How to Overcome Resistance in Mutation Driven Therapies

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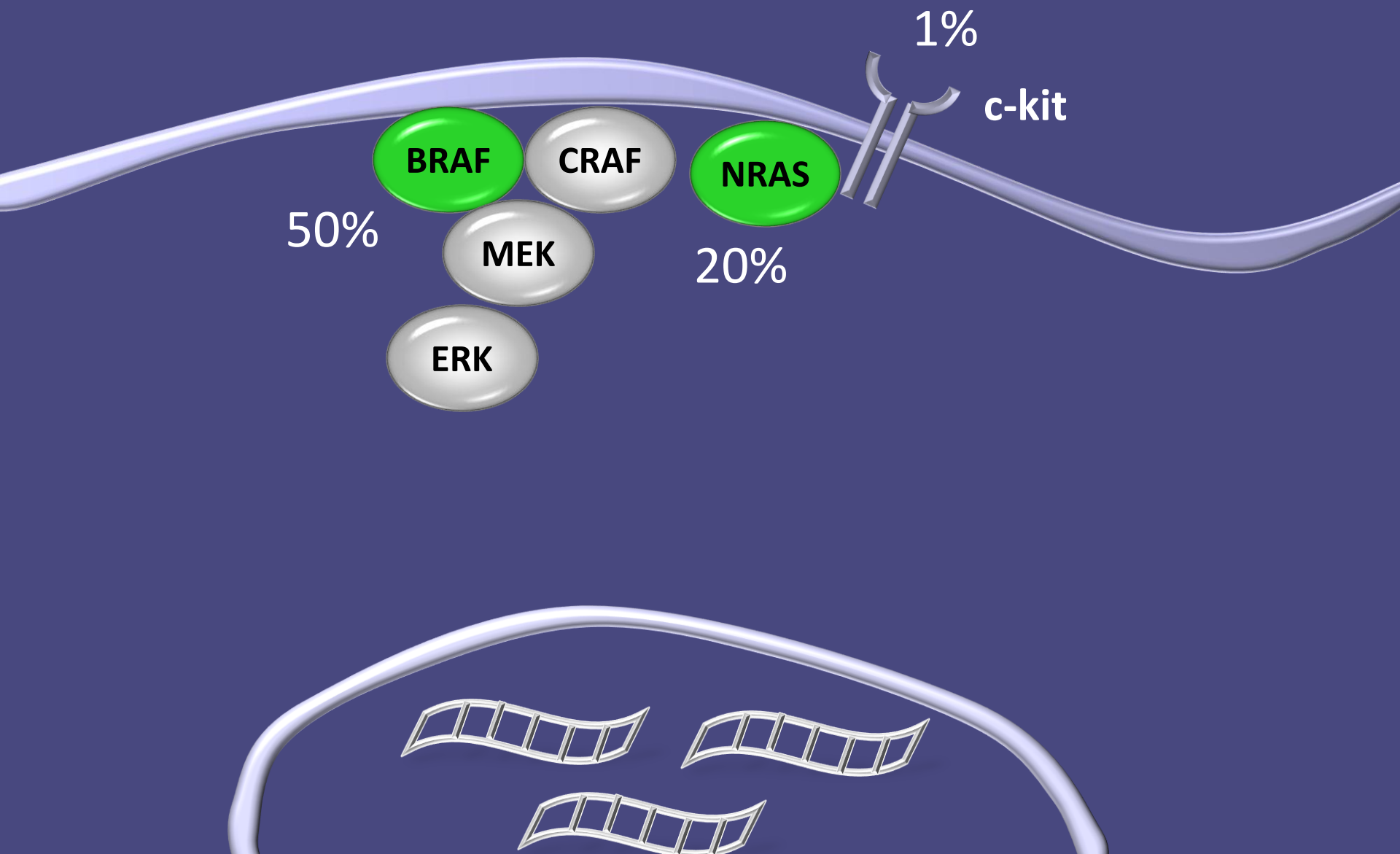
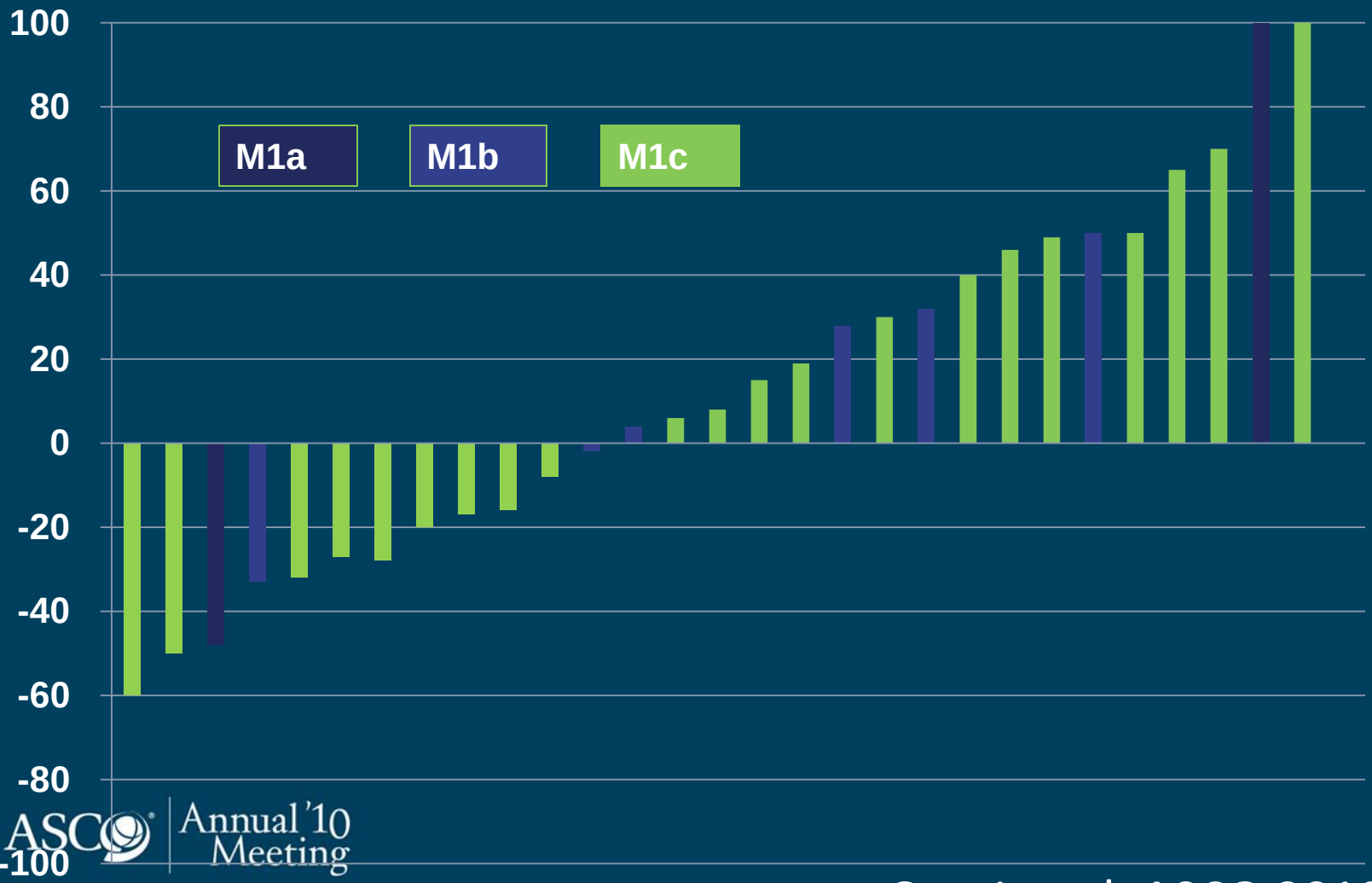
Driver mutations in melanoma



