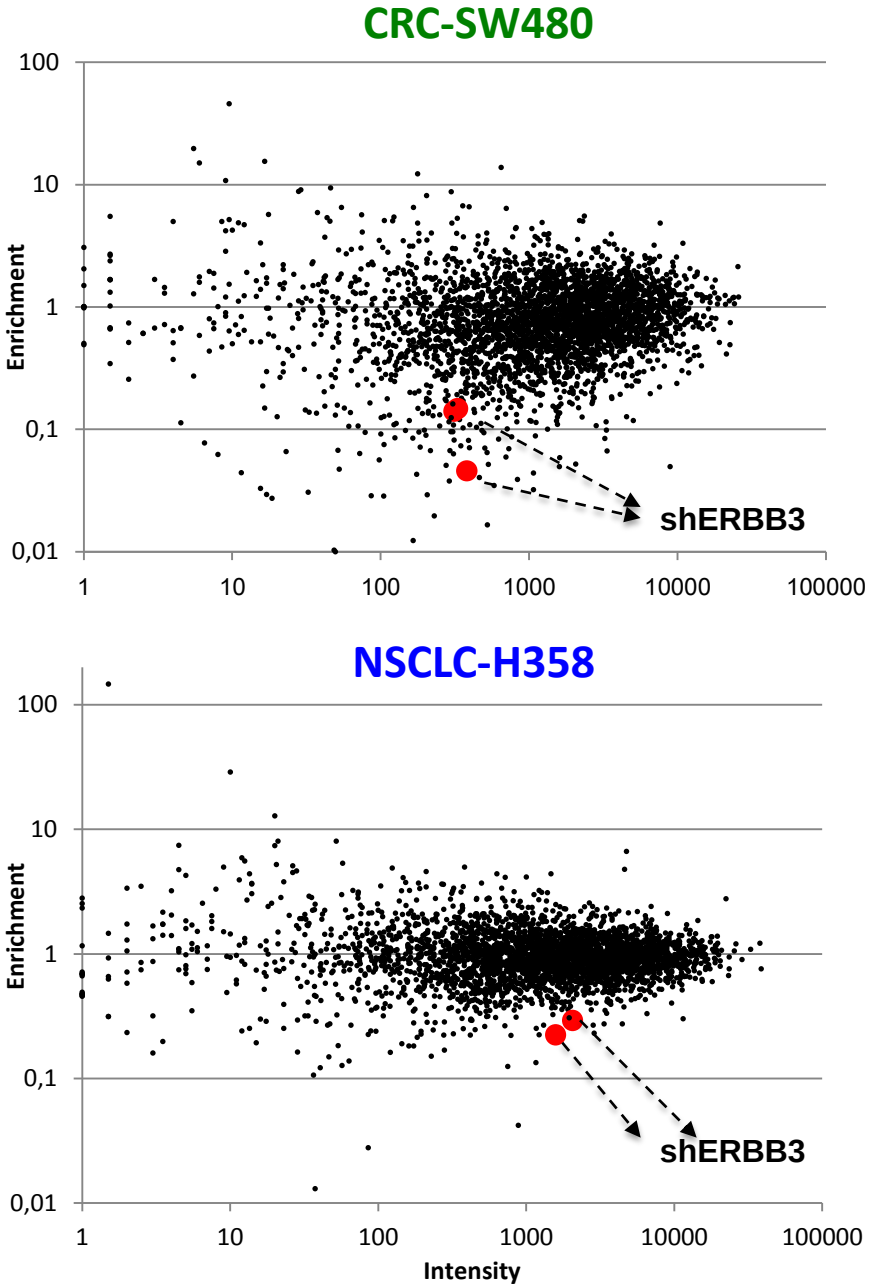


CRC: SW620(*KRAS*^{G12V})

