Targeted therapy for melanoma

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Memorial Sloan-Kettering Cancer Center

Disclosures

- I will discuss off-label use of trametinib.
- I have served as a consultant for Pfizer, Novartis, Loxo Oncology.

How do we accelerate drug discovery?

1. Define the Targets – **V600E BRAF**

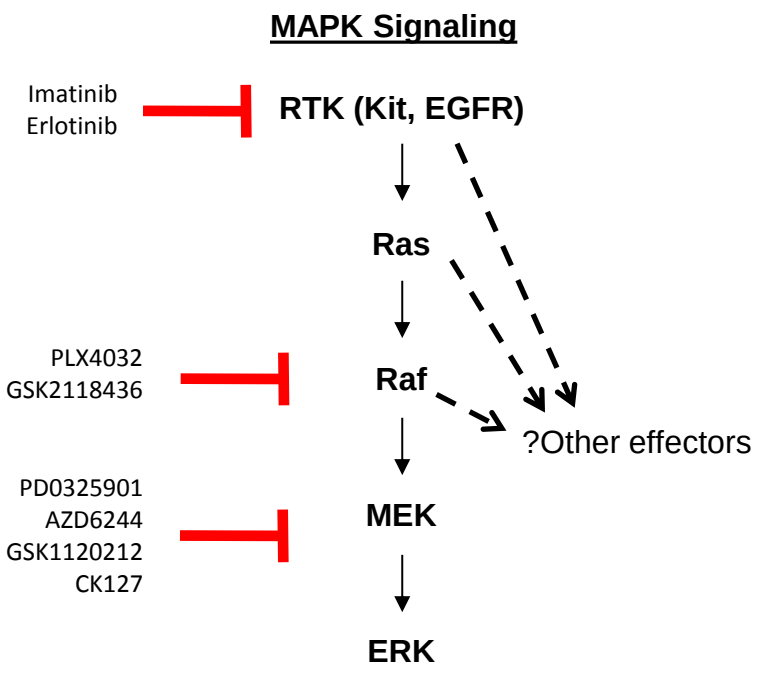
2. Identify a "drug" – **MEK/RAF inhibitor**

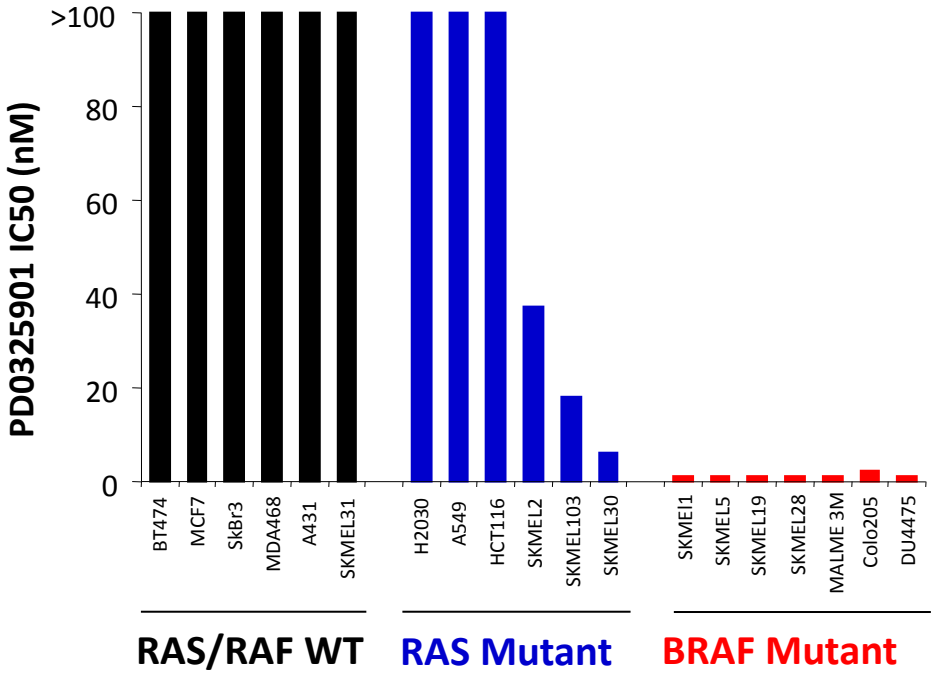
3. Identify the Patients - **Tumor harbors a BRAF mutation**

If correct "Target" and correct "Patient" – Why no Response/Cure?

- Inadequate pathway inhibition → Resistance
- Other co-mutations (need combo) → Resistance
- Rapid adaptation → Resistance

BRAF mutation predicts for sensitivity to MEK inhibition





Solit et al., Nature, 2006

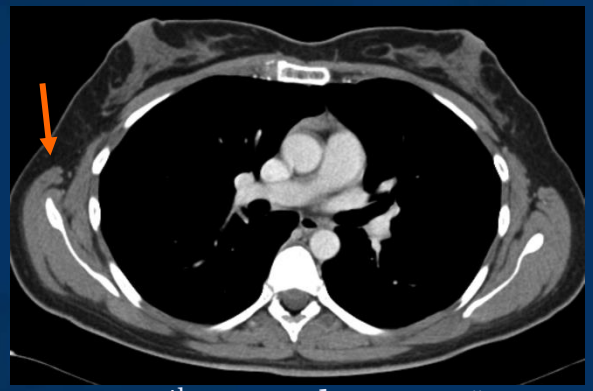
Summary of objective tumor responses

Patients with RECIST measurable disease at entry to study

Objective tumor response/ unconfirmed response	No. of patients (%), n=21
Complete response	1 (4.8)
Unconfirmed partial response	1 (4.8)
Stable disease ≥6 weeks	6 (28.6)
Progressive disease	4 (19.0)
Not evaluable	9 (42.9)



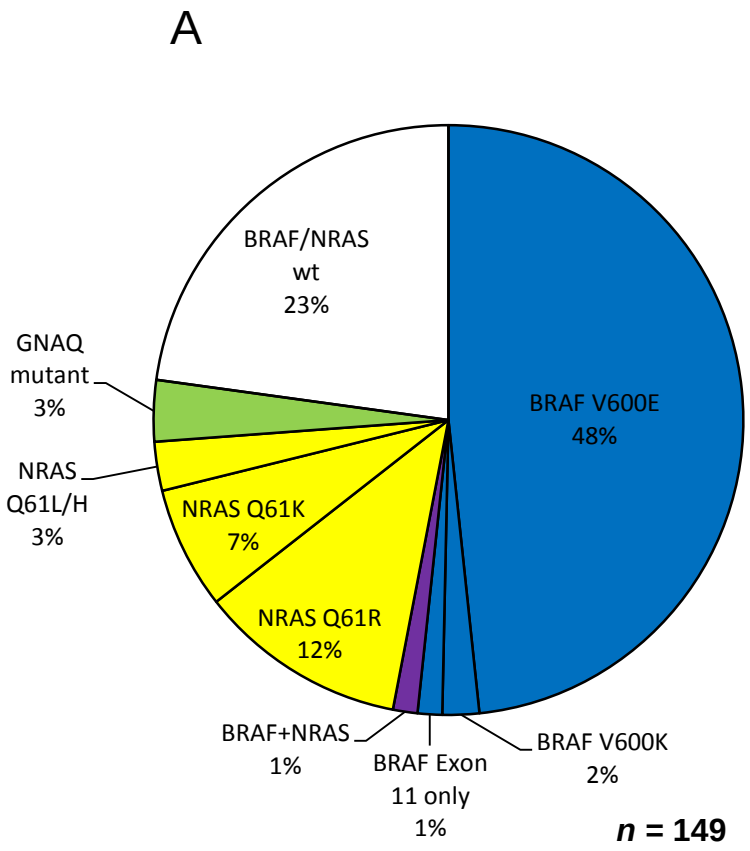
24th July 2007*

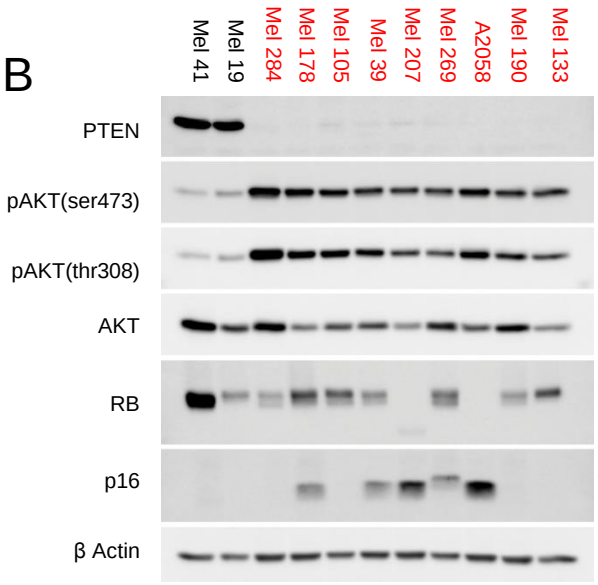


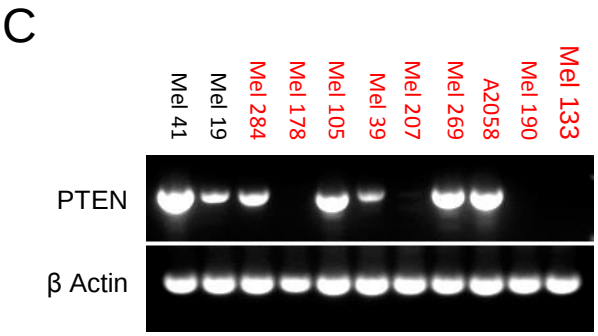
7th November 2007*

* BRAF mutation positive melanoma patient with a complete response after 16 weeks of therapy

PTEN null melanoma cells harboring V600E BRAF mutation





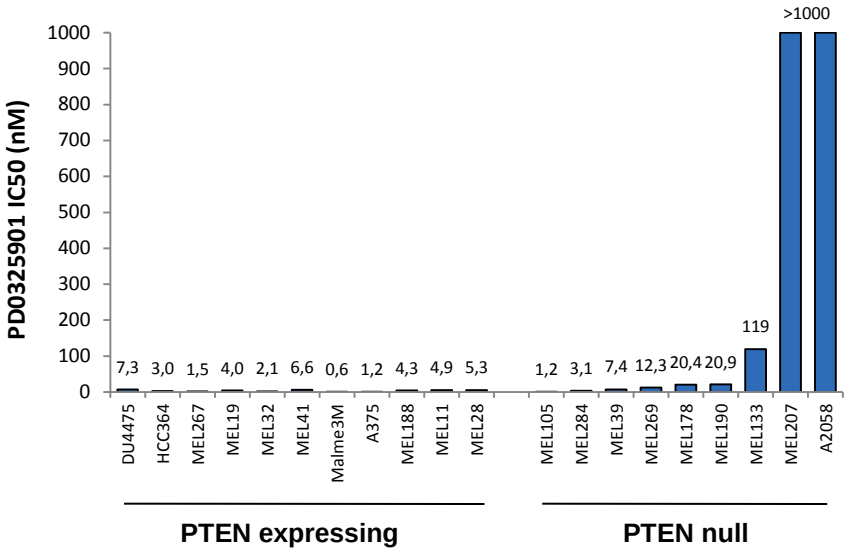


PTEN null/low
PTEN expressing

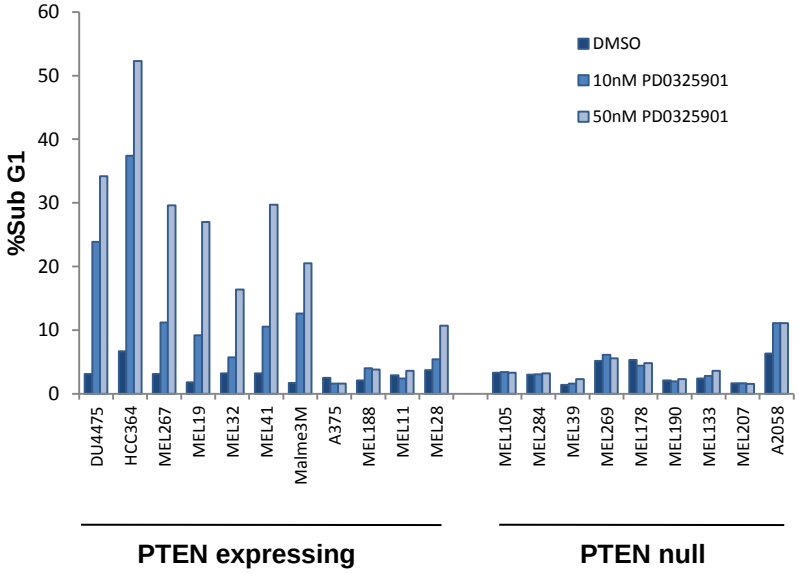
Xing et al., Oncogene, 2011

BRAF mutant/PTEN null cells exhibit a cytostatic response to MEK-inhibition

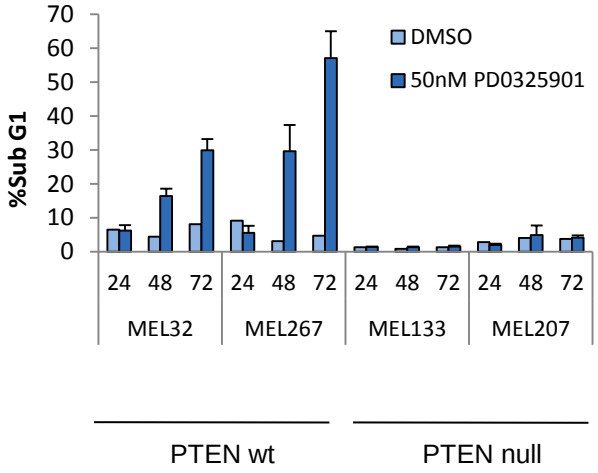
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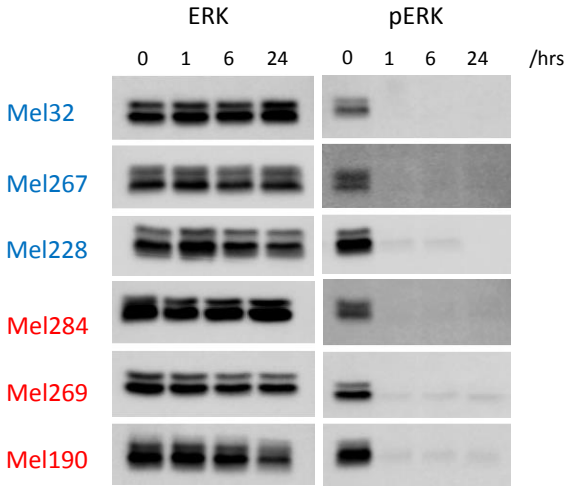
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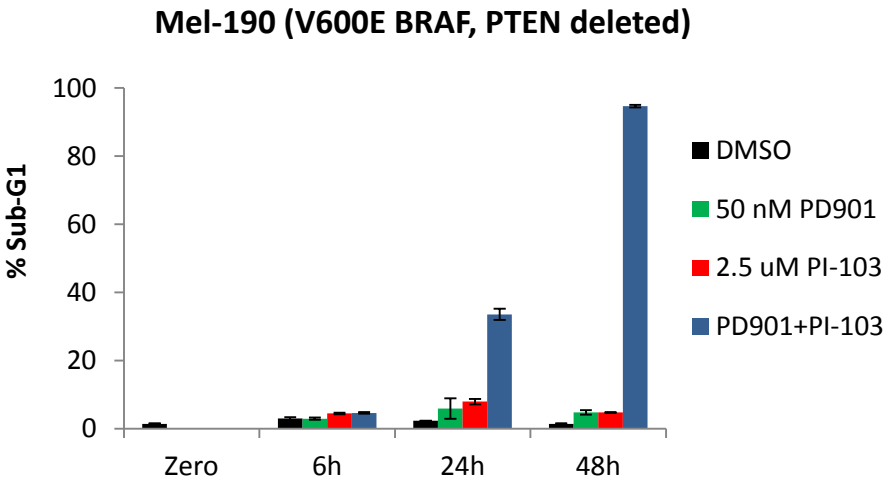


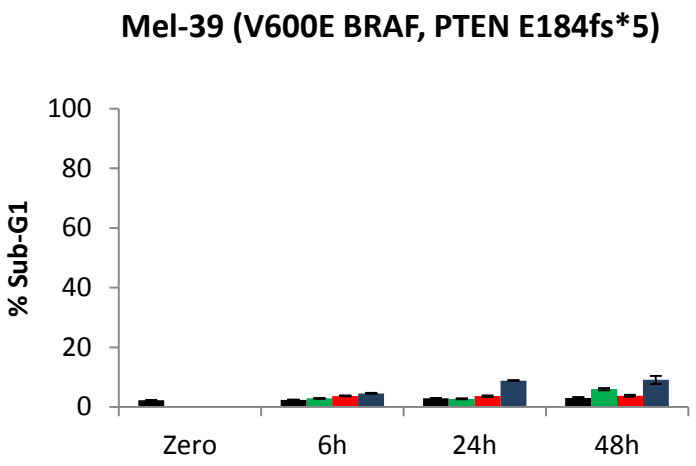
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Xing et al., Oncogene, 2011

Concurrent MEK/PI3K inhibition is synergistic in some BRAF mutant/PTEN null models