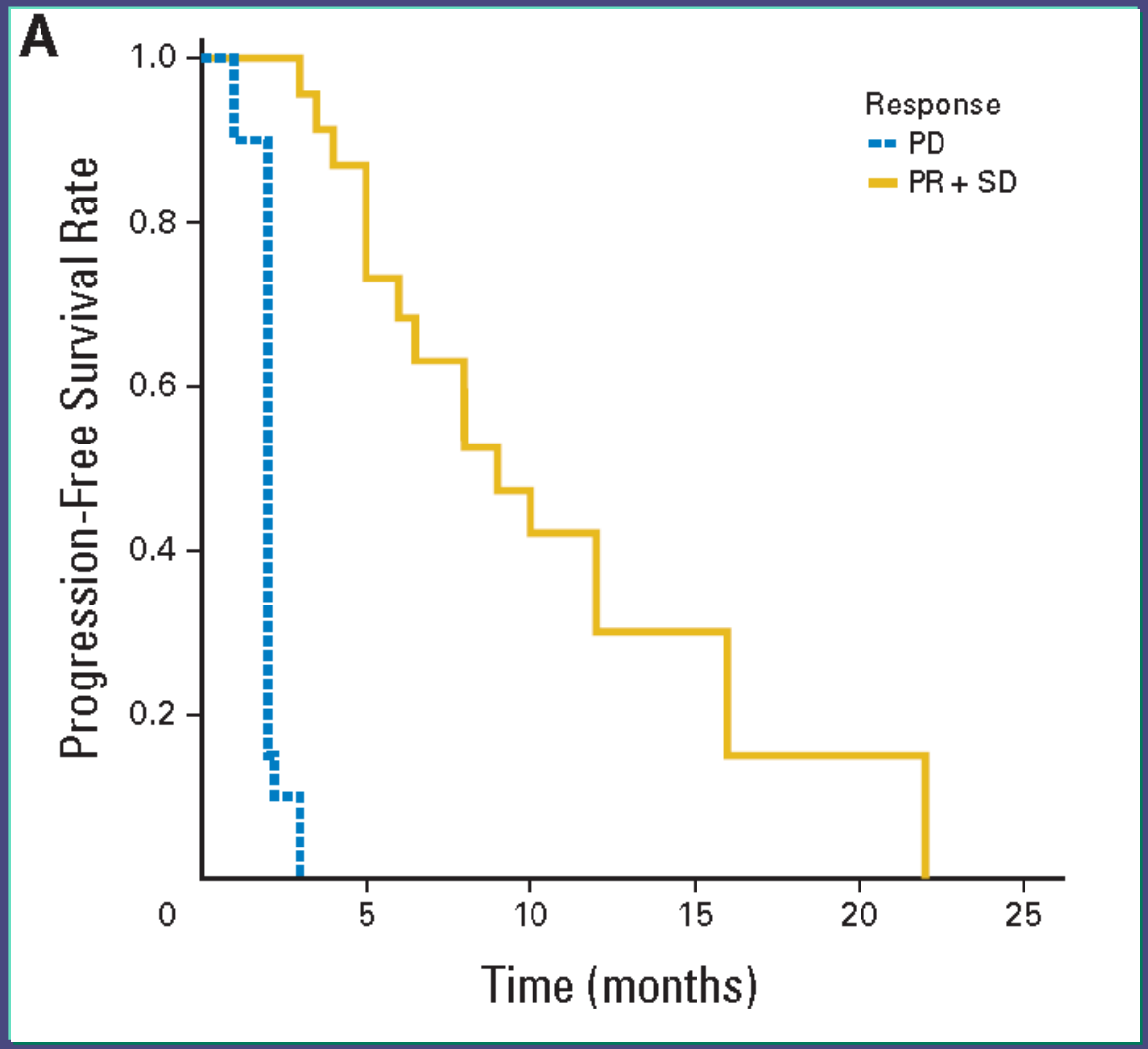
Imatinib in CKIT mutant/amplified melanoma: Change in tumor size