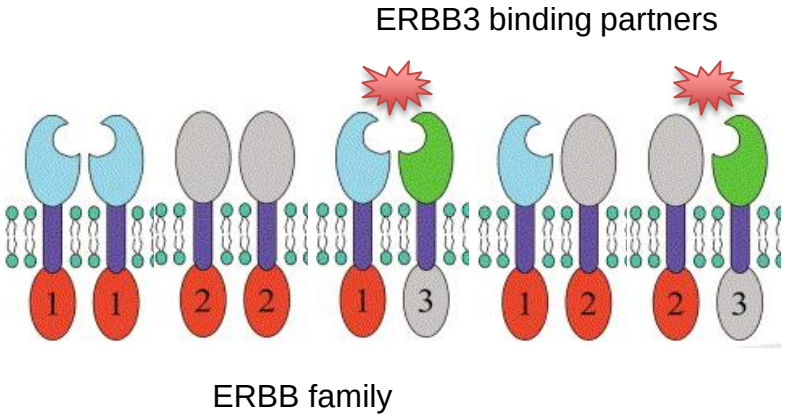


NSCLC: H358 (*KRAS*^{G12C})

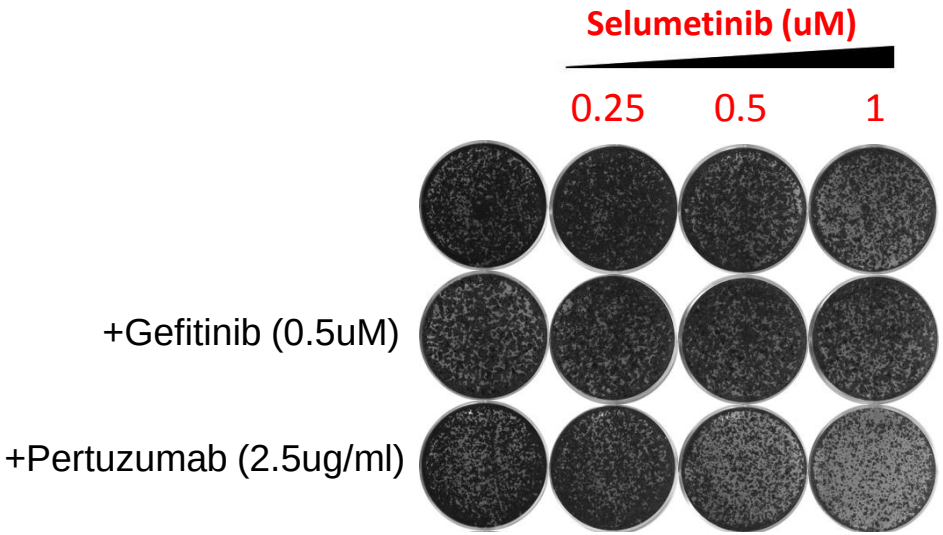
RNAi screen for enhancers of MEK inhibitors