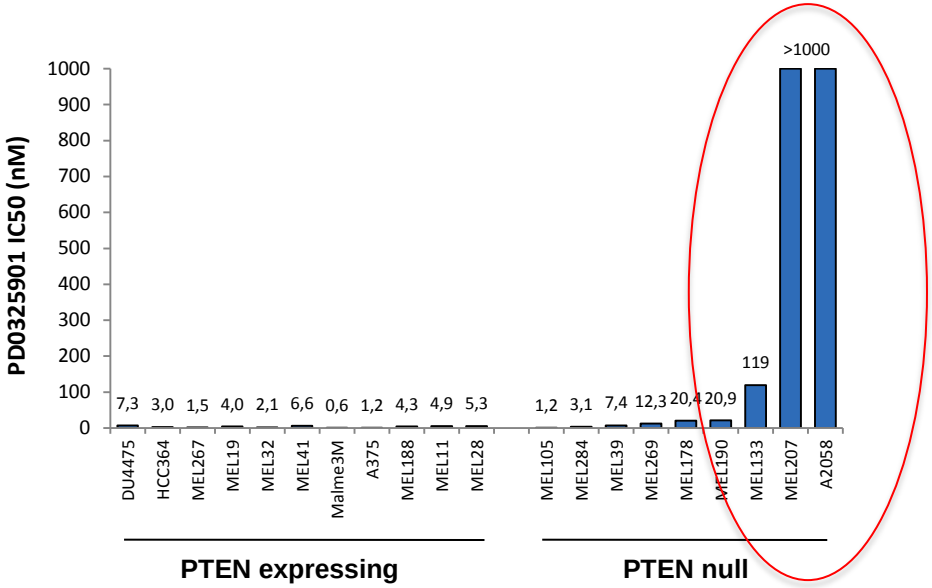




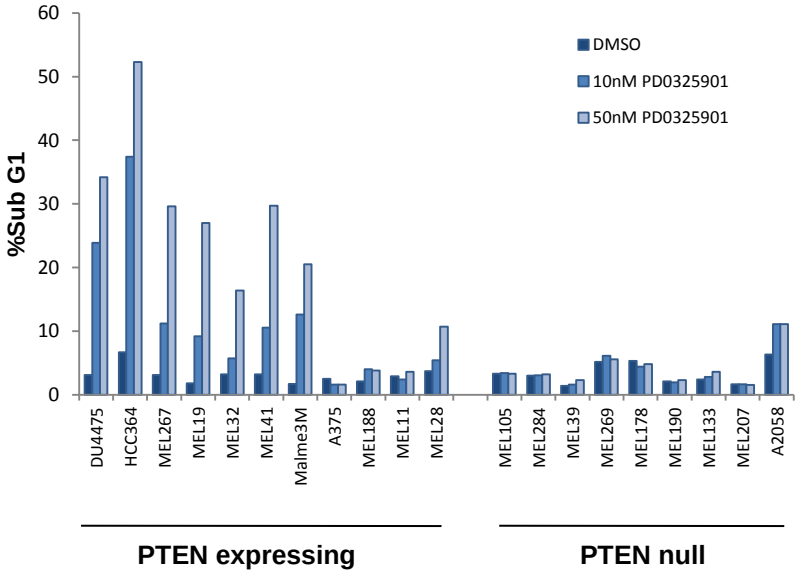
Xing et al., Oncogene, 2011

BRAF mutant/PTEN null cells exhibit a cytostatic response to MEK-inhibition

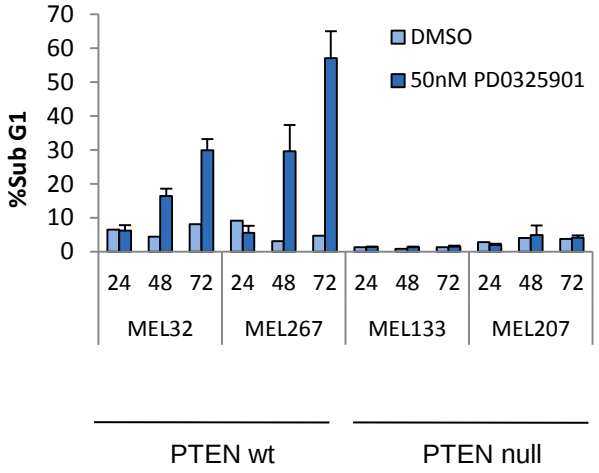
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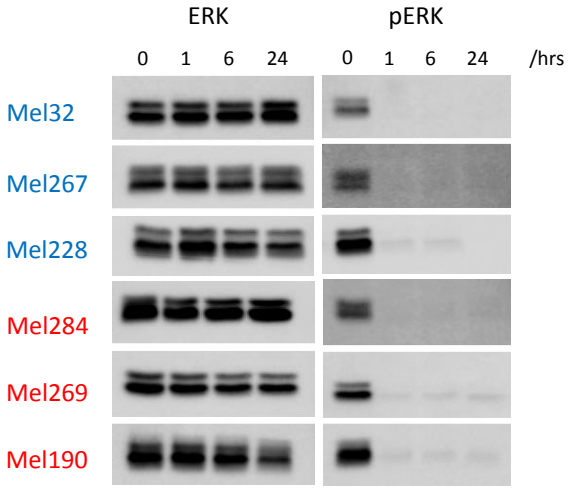
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C

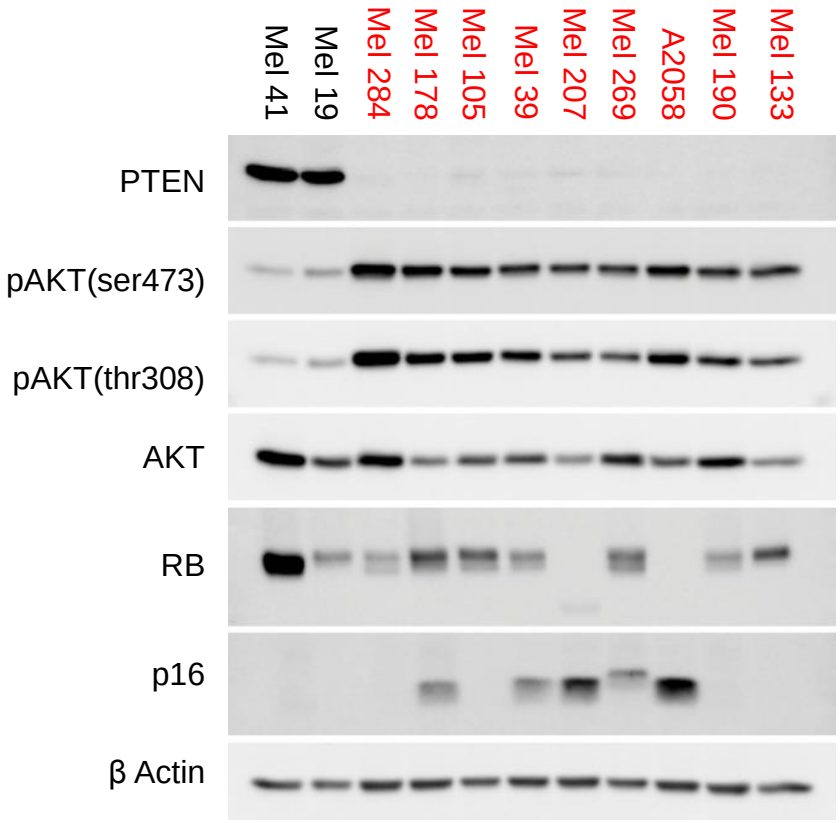


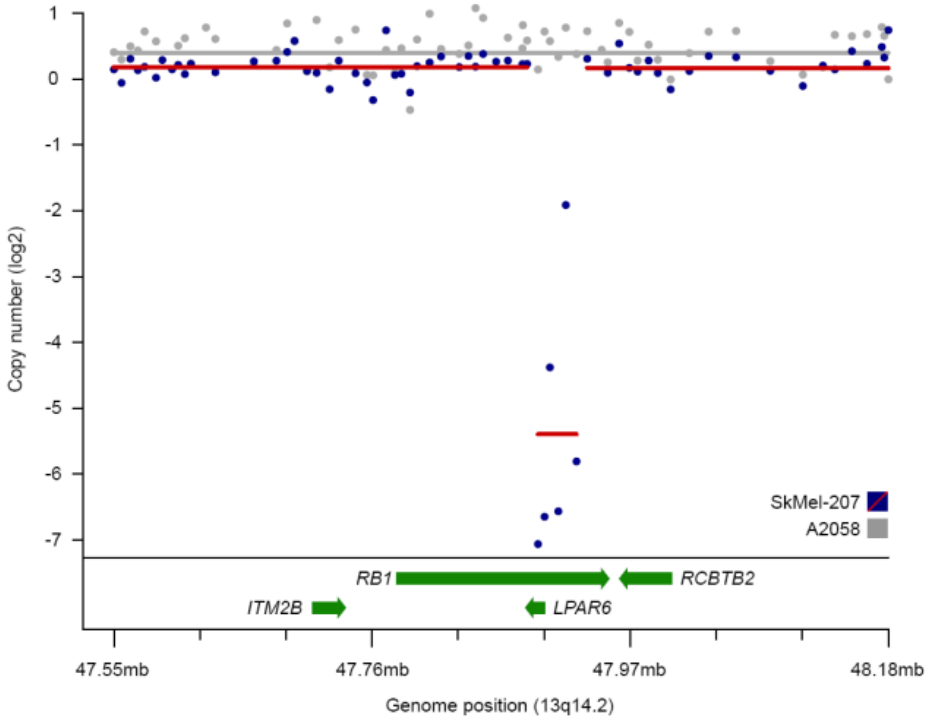
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Xing et al., Oncogene, 2011

Melanomas with RB1 mutation/deletion are wild-type for p16

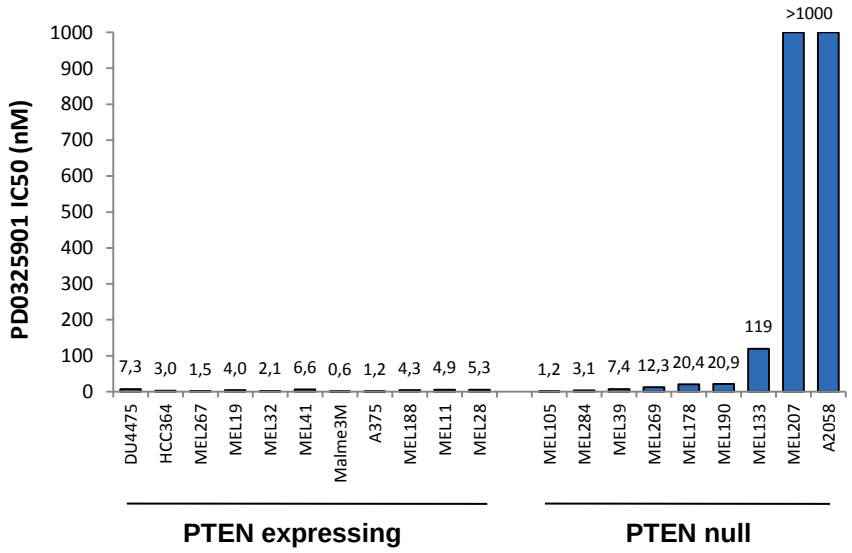




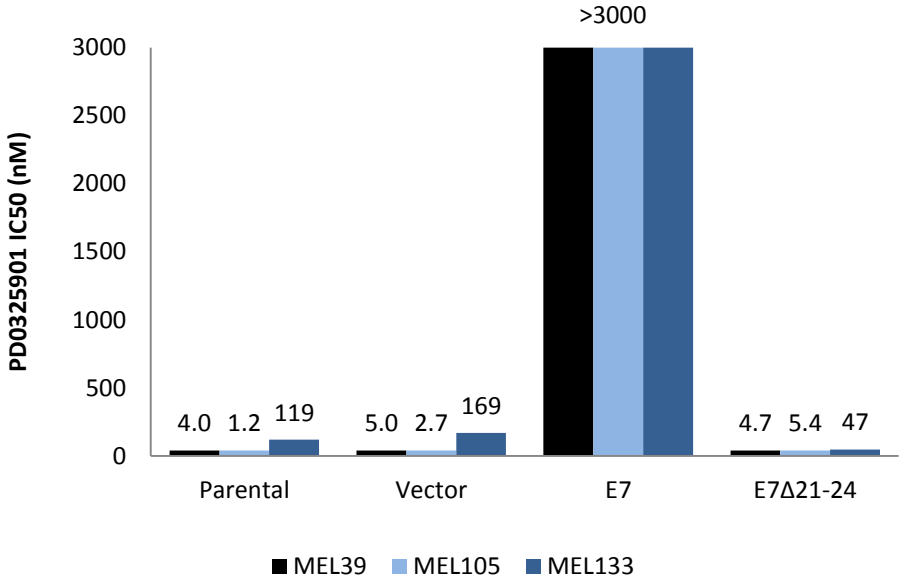
Xing et al., Oncogene, 2011

Loss of RB function is sufficient to confer MEK-independence in BRAF mutant/PTEN null melanoma

A



B



Xing et al., Oncogene, 2011

Model

	CDKN2A deletion	PTEN loss +/- CDKN2A	PTEN loss + RB1 loss
	+	+	+
$BRAF^{V600E}$	$BRAF^{V600E}$	$BRAF^{V600E}$	$BRAF^{V600E}$
↓	↓	↓	↓
Senescence	Transformation	Transformation	Transformation



RAF/MEK-dependence

We have gotten good at identify BRAF mutations. Can we prospectively identify patients with PTEN, RB1 loss in the clinic?

Are there key non-MEK effectors of BRAF?

RTK (Kit, EGFR)