ASCO Annual '10 Meeting

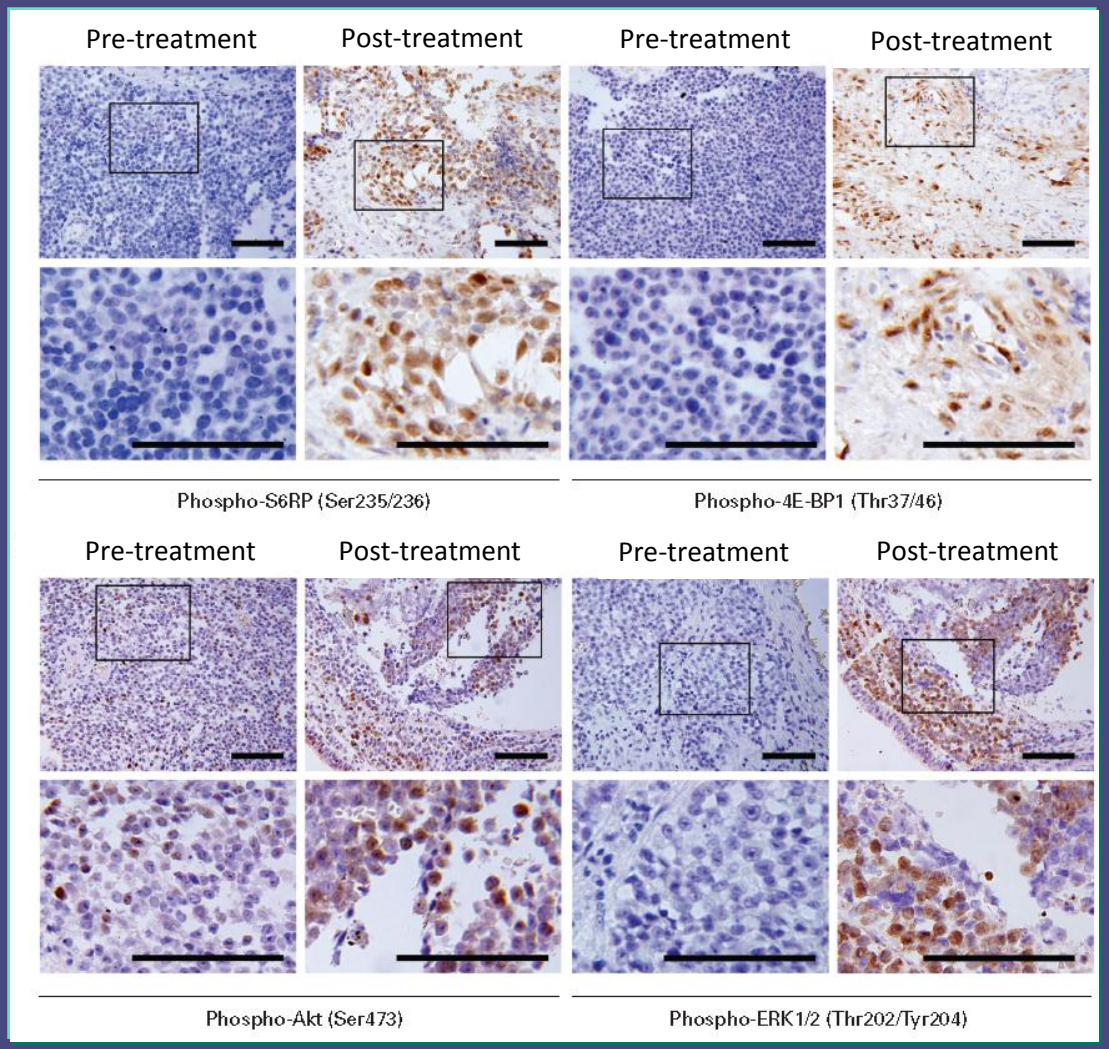
Guo J et al, ASCO 2010

Progression-free survival based on best