ERBB3 activation is mostly dependent on heterodimerization



Targeting EGFR and ERBB2 sensitizes *KRAS* mutant cells to MEK inhibitor

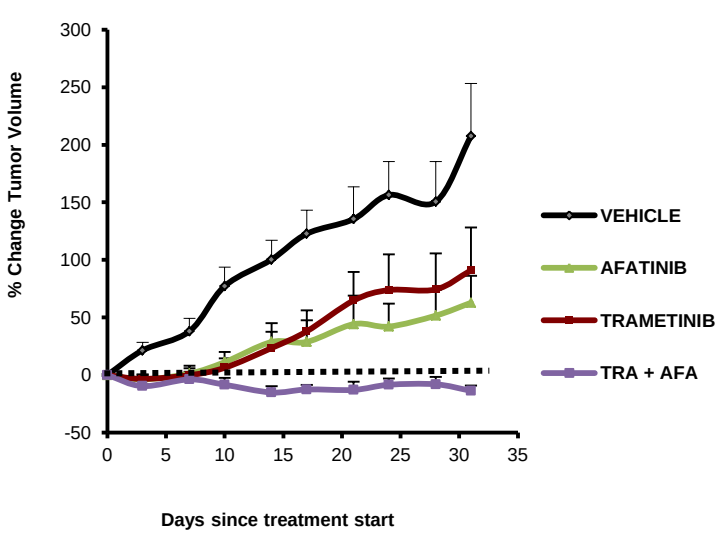


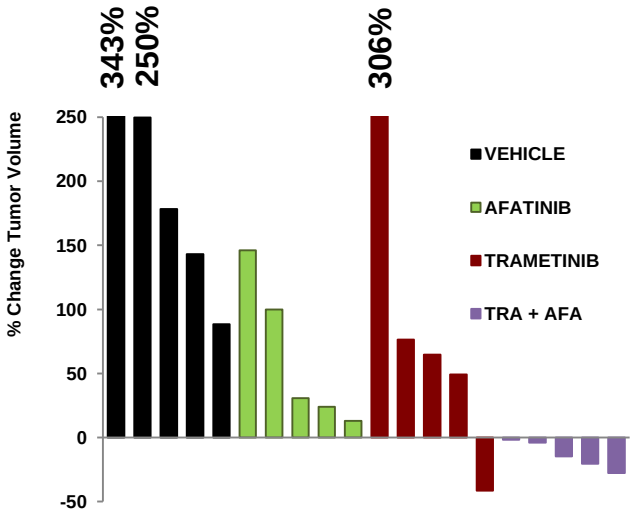
H358 ($KRAS^{G12C}$)

Also seen in H2030, H2122,SW837, SW480 and SW620

- Gefitinib: EGFR inhibitor
- Pertuzumab: ERBB2-targeting monoclonal antibody
- Afatinib: EGFR and ERBB2 inhibitor
- Dacomitinib: EGFR, ERBB2 and ERBB4 inhibitor

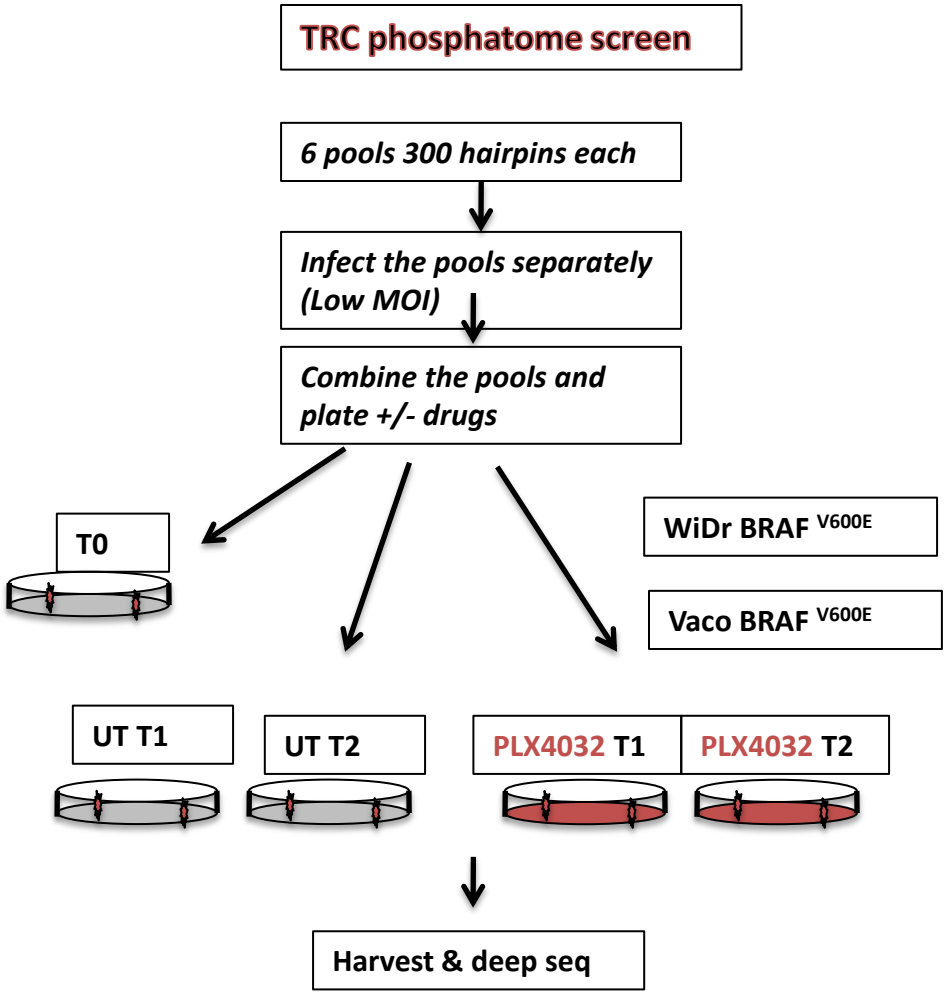
Targeting EGFR and ERBB2 sensitizes *KRAS* mutant cells to MEK inhibitor in a xenograft model