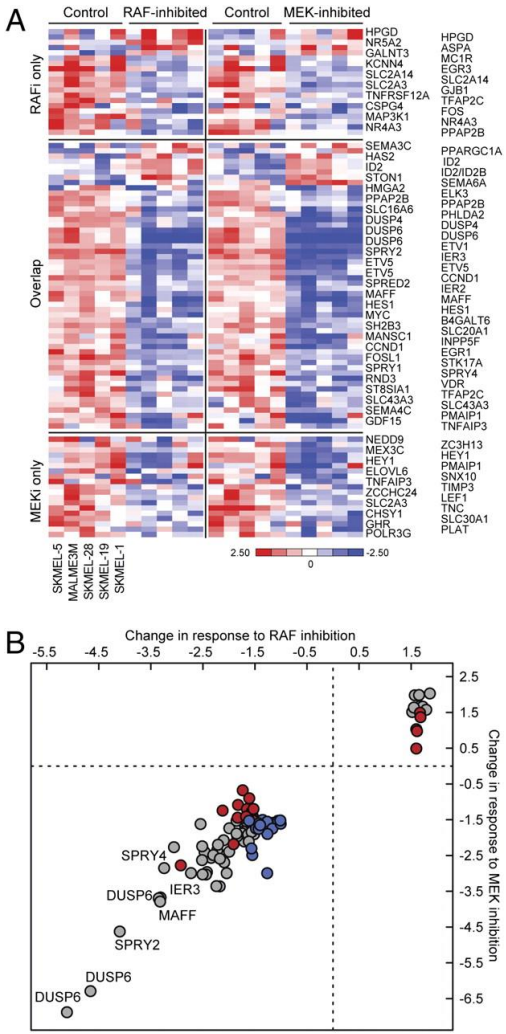
Ras

vemurafenib — **Raf**

PD0325901
AZD6244
GSK212 — **MEK**

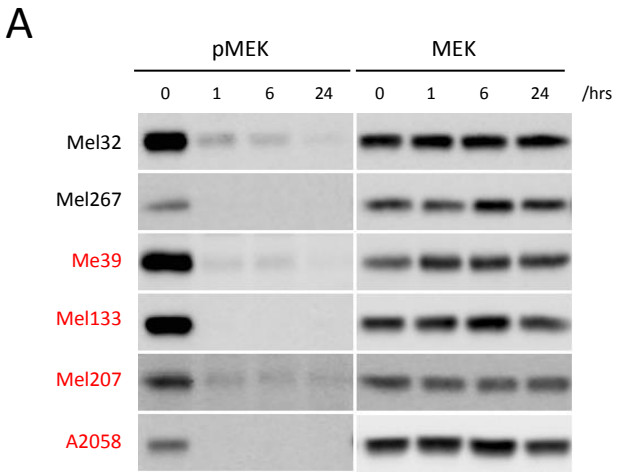
?Other effectors

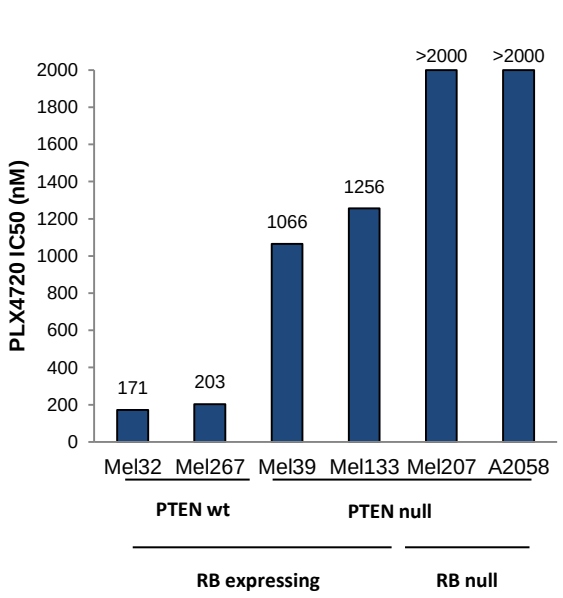
ERK

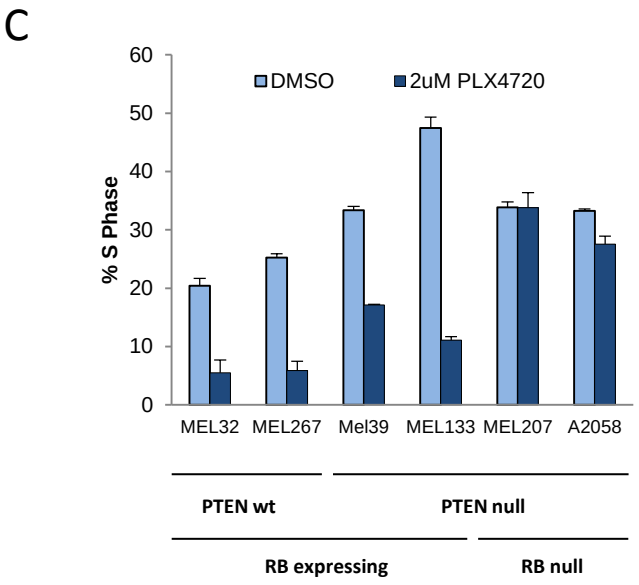


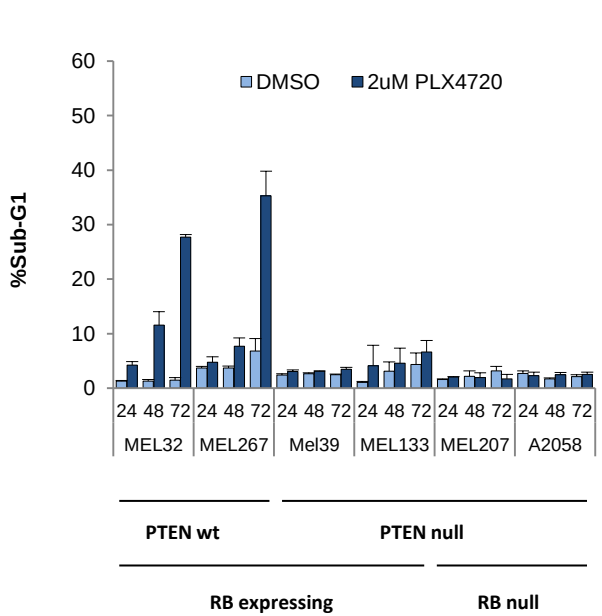
Joseph E W et al. *PNAS*, 2010

PTEN/RB null, BRAF^{V600E} models are resistant to RAF inhibition

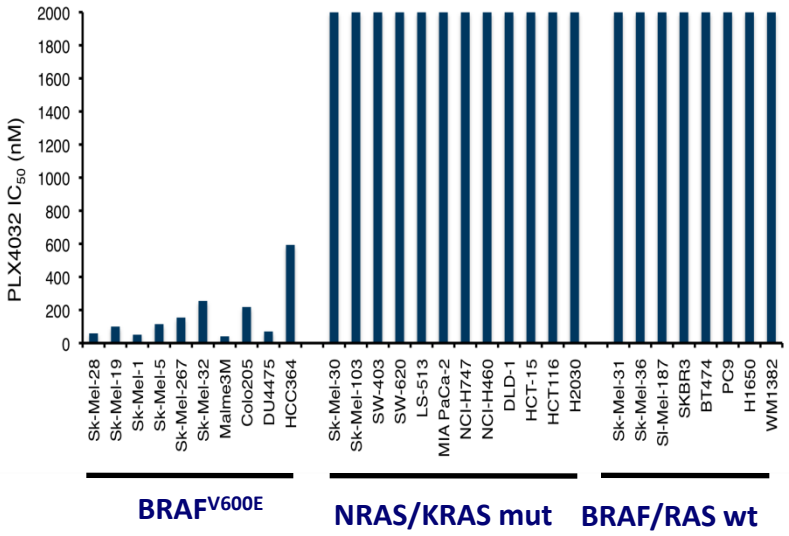




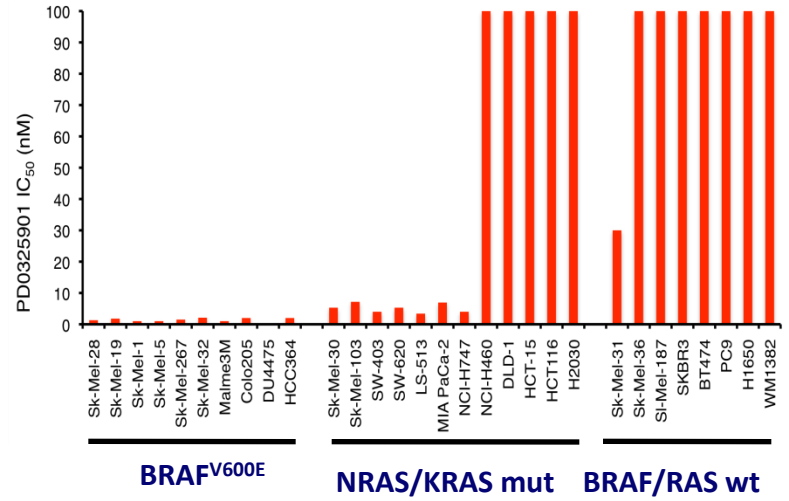


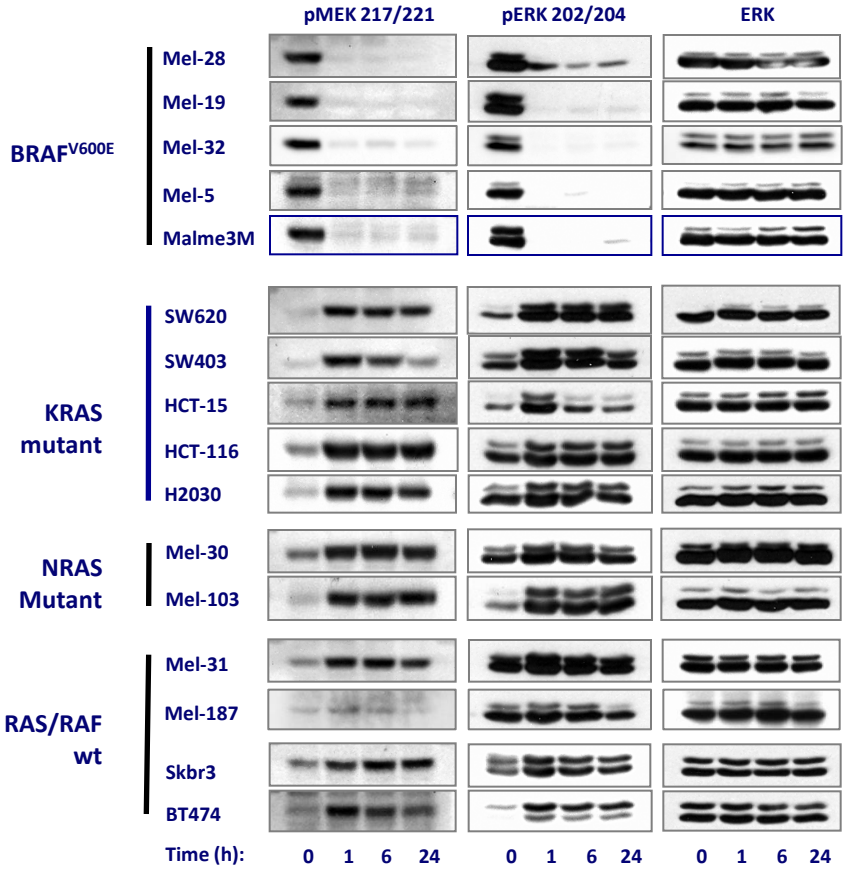


PLX-4032 (RAF inhibitor)



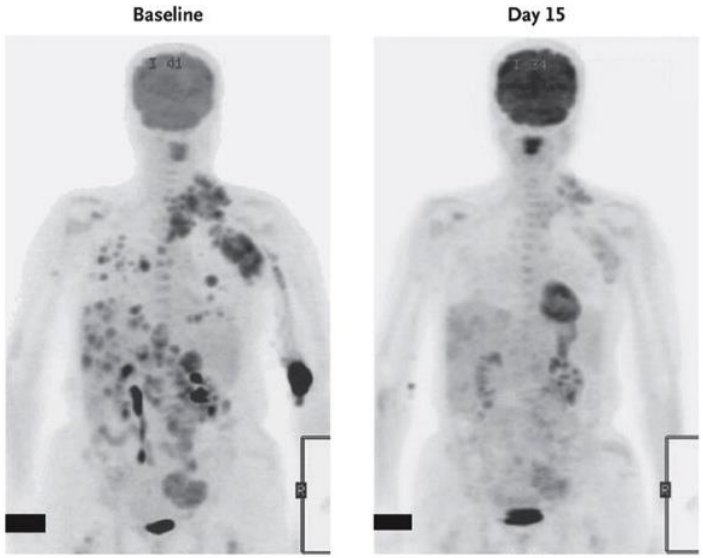
PD0325901 (MEK1/2 inhibitor)





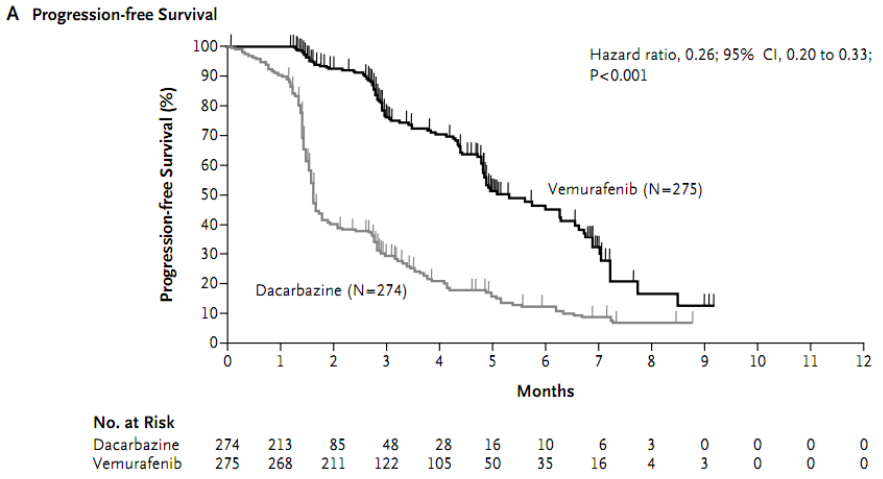
Joseph E W et al. PNAS 2010;107:14903-14908

Dramatic Responses to PLX4032 (vemurafenib) in patients with advanced V600E BRAF mutant melanoma



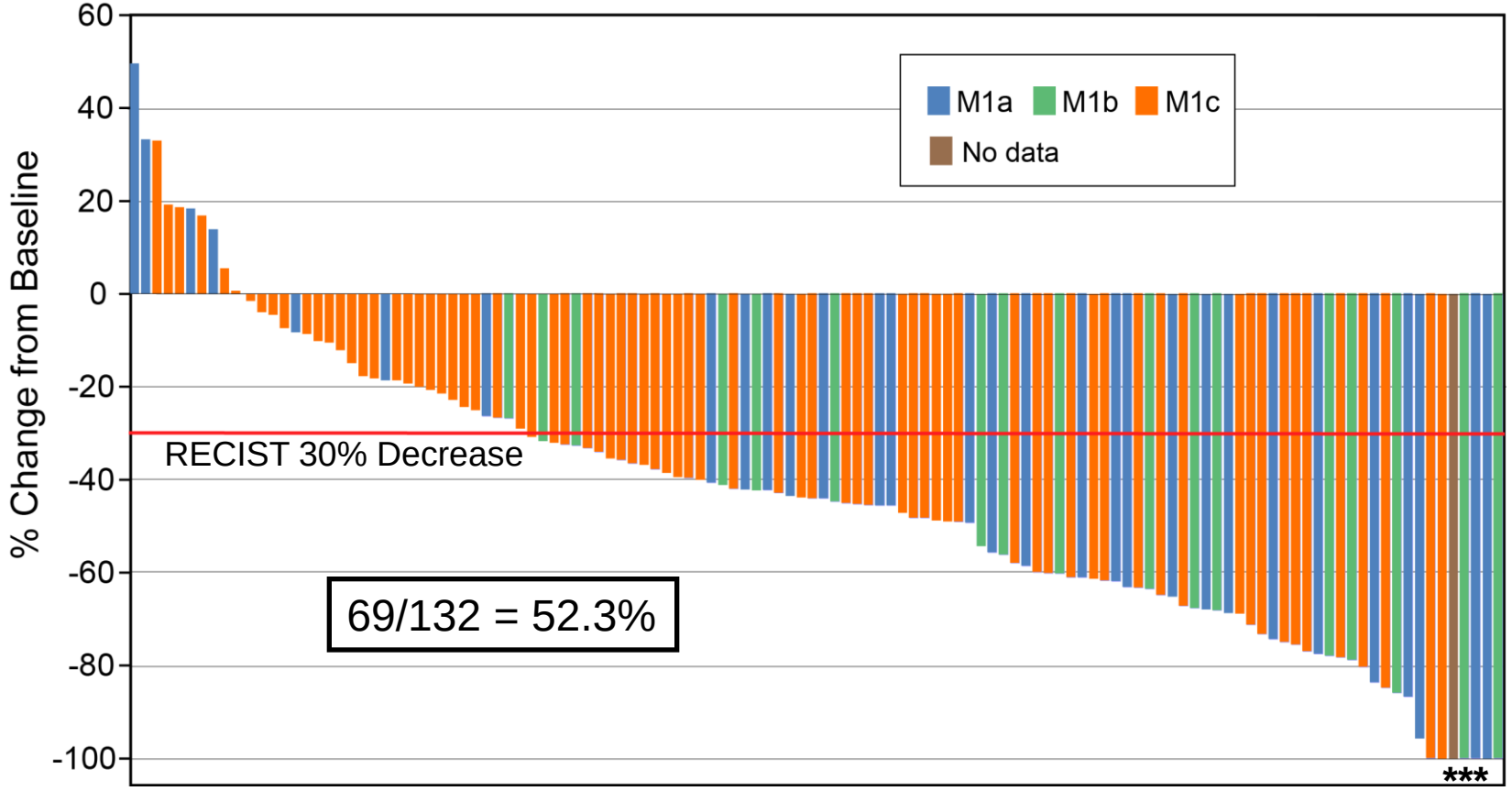
PreTx 15 days

Progression-Free Survival



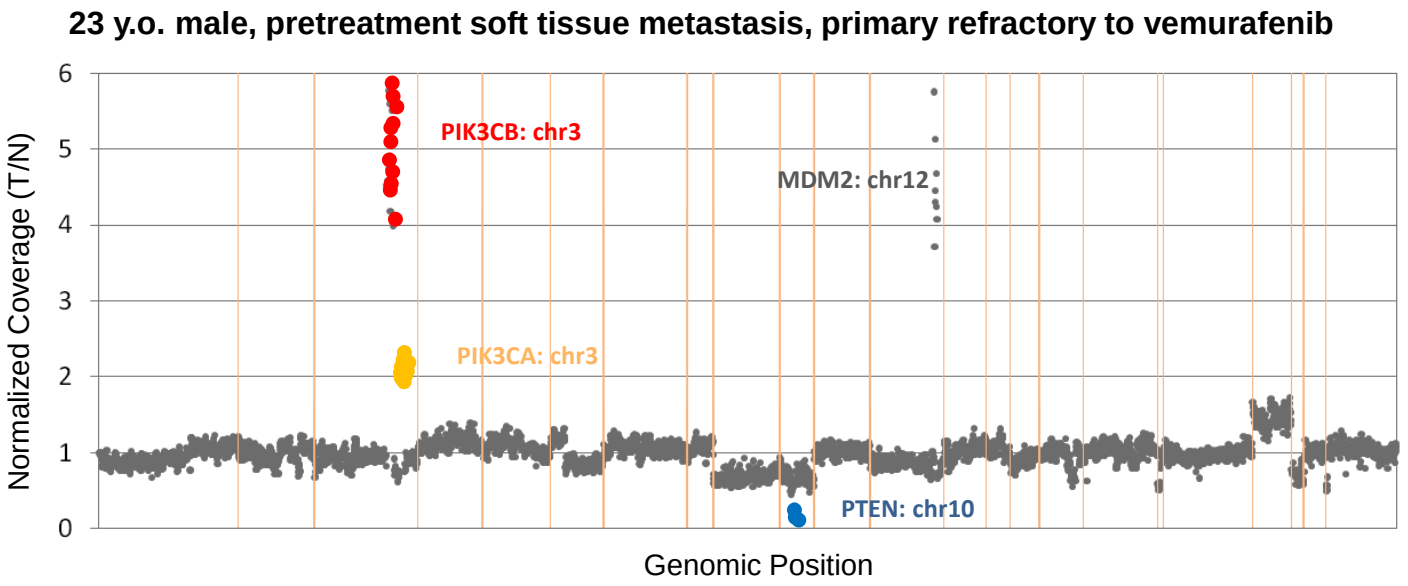
Flaherty et al., NEJM, 2010

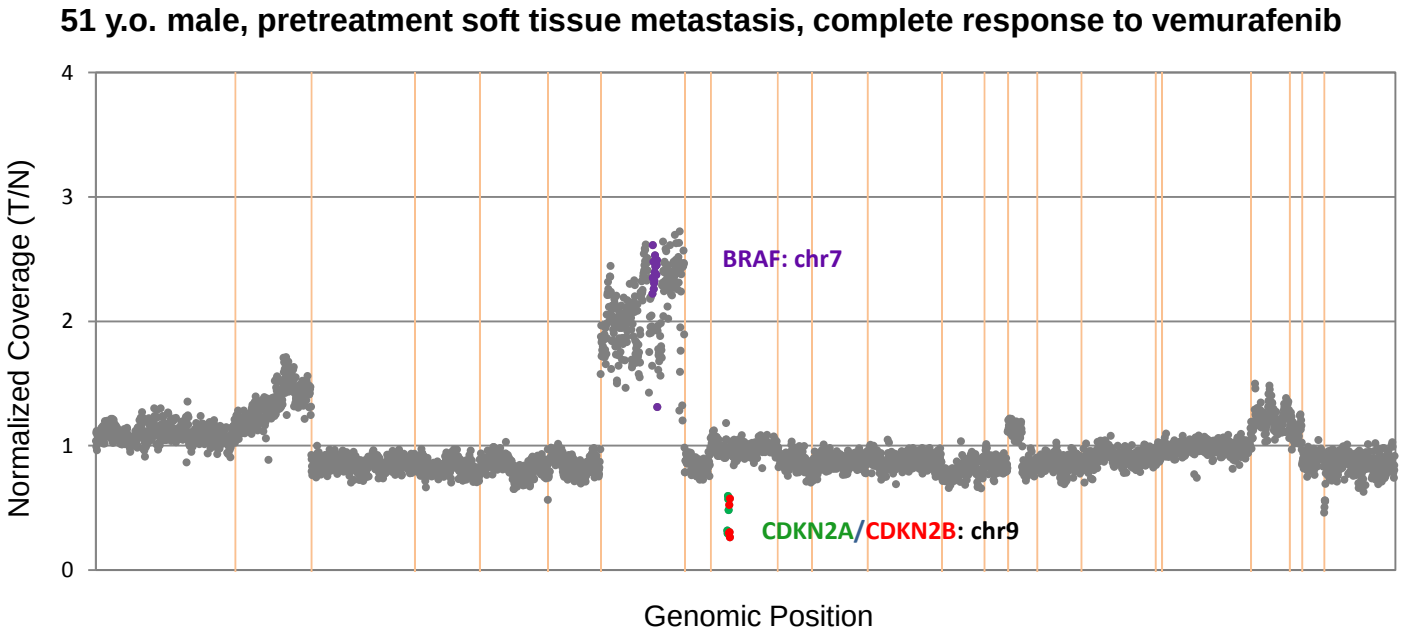
Best overall response
(independently reviewed)