response to imatinib



Guo J et al. JCO 2011

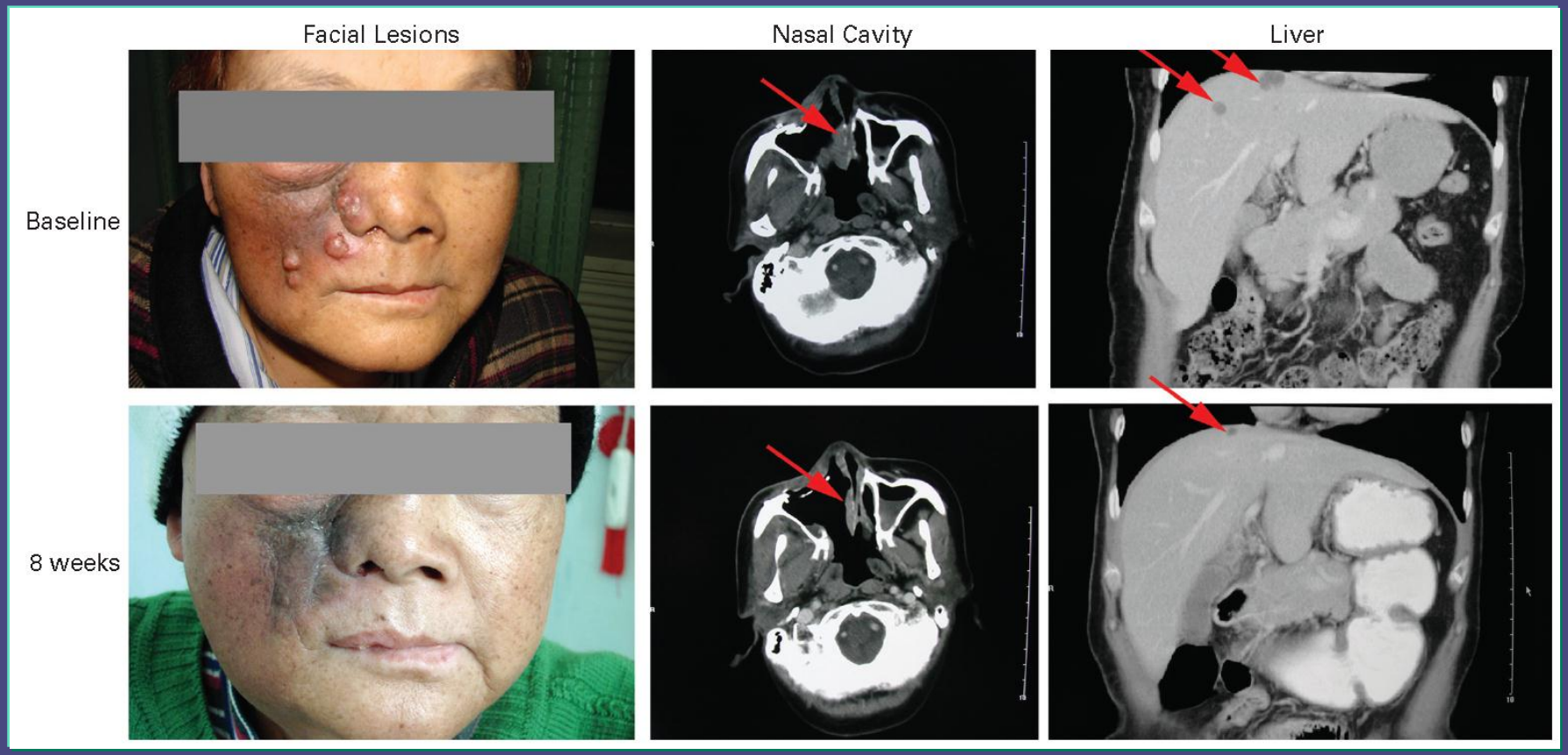
Evidence of reactivation of AKT signaling