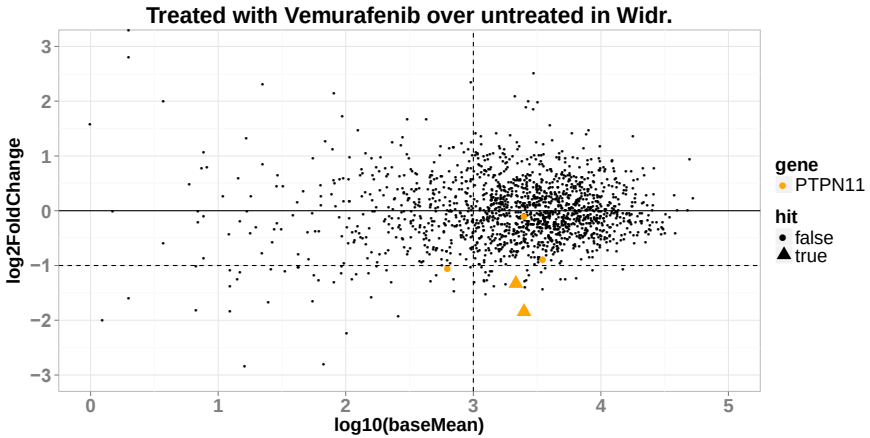




H2122 xenografts

Genetic screen to identify phosphatases synthetic lethal with BRAF inhibition in *BRAF* mutant CRC