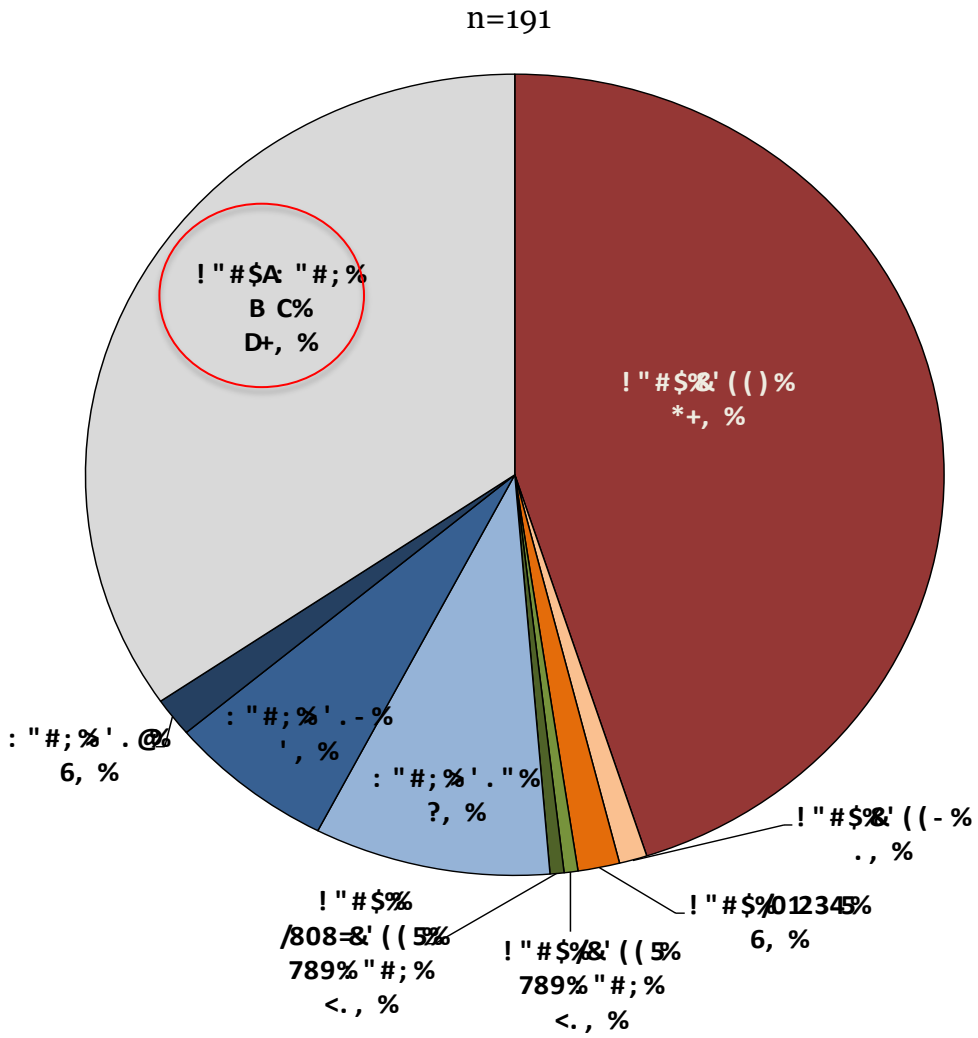
Sosman et al, ASCO 2011

Early experience in vemurafenib-treated patients

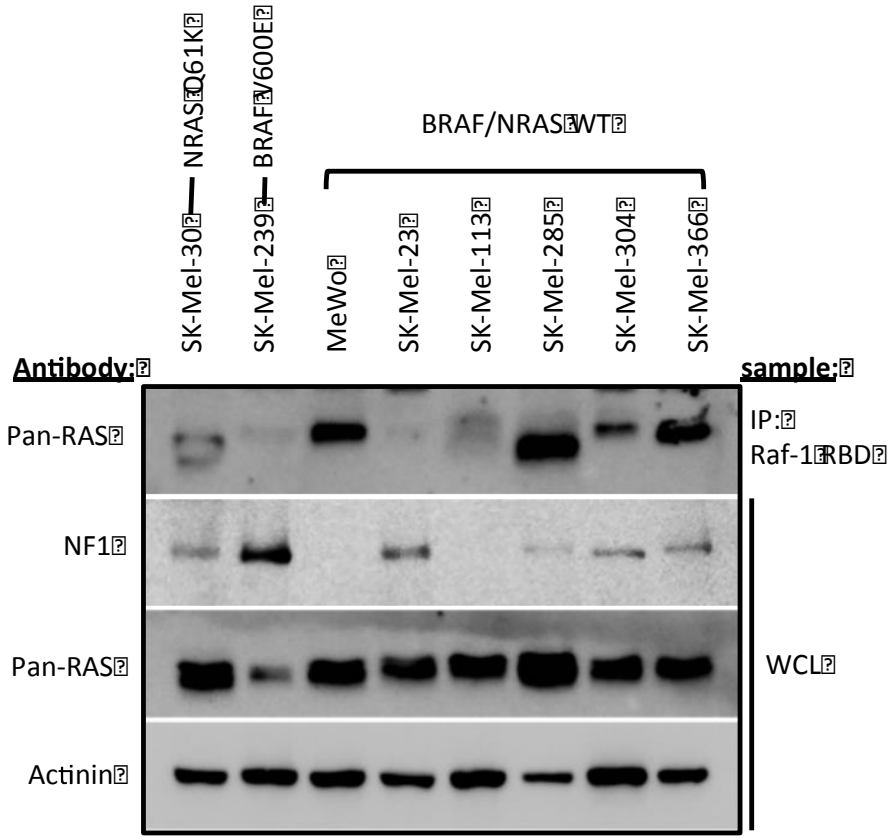




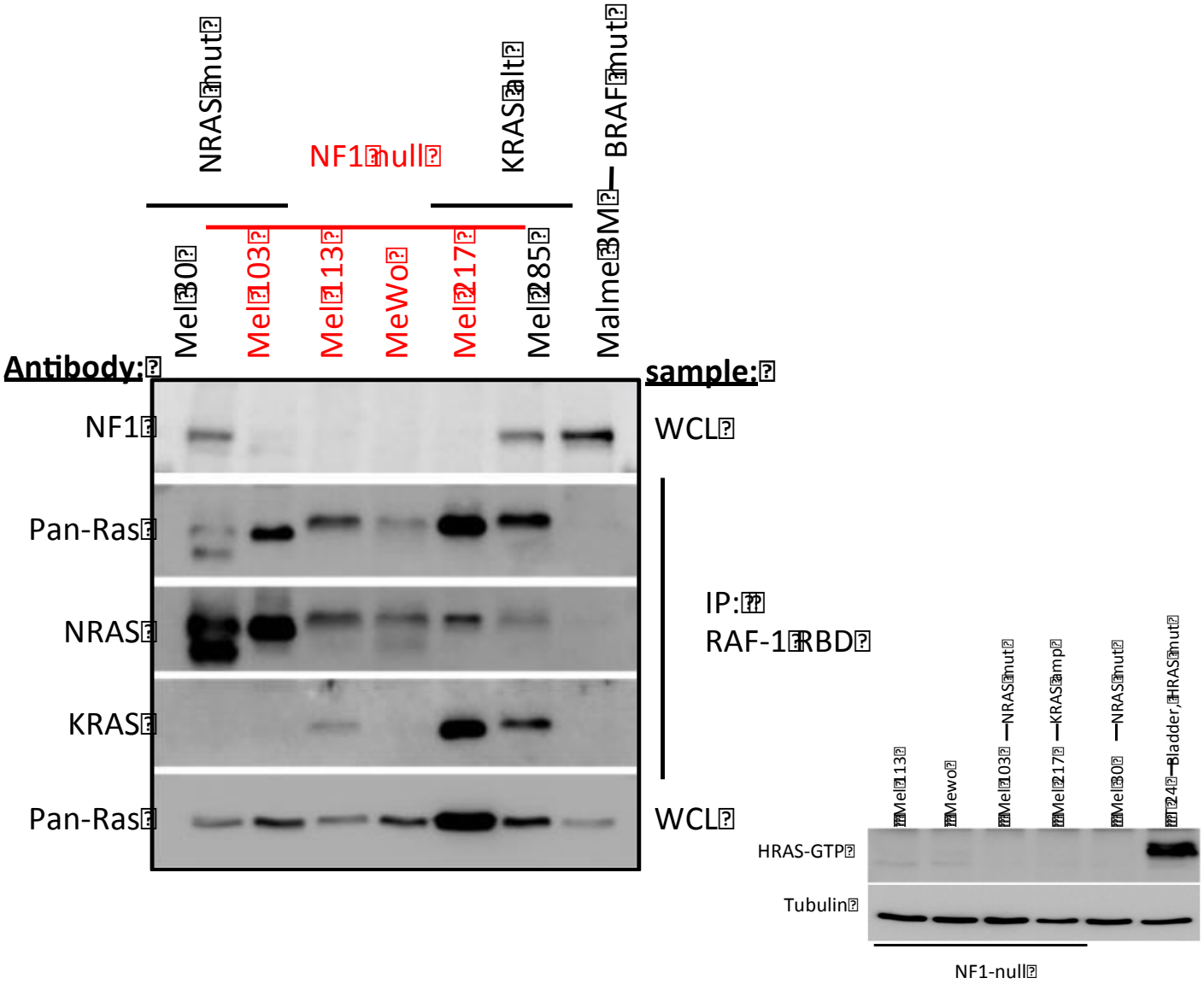
66 of 191 melanoma cell lines (35%) are wild-type for BRAF and NRAS



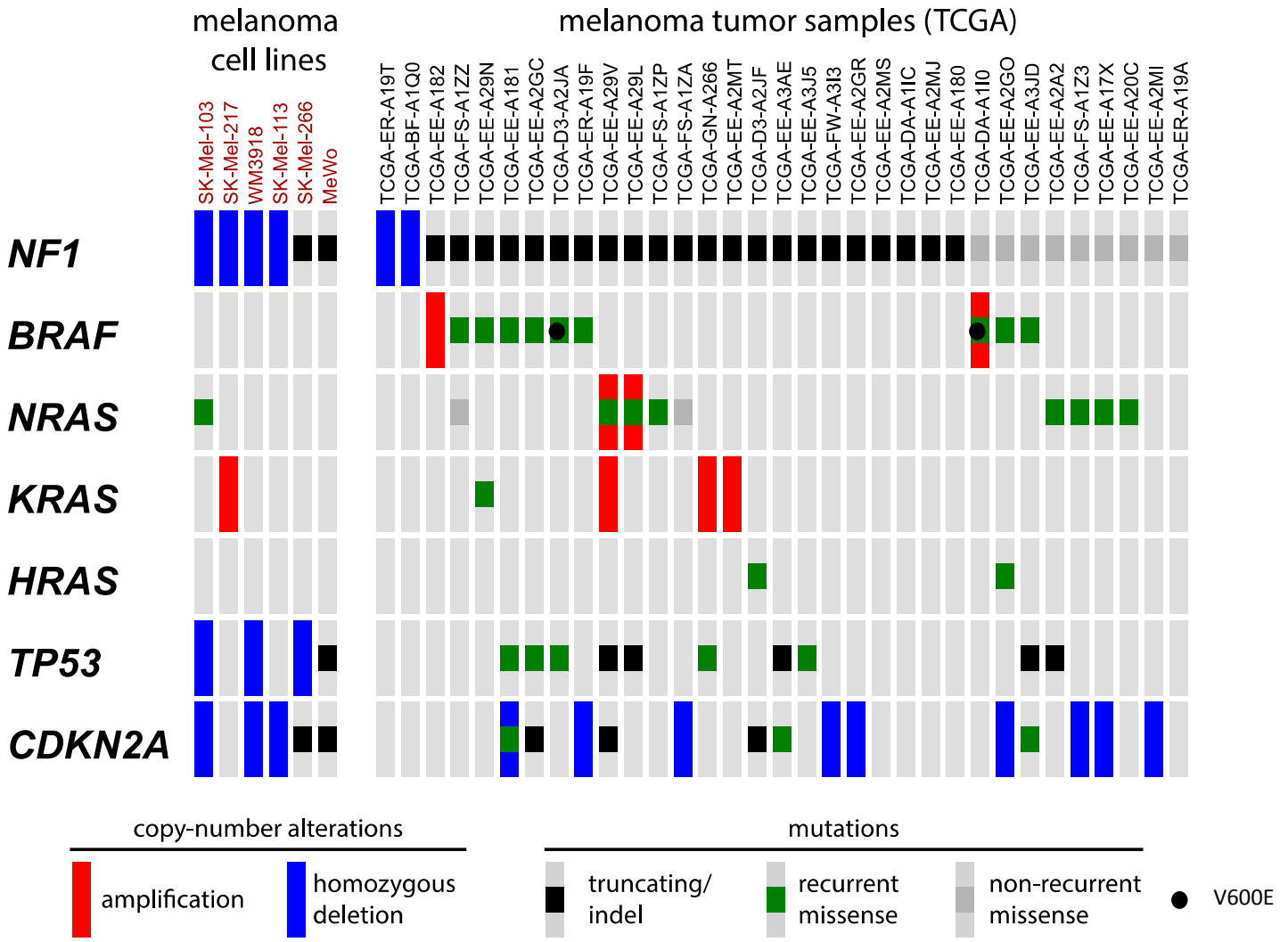
NF1 is lost in some cell lines with active RAS



NF1-null cell lines have activation of N- and KRAS

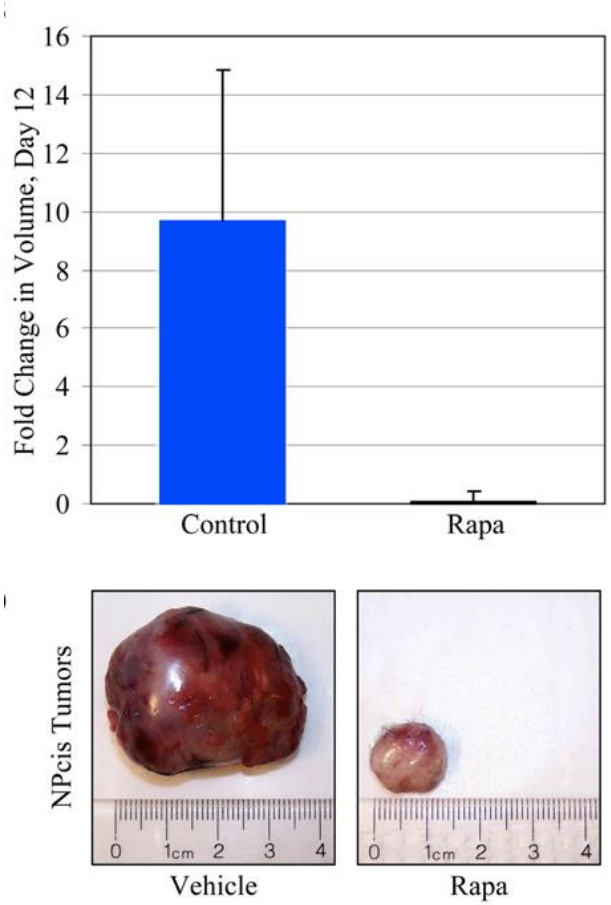


Genomic alteration of *NF1* overlaps with *TP53*, *CDKN2A*, and RAS in melanoma cell lines and tumors