pMEK & cyclin D not detectable

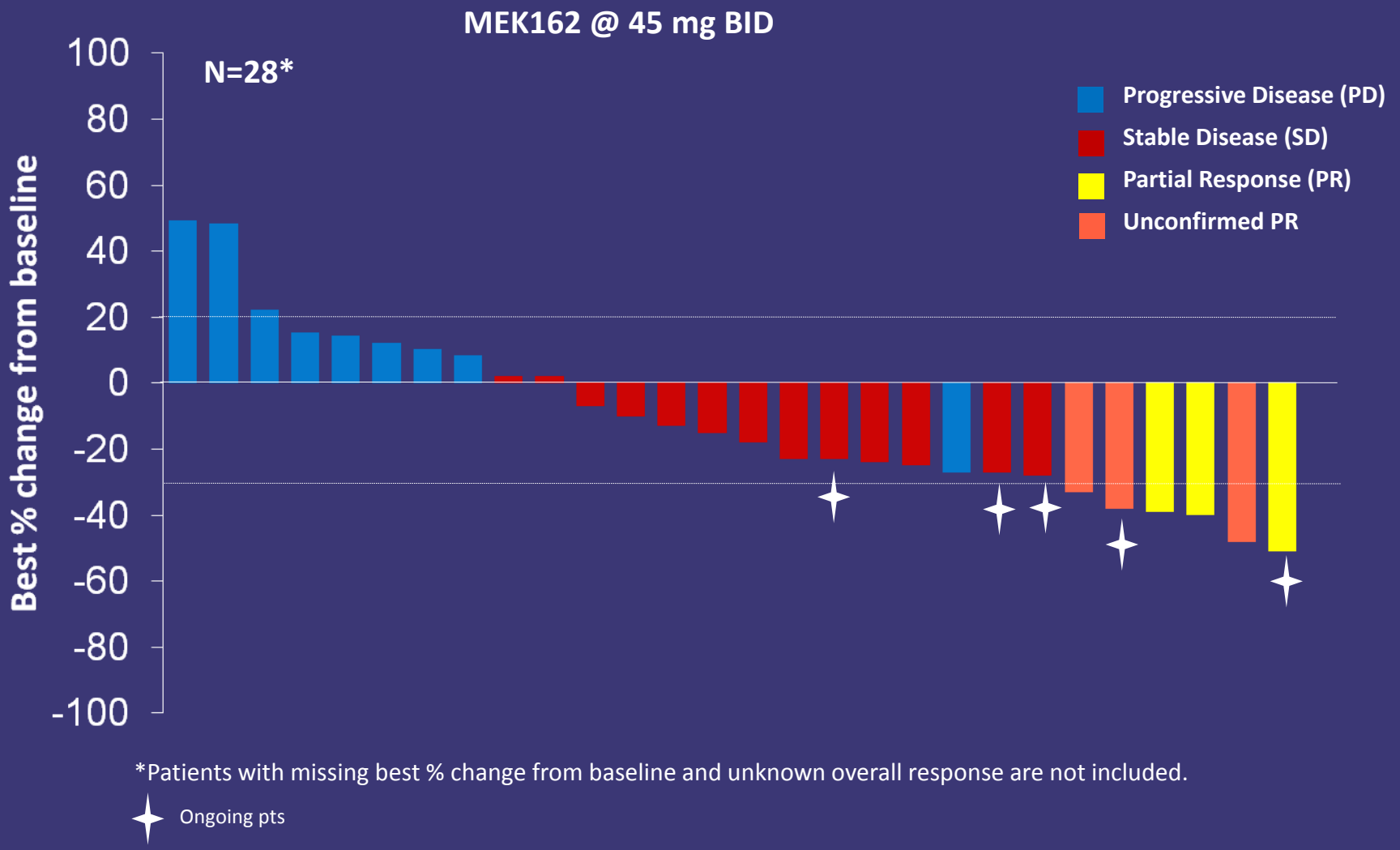
Si L et al. JCO 2011; 30(4):e37-40

Response to single-agent everolimus



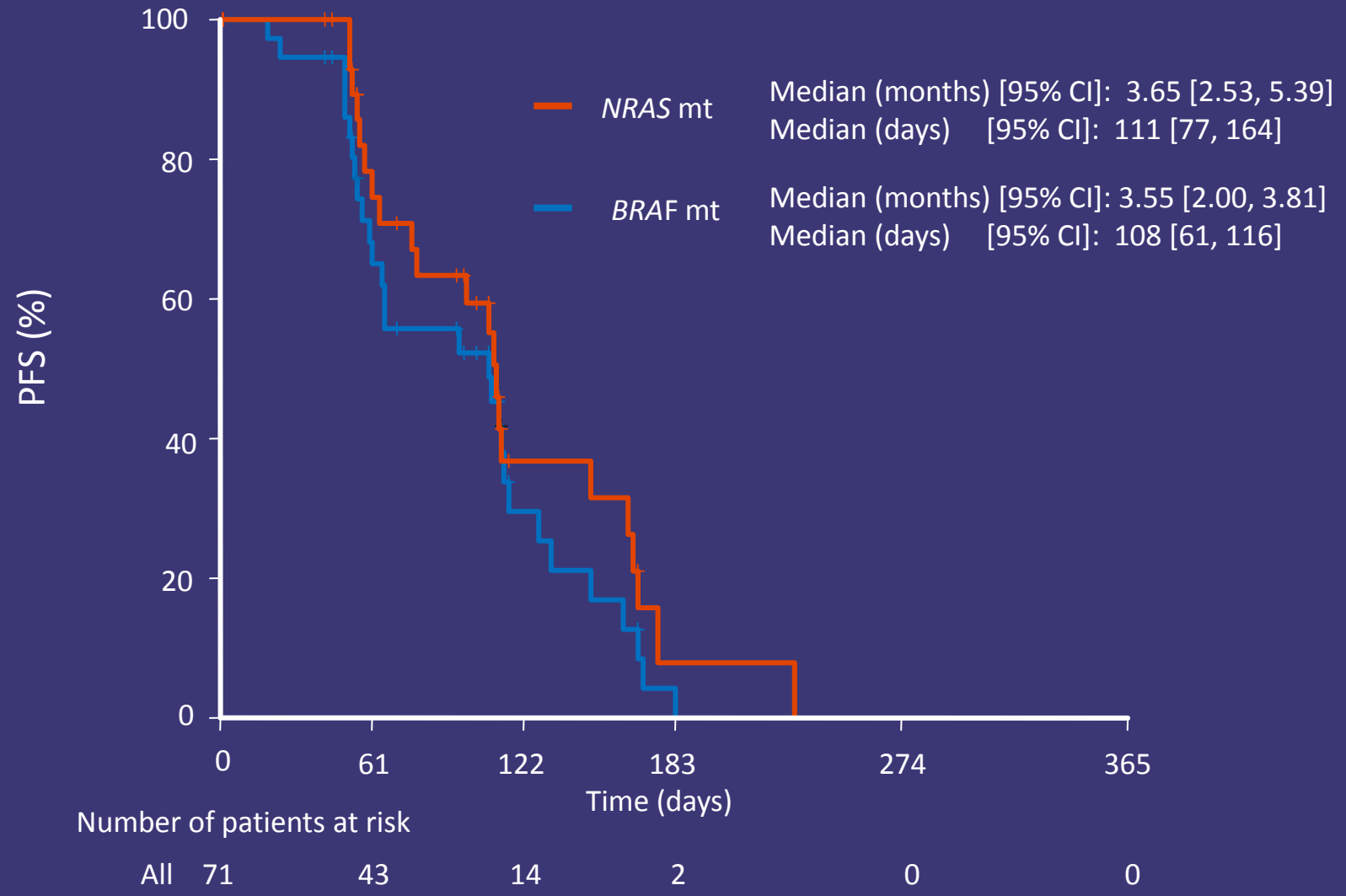