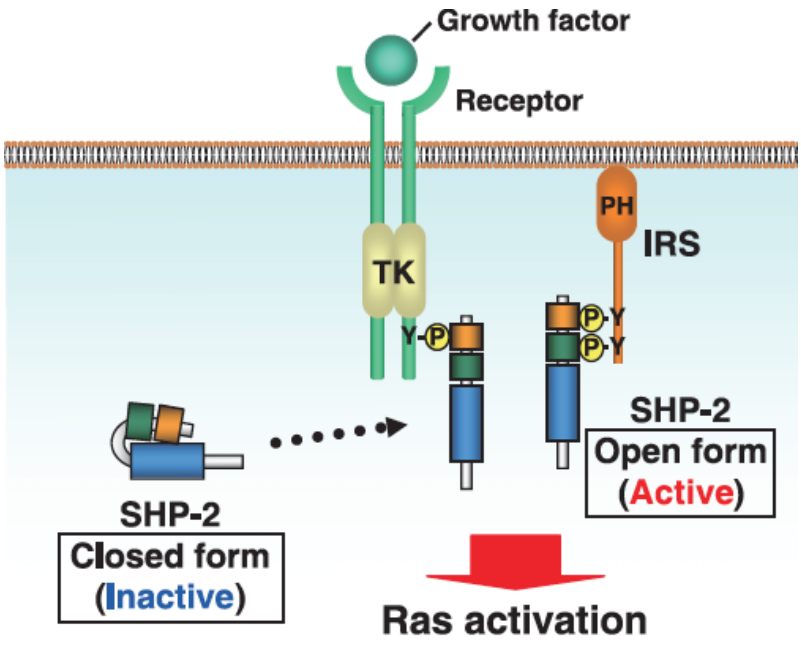


Result from the screen

PTPN11/SHP2

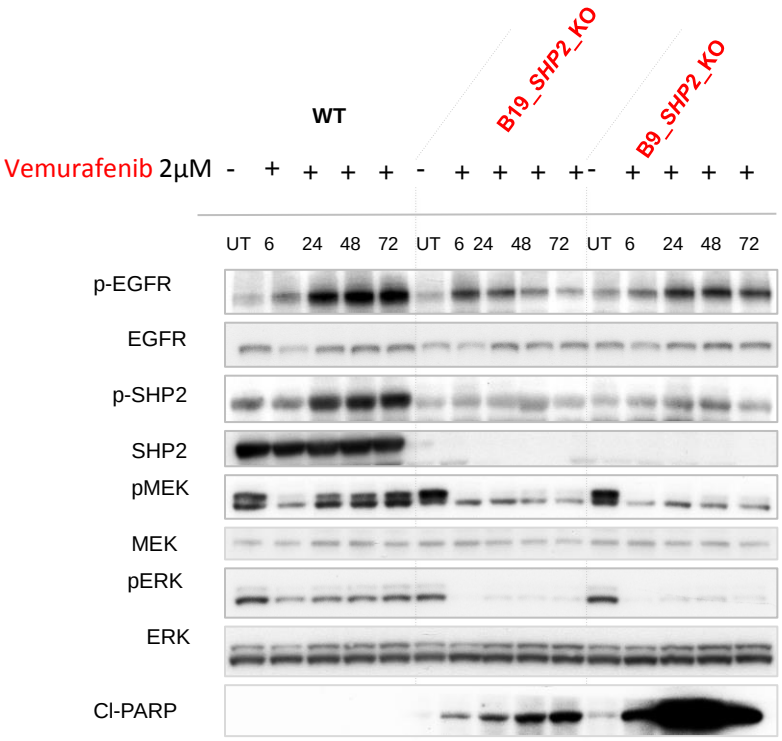
PTPN11/SHP2 is required for RTK signaling

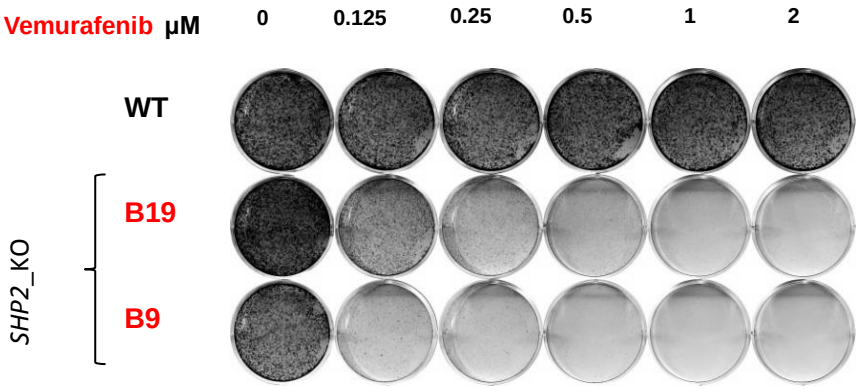
- Is a member of a family of cytoplasmic Src homology 2 (SH2) domain-containing protein tyrosine phosphatases.
- The N-SH2 domain selectively bind to phosphotyrosyl motifs on RTKs
- Is required for activation of RAS signaling downstream of RTKs