Nikolaus Schultz

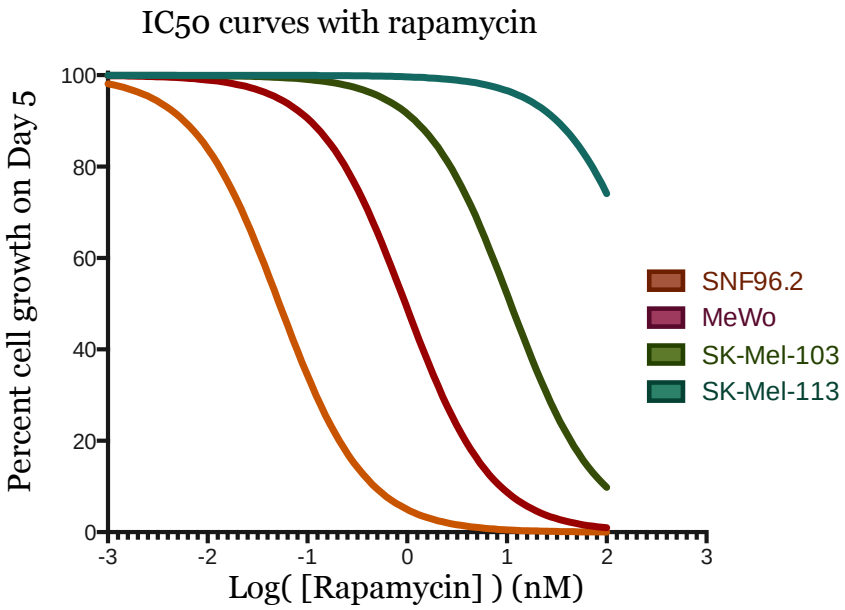
$NF1^{-/-}$ MPNSTs are dependent on mTOR and sensitive to Rapamycin

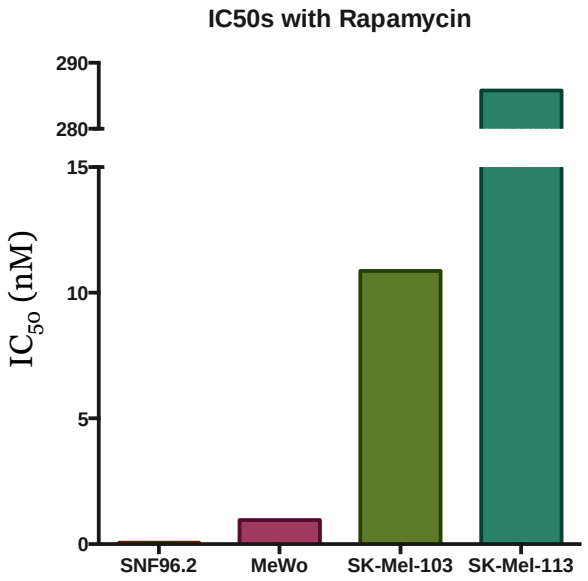


(Johannessen, Johnson et al. 2008)

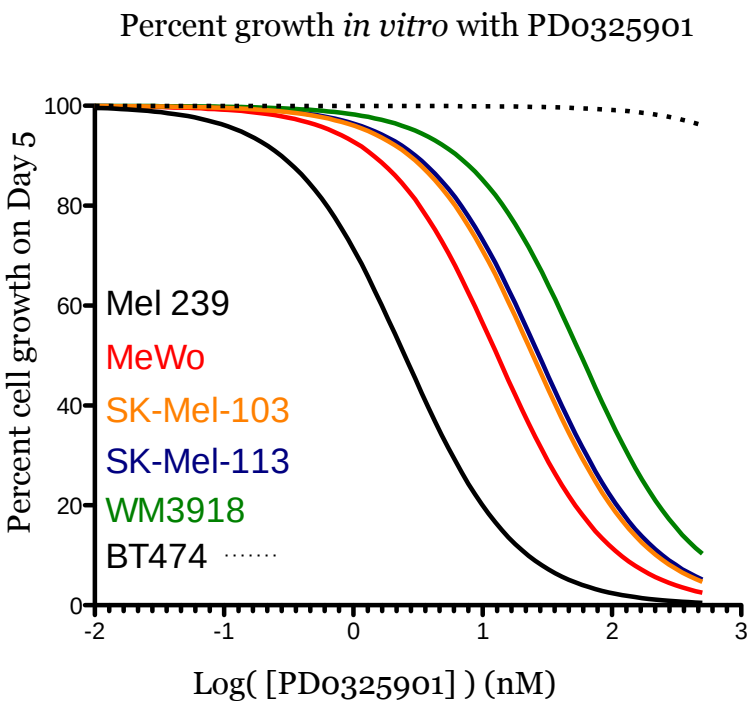
Are NF1-null melanoma cell lines also dependent on mTOR?

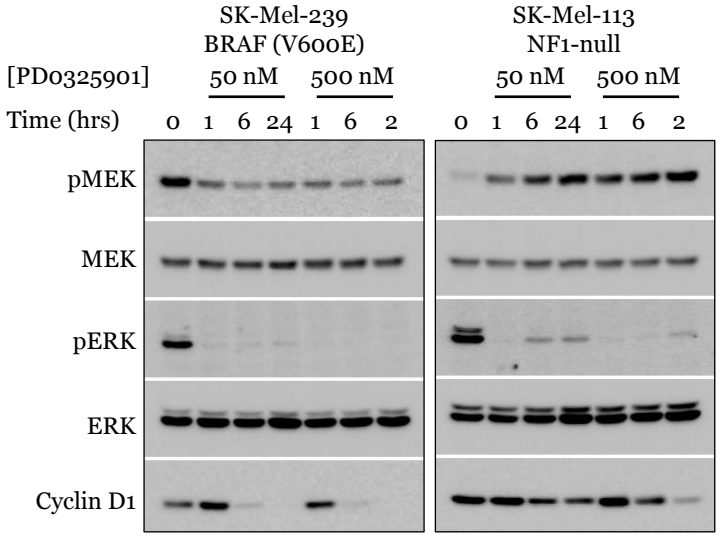
NF1-null melanoma cell lines do not display uniform sensitivity to mTOR inhibition with Rapamycin



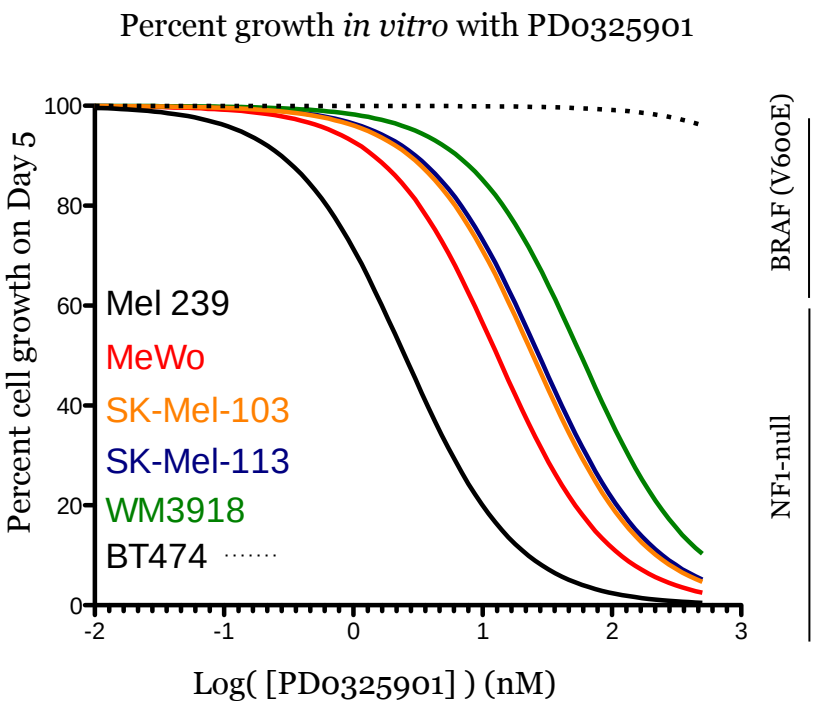


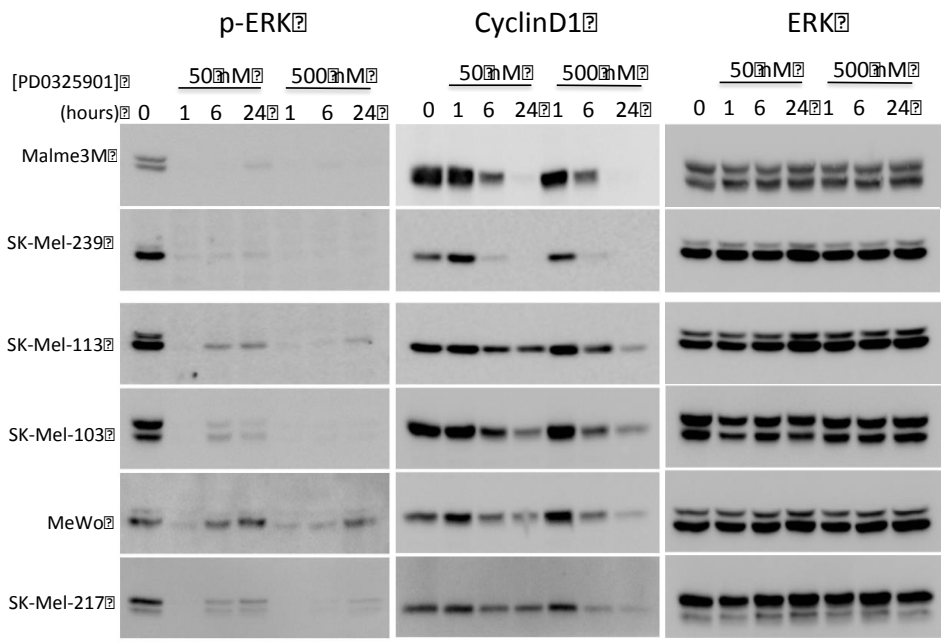
NF1 null cell lines are sensitive to the MEK inhibitor PD0325901 by growth *in vitro*, though less than BRAF(V600E) cell lines



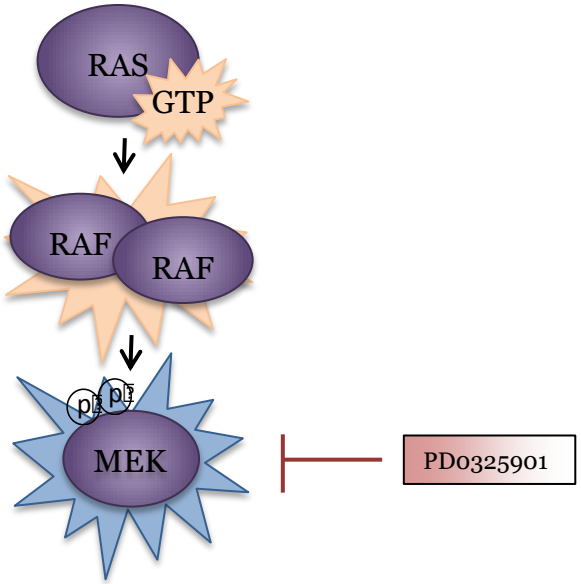


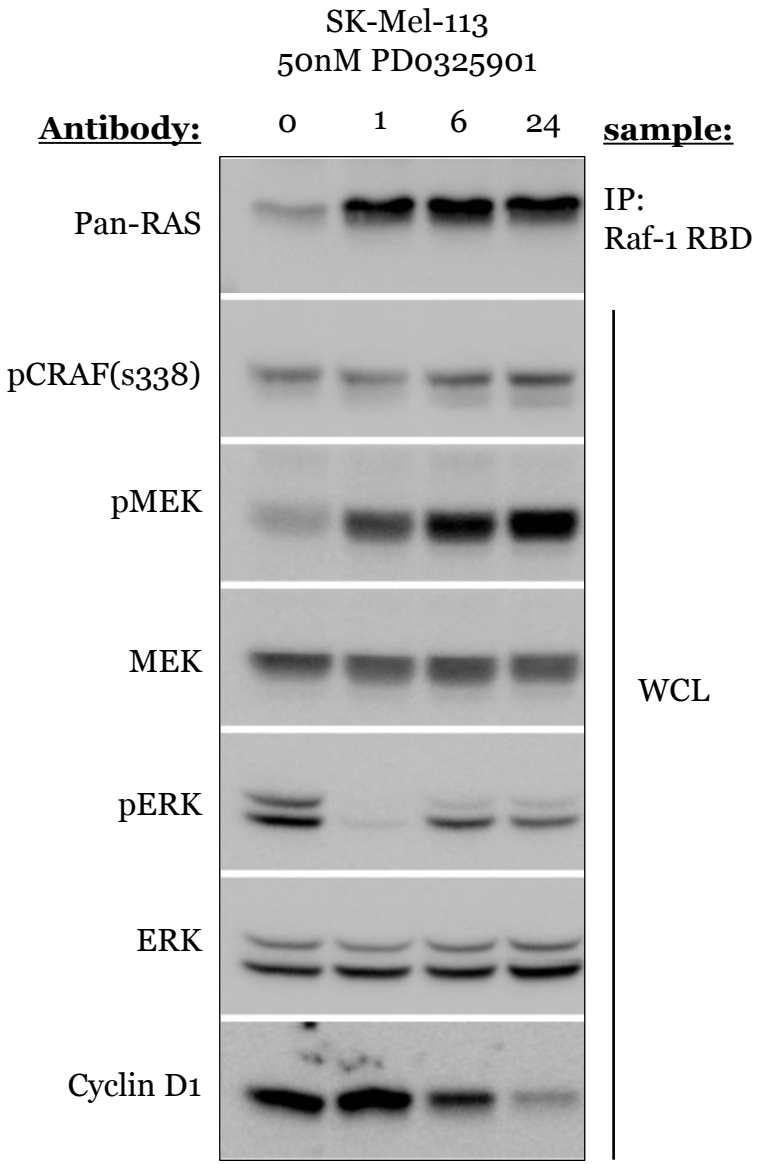
Relative resistance of NF1 null cells to MEK inhibition is associated with rebound in ERK activity and cyclin D1 expression.



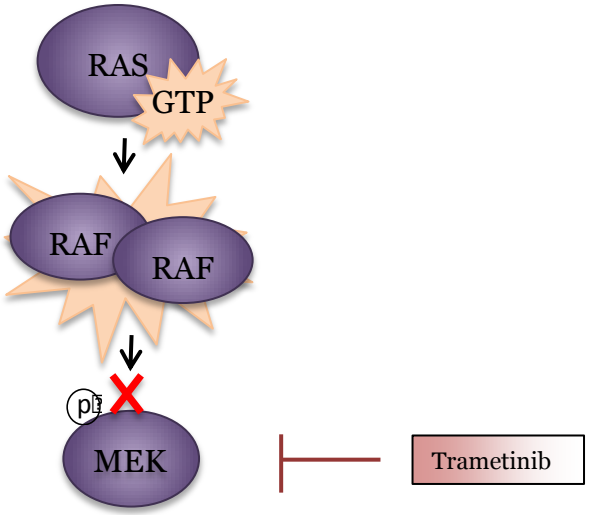


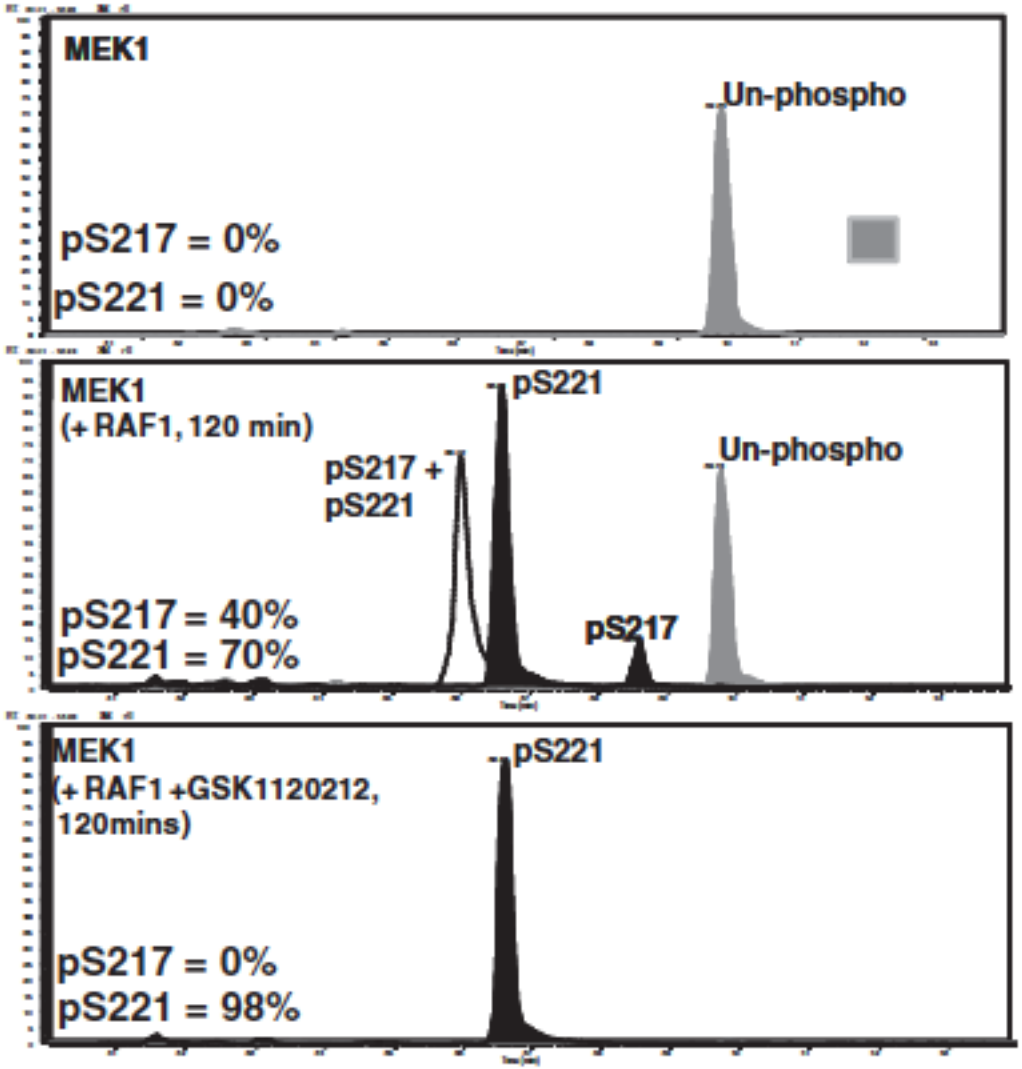
Treatment with the MEK inhibitor PD0325901 in NF1 null cell line Mel 113 results in RAS and MEK hyperactivation and rebound ERK activation