Si L et al. JCO 2011; 30(4):e37-40

Single-agent MEK inhibition in NRAS mutant melanoma



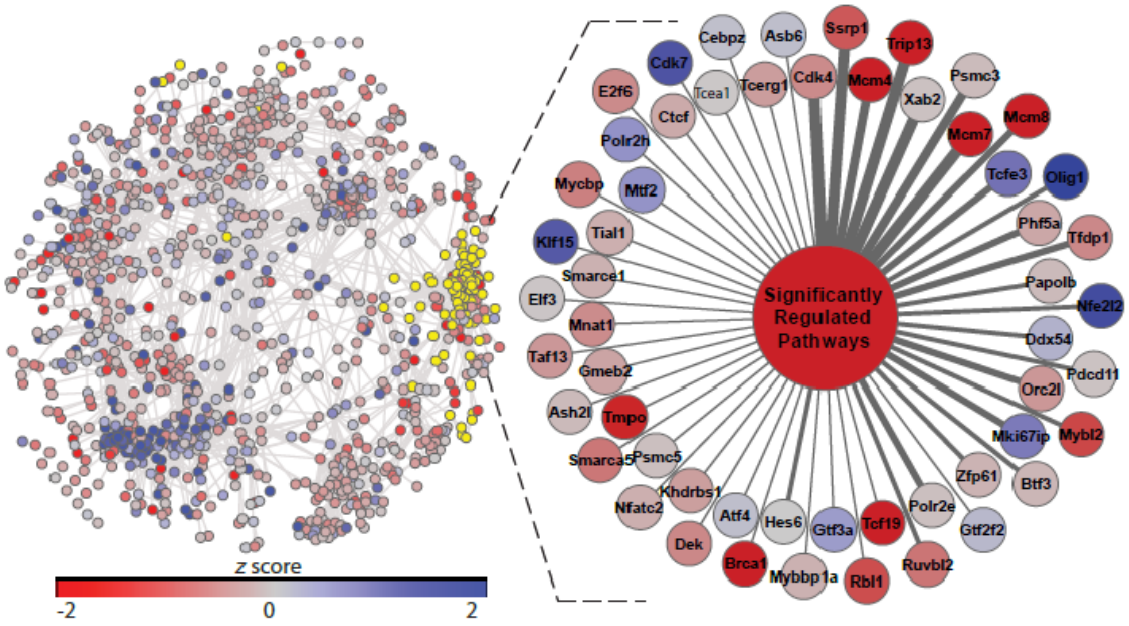
Ascierto P et al. J Clin Oncol 30, 2012 (suppl; abstr 8