BRAF mutant CRC cells lacking PTPN11/SHP2 are sensitive to vemurafenib

VACO 432 *BRAF* ^{V600E}*CRC*

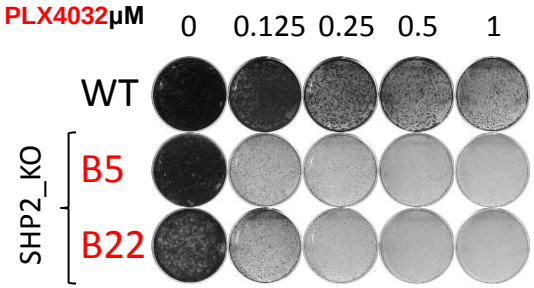


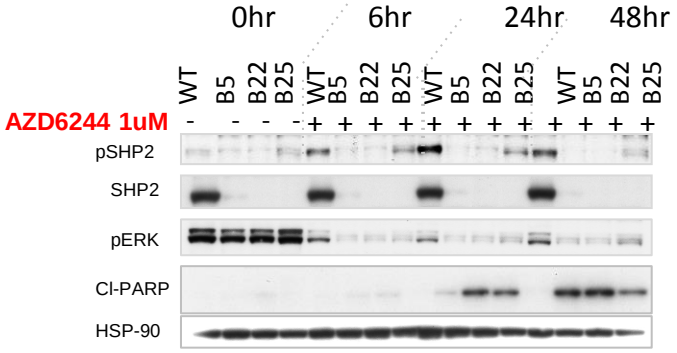


Also seen in Widr and KM20

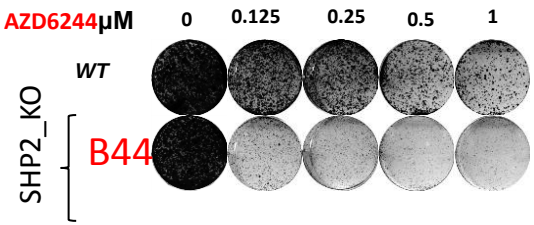
Loss of PTPN11/SHP2 also confers sensitivity to MEK inhibition in *KRAS* mutant tumors