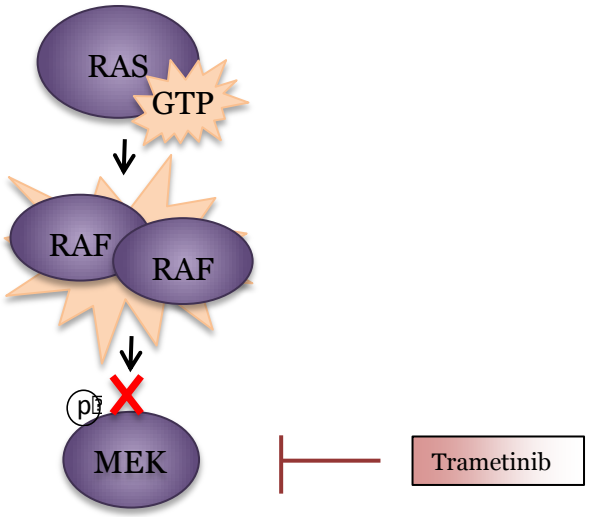
The MEK inhibitor trametinib (GSK1120212) inhibits MEK activation as well as MEK kinase activity

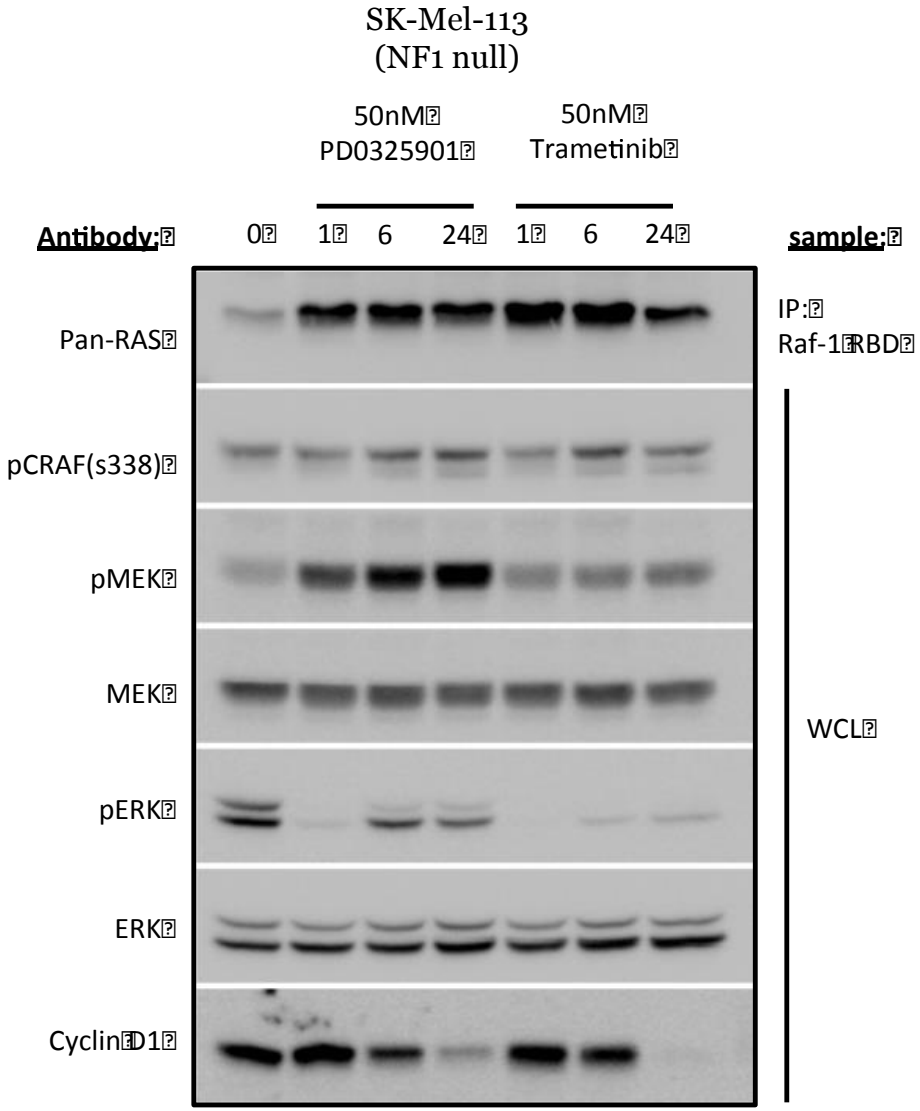




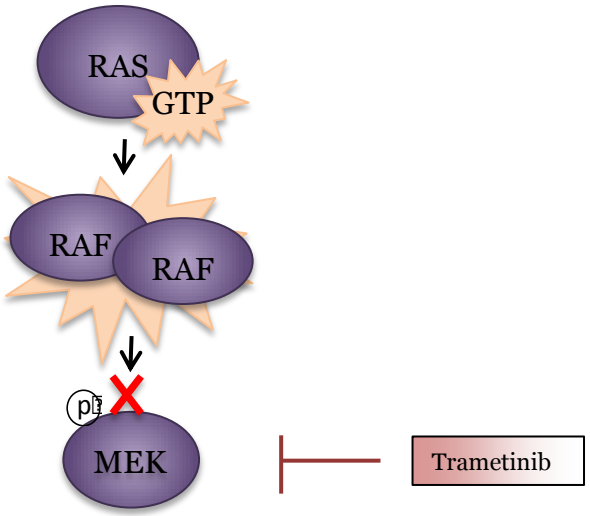
(Gilmartin, Bleam et al. 2011)

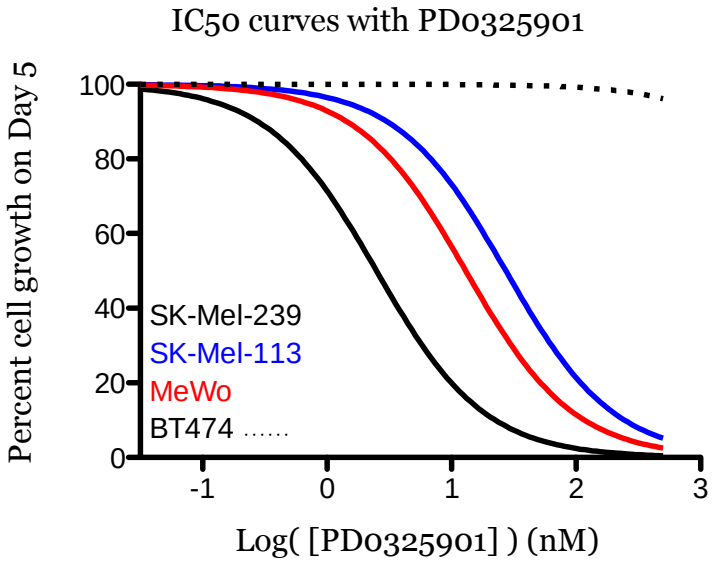
Inhibition of MEK hyperphosphorylation despite RAS and RAF hyperactivation is associated with durable inhibition of pERK and CyclinD1

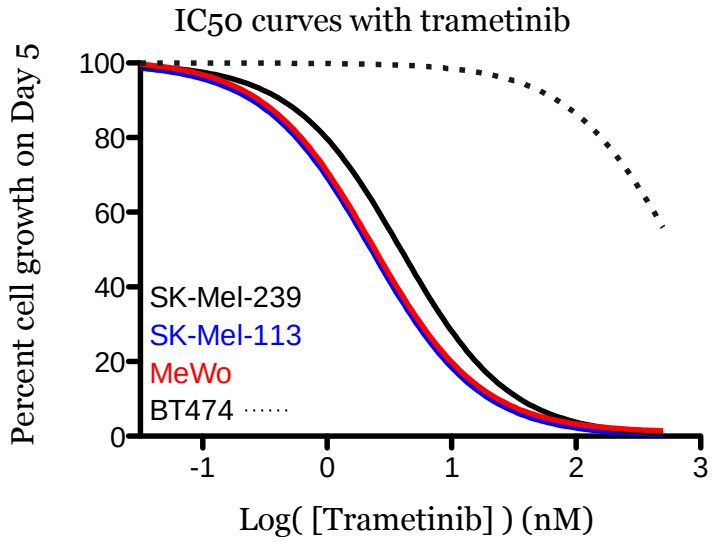




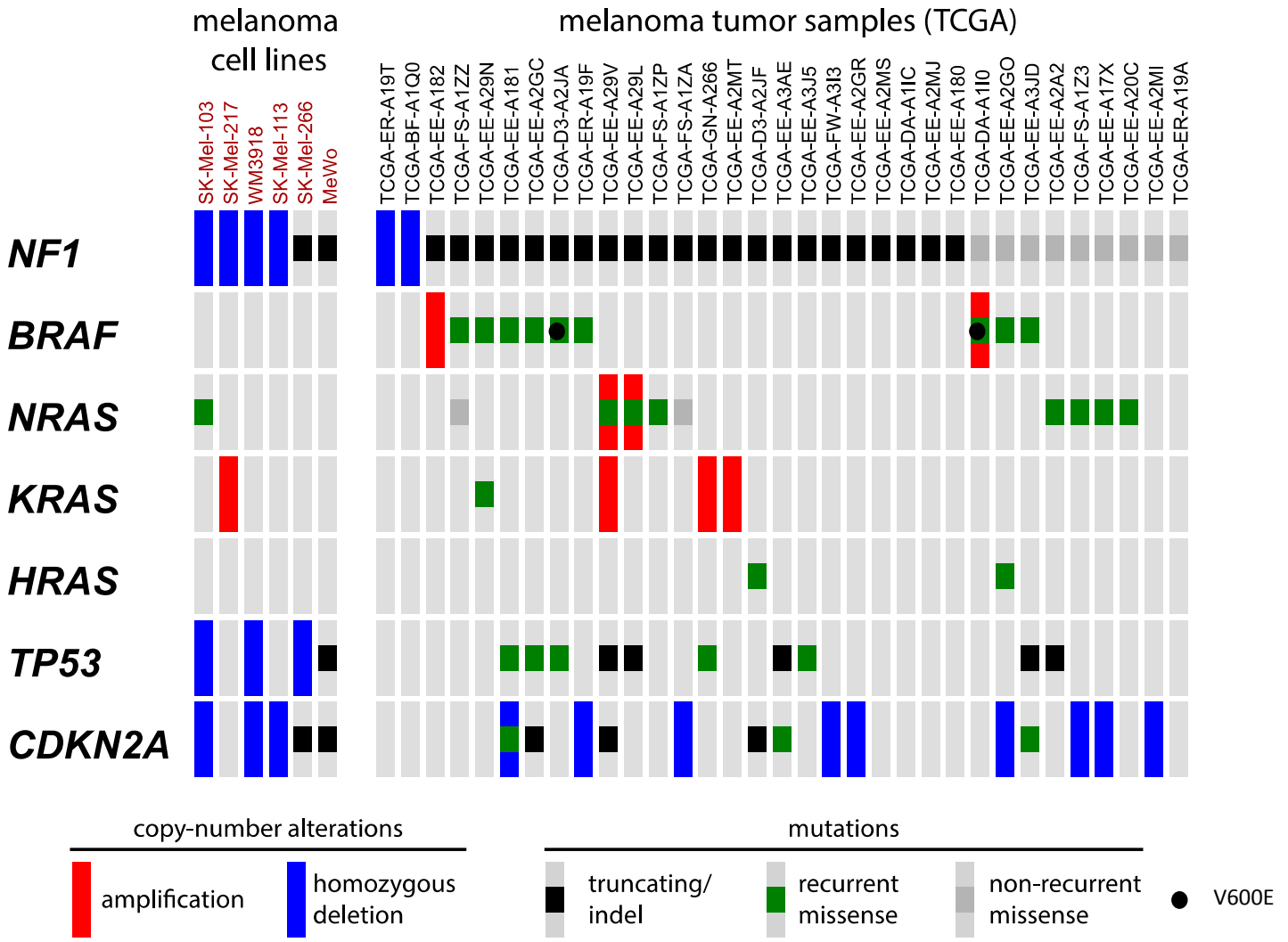
Trametinib inhibits growth similarly in NF1-null and BRAF (V600E) cells





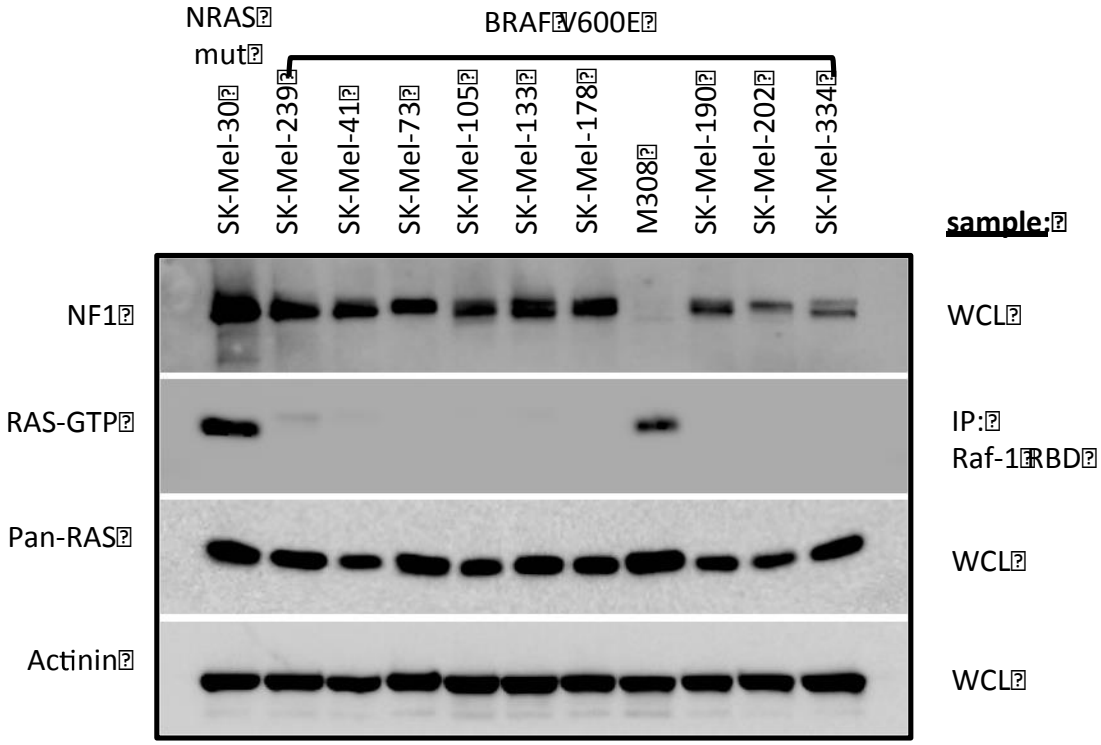


Genomic alteration of *NF1* overlaps with *TP53*, *CDKN2A*, and RAS in melanoma cell lines and tumors



Nikolaus Schultz

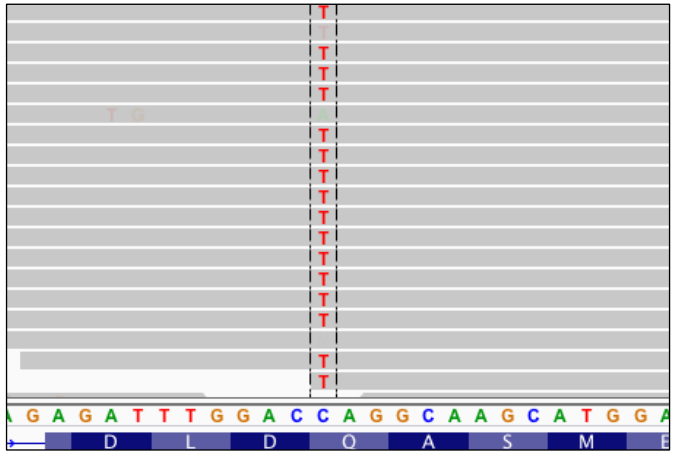
RAS-GTP is elevated in a BRAF(V600E) cell line with NF1 loss



Li Kong

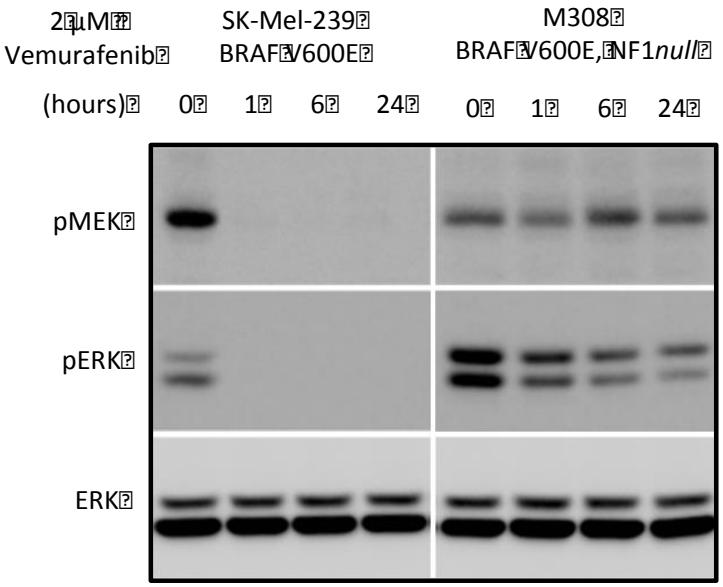
M308
BRAF (V600E), NF1 Q1070*
(89% / 243)

C→T

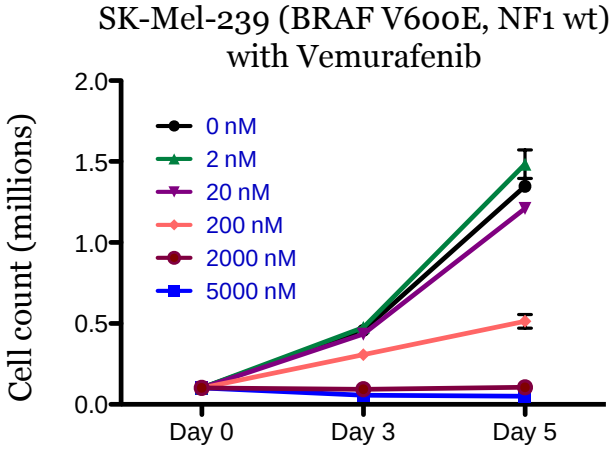


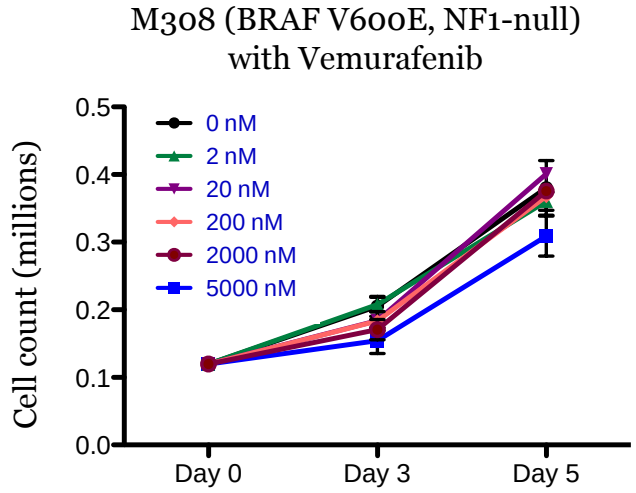
In collaboration with the Berger lab

NF1 null BRAF(V600E) cell line M308 is insensitive to the RAF inhibitor Vemurafenib

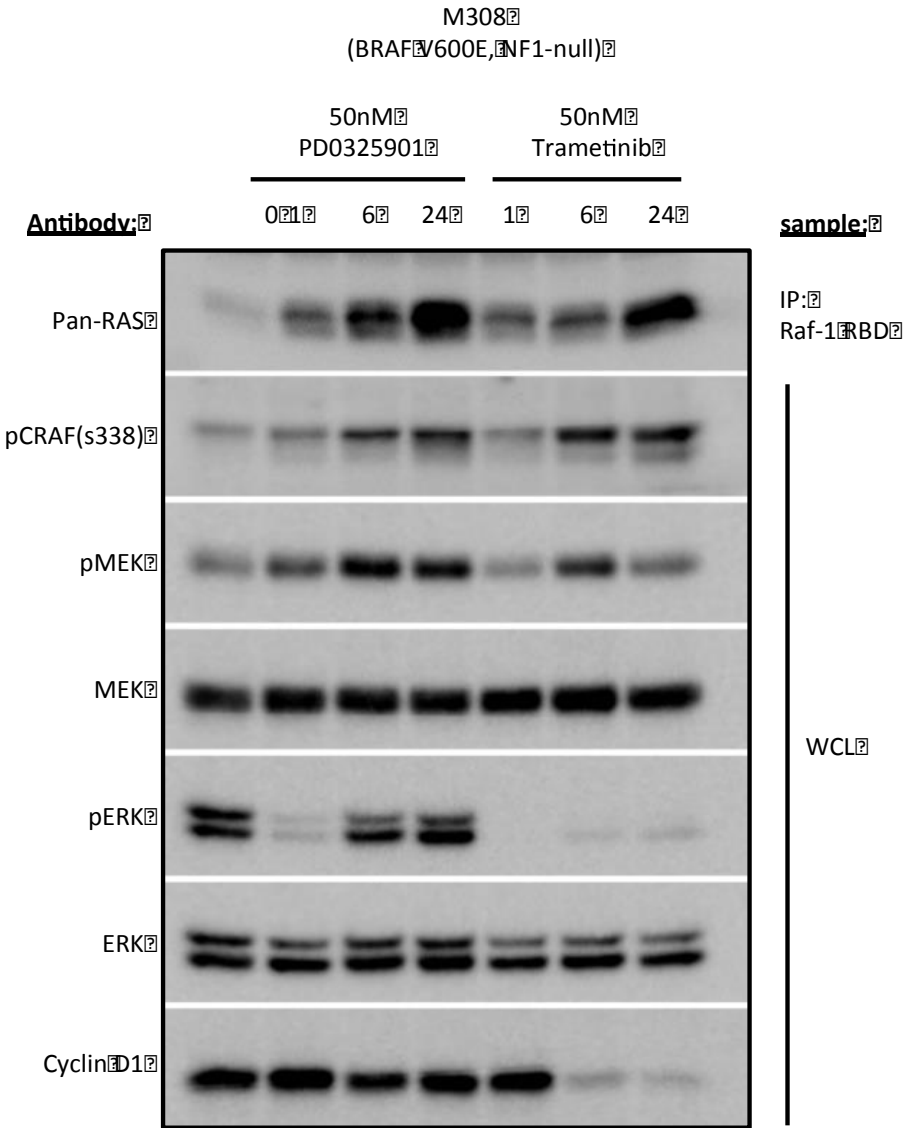


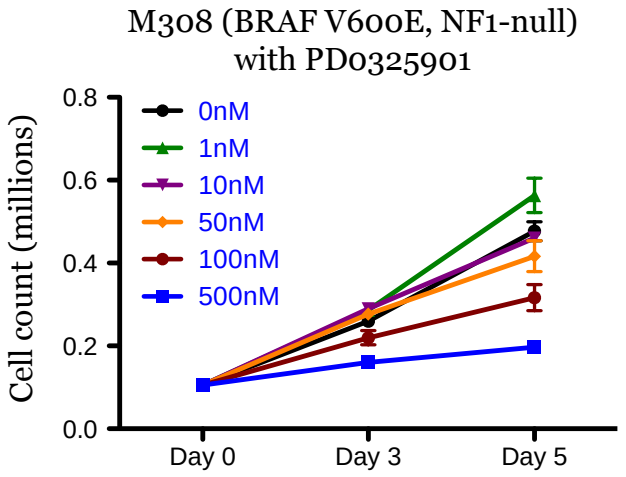
Li Kong

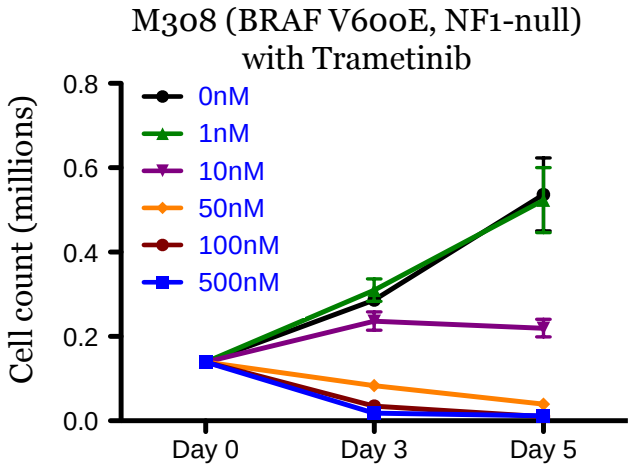




The MAPK pathway in NF1 null BRAF(V600E) cell line M308 is durably inhibited with trametinib but not PD0325901







Summary

- NF1 mutations are common in patients with melanoma.
- Loss of NF1 is associated with RAS activation.
- NF1 loss is not associated with maximal activation of RAS.
- NF1 mutations commonly co-occur with mutations in RAS and BRAF.
- Co-mutation of NF1 with BRAF is associated with activation of RAS and resistance to RAF inhibitors.
- MEK inhibitors that abrogate RAF phosphorylation of MEK are more effective in tumors with NF1 loss.

MSKCC Center for Molecular Oncology Profiling Initiative

Primary Goal – Define the molecular driver in every patient. Begin with the 12,000/year with recurrent/metastatic disease.

Secondary Goal – Identify germline variants that contributed to cancer initiation.

Major Hurdle: Genotyping is only "standard of care" for select solid tumors (Lung, Colorectal, Melanoma, GIST, ?Thyroid).

MSKCC Plan: We will perform free IMPACT (341 genes) testing on a large cohort of patients from each RNB cancer type. This takes cost out of the equation; for efficiency same assay for all patients. Results reported in the chart.

Patients are enrolled on IRB 12-245. At enrollment, consent obtained for: IMPACT, whole exome/genome/etc for discovery, review of germline data with a mechanism to return relevant germline results to patient.

Primary endpoint will be to determine whether treatment was impacted by the genotyping results.

cBioPortal for Cancer Genomics

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Memorial Sloan Kettering Cancer Center

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DMP MSK-IMPACT Clinical Runs (MSKCC 2014) Query this study

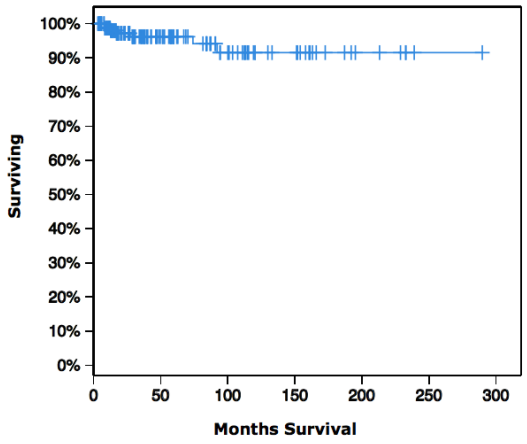
Targeted (341 cancer genes) sequencing of various tumor types via MSK-IMPACT on Illumina HiSeq sequencers. **1221 samples from 1200 patients.**

Study Summary | Clinical Data | Mutated Genes

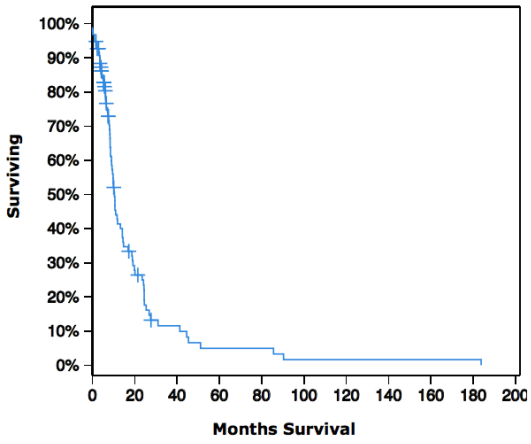
Select cases by IDs | Query all cases | View all cases

Add Chart

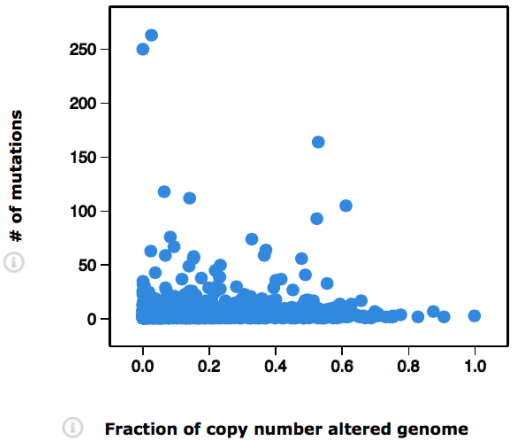
Overall Survival



Disease Free Survival

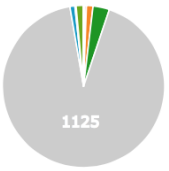


Mutation Count vs CNA



CANCER TYPE	#
Breast Carcinoma	216
Non-Small Cell Lung Cancer	150
Colorectal Adenocarcinoma	84
Esophagogastric Adenocarcinoma	76
Prostate Carcinoma	71
Soft Tissue Sarcoma	67
Bladder/Urinary Tract	51
Thyroid Carcinoma	42
Non-Seminomatous Germ Cell Tumor	42
Endometrial Carcinoma	38
Diffuse Glioma	37
Ovarian Carcinoma	33

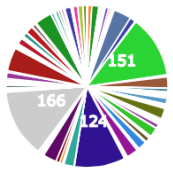
Grade



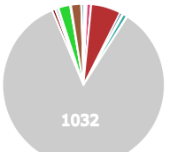
HISTOLOGY SECONDARY

T STAGE

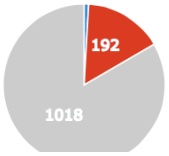
CANCER TYPE DETAILED



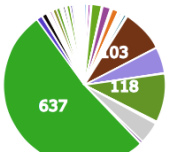
histological type



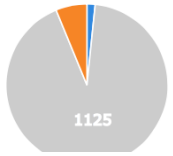
Overall Survival Status



Metastatic site



Disease Free Status



▸ **Modify Query**

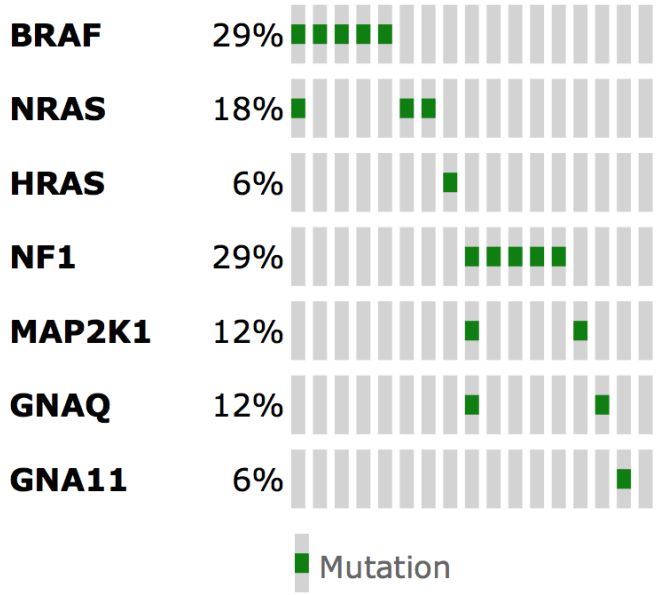
OncoPrint | Mutual Exclusivity | Mutations | Survival | Network | IGV | Download | Bookmark

OncoPrint (What are OncoPrints?)