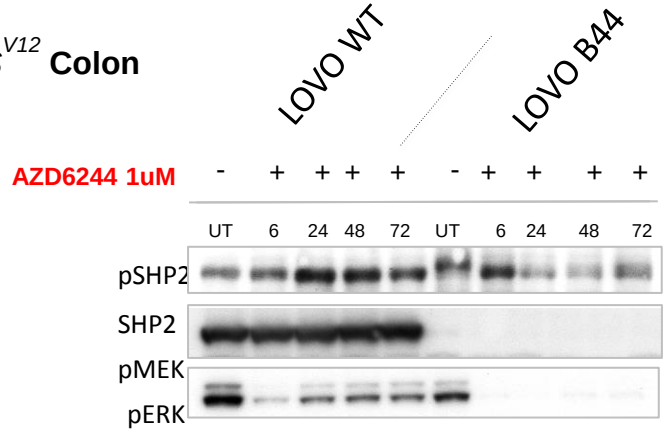
PANC10.05 *KRAS* ^{V12}*PDAC*

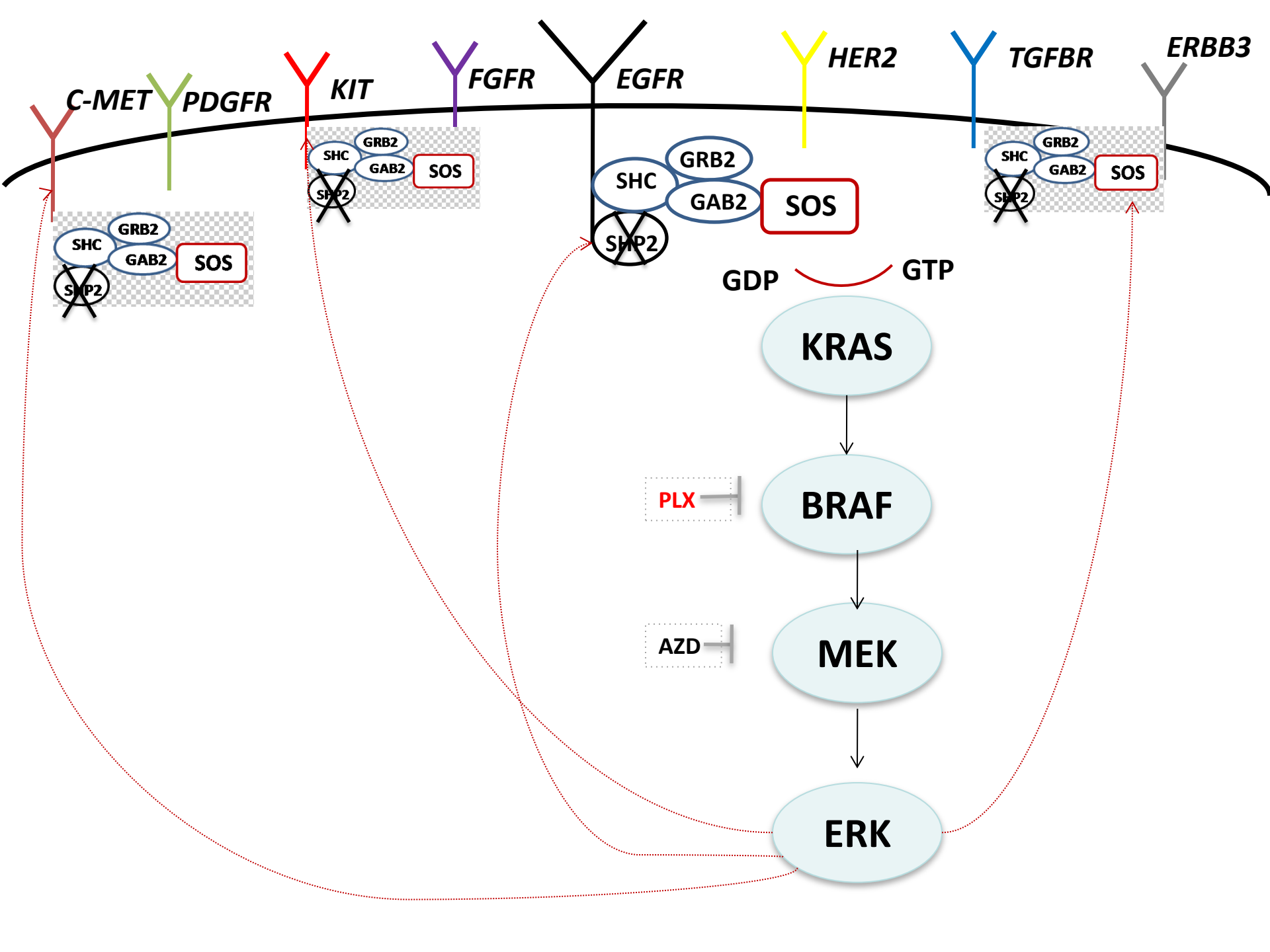




LOVO *KRAS*^{V12} **Colon**






C-MET
PDGFR
KIT
FGFR
EGFR
HER2
TGFBR
ERBB3
GRB2
SHC
GAB2
SOS
SHP2
GDP
GTP
KRAS
PLX
BRAF
AZD
MEK
ERK

Acknowledgements

The people involved:

Chong Sun
Liqin Wang
Sidong Huang
Anirudh Prahallad
Prashanth Kumar
Wipawadee Grernrum
Roderick Beijersbergen

Collaborators:

Jan Schellens (NKI)
Robin van Geel (NKI)
Caroline Robert (IGR)
John Haanen (NKI)
Jelle Wesseling (NKI)
Federica Di Nicolantonio (IRCC)
Alberto Bardelli (IRCC)

Our funding sources:

NWO
European Research Council Executive Agency erc
Cancer Systems Biology Center
STAND UP TO CANCER
KNAW
RATHER Rational Therapy for Breast Cancer
CancerGenomiCs.nl
EurocanPlatform
COLTHERES personalized therapies
KWF KANKER BESTRIJDING
MERCK
AstraZeneca