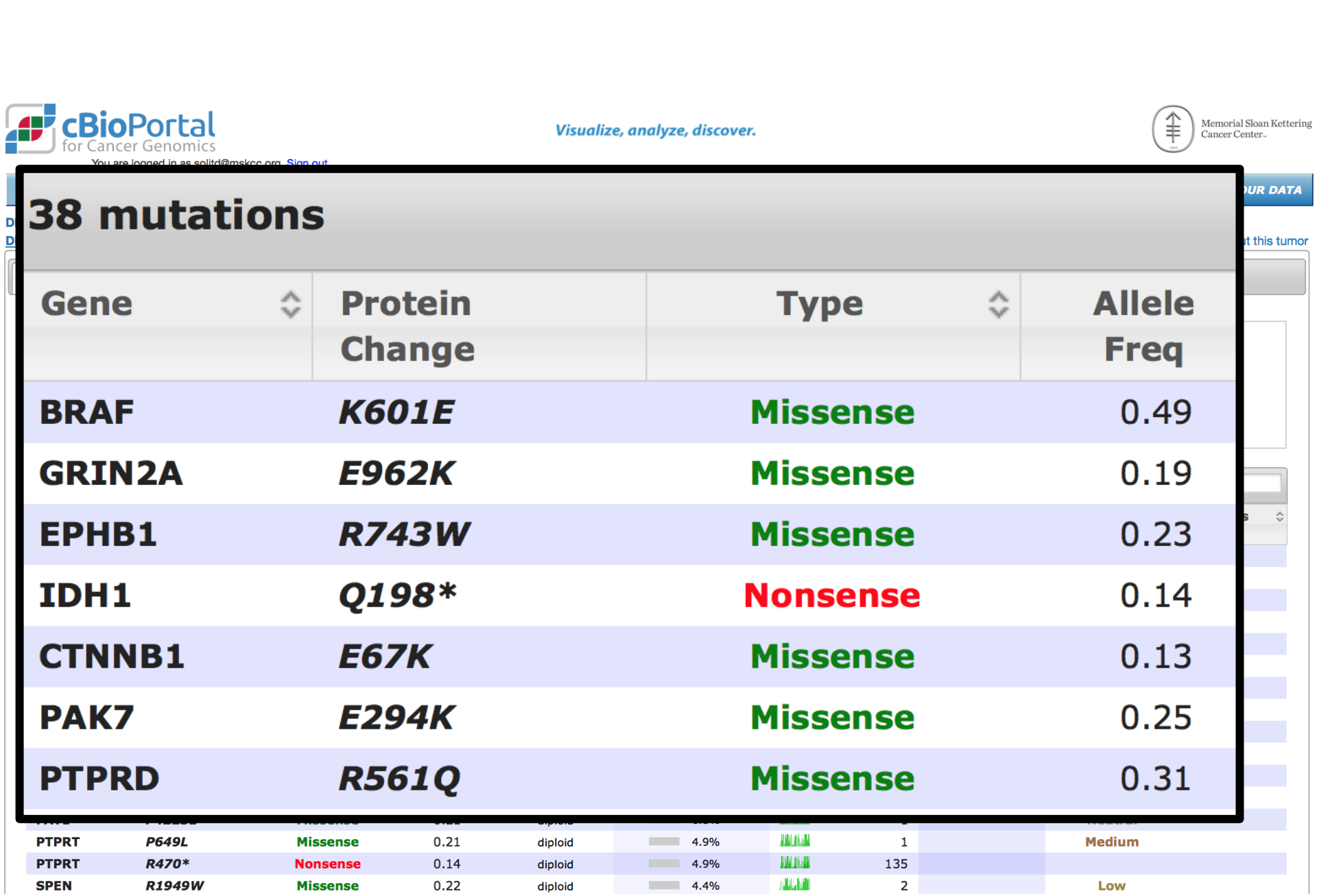
▸ **Customize**

Case Set: User-defined Case List: User defined case list.

Altered in 16 (94%) of cases



Copy number alterations are putative.


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for Cancer Genomics
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You are logged in as solitd@mskcc.org. Sign out
38 mutations
Gene
Protein Change
Type
Allele Freq
BRAF K601E Missense 0.49
GRIN2A E962K Missense 0.19
EPHB1 R743W Missense 0.23
IDH1 Q198* Nonsense 0.14
CTNNB1 E67K Missense 0.13
PAK7 E294K Missense 0.25
PTPRD R561Q Missense 0.31
PTPRT P649L Missense 0.21 diploid 4.9% 1 Medium
PTPRT R470* Nonsense 0.14 diploid 4.9% 135
SPEN R1949W Missense 0.22 diploid 4.4% 2 Low

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Gene Set / Pathway is altered in 94.1% of all cases.

DMP MSK-IMPACT Clinical Runs (MSKCC 2014)/User-defined Case List: (17)/User-defined List/7genes

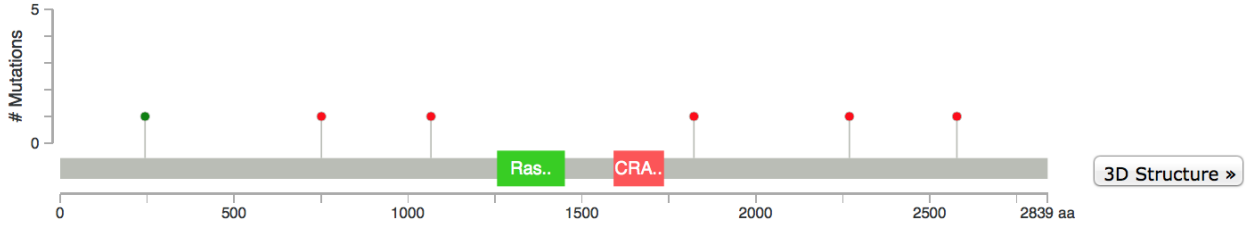
Modify Query

OncoPrint | Mutual Exclusivity | Mutations | Survival | Network | IGV | Download | Bookmark

BRAF | GNA11 | GNAQ | HRAS | MAP2K1 | NF1 | NRAS

NF1: [Somatic Mutation Rate: 29.4%]

NF1_HUMAN



3D Structure »

Show / hide columns | Showing 6 mutation(s) | Search:

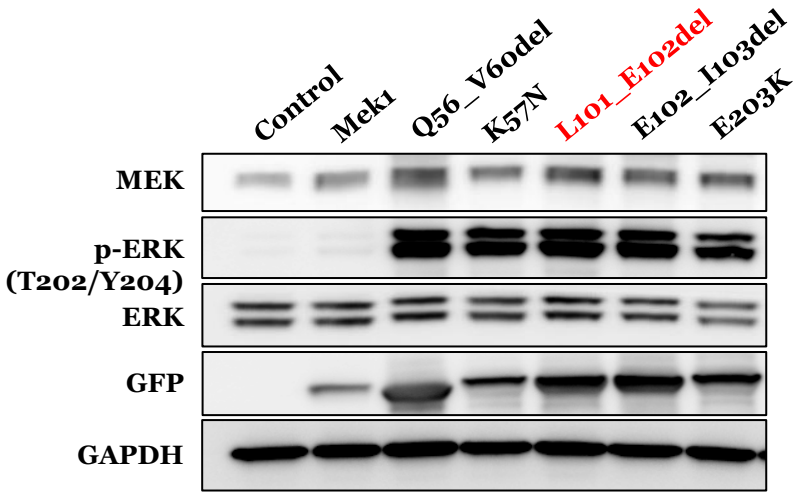
Case ID	AA change		Type	Copy #	Mutation Assessor	Allele Freq (T)	#Mut in Sample
DMP0546	*R1066_splice*		Splice	diploid		0.51	39
DMP0639	*E244K*		Missense	diploid	Neutral	0.22	164
DMP0639	*Q1822**	3D	Nonsense	diploid		0.50	164
DMP0647	*G751_splice*		Splice	diploid		0.35	8
DMP0938	*E2578**		Nonsense	diploid		0.71	2
DMP1155	*R2269fs*		FS del	diploid		0.60	74

DMP MSK-IMPACT Clinical Runs (MSKCC 2014)

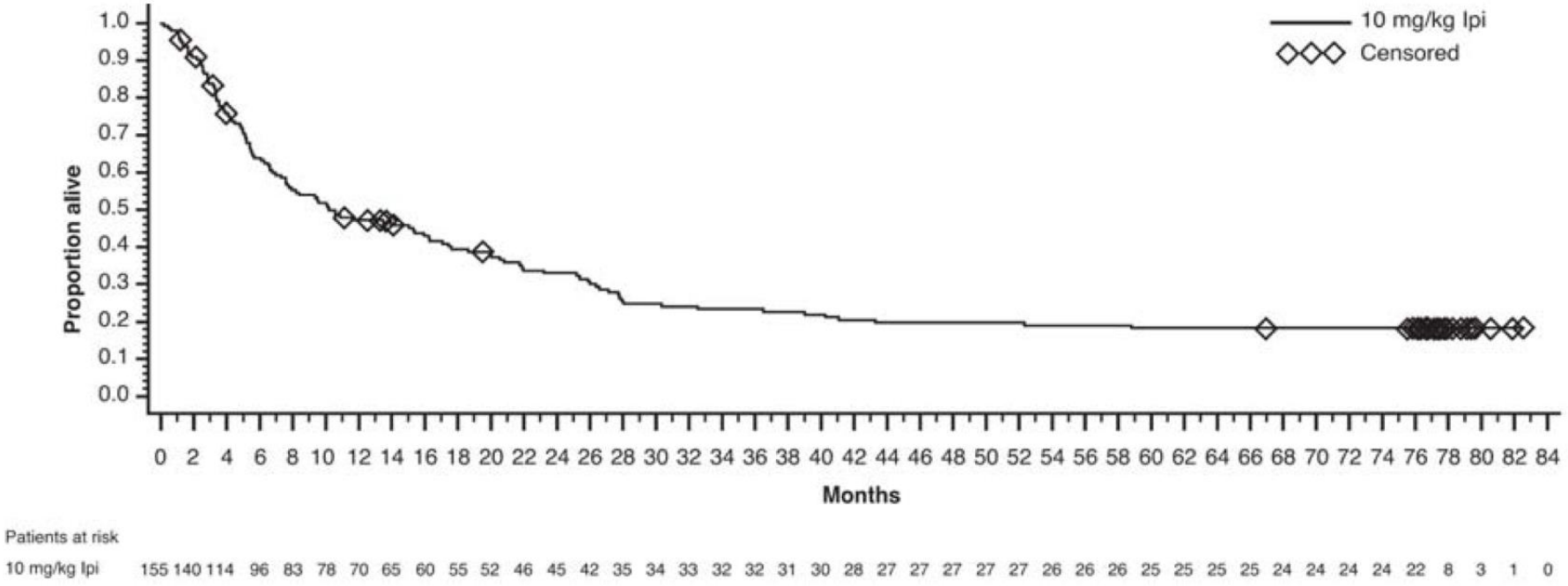
DMP08

5 mutations

Gene	Protein Change	Type	Allele Freq
PIK3CD	*N334K*	Missense	0.35
CDKN2AP16INK4A	*R112P*	Missense	0.28
ROS1	*S141R*	Missense	0.07
GATA3	*S370R*	Missense	0.07
MAP2K1	*LE101del*	Deletion	0.27

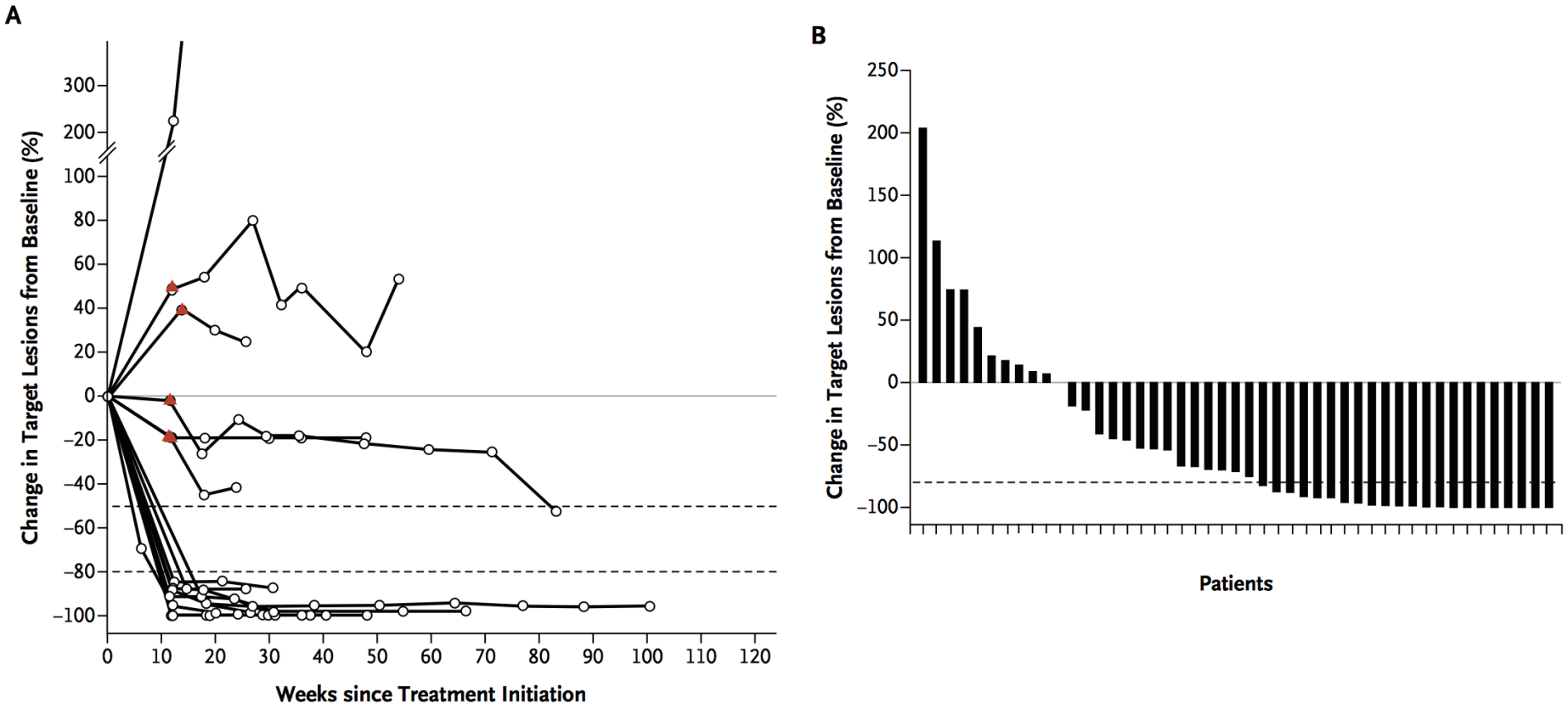


Do we still need targeted therapies for melanoma in an era of active immunotherapy

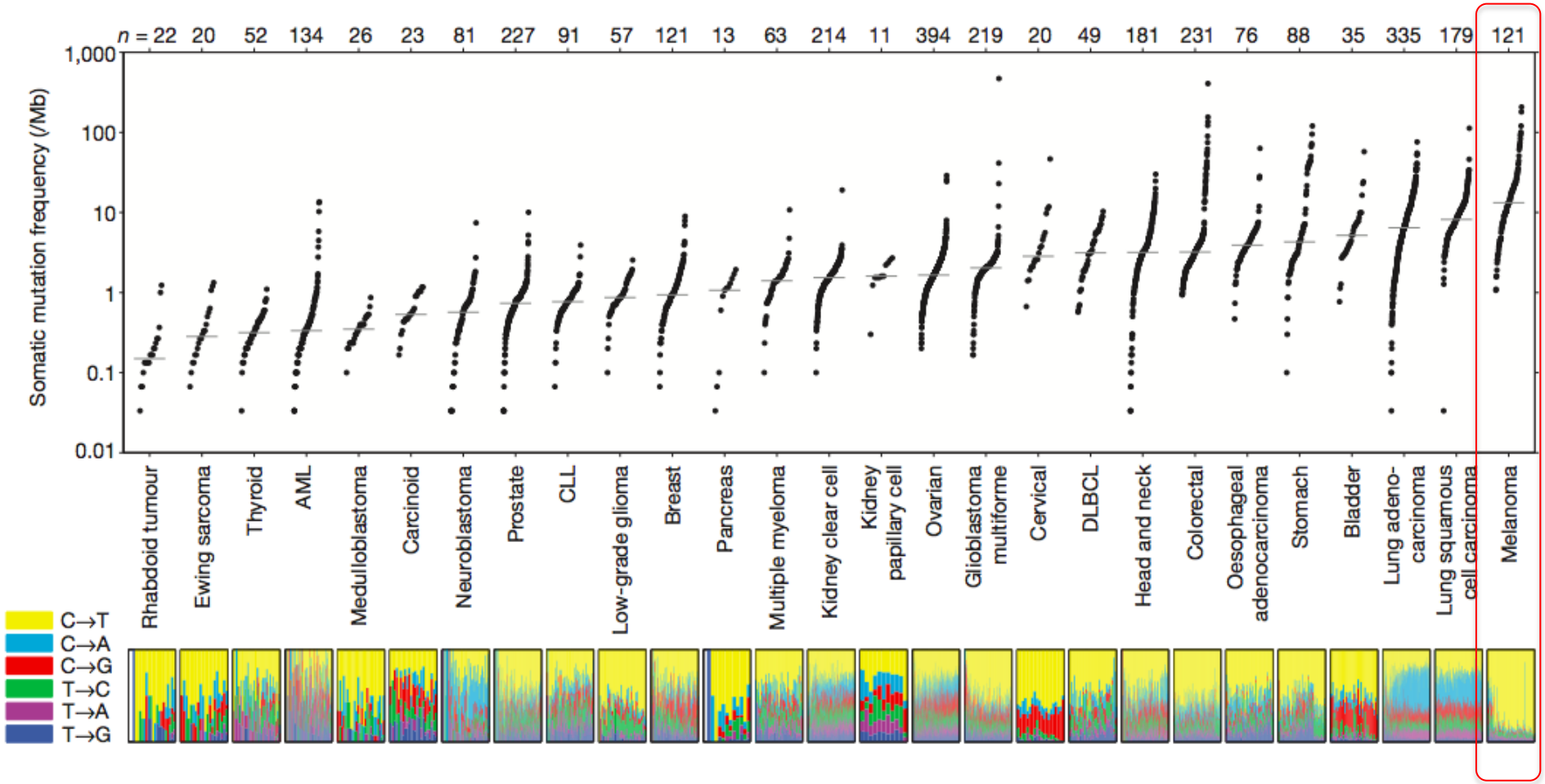


Lebbe et al., Annals of Oncology, in press

Do we still need targeted therapies for melanoma in an era of active immunotherapy



Wolchok et al., NEJM, 2014



Lawrence et al., Nature, 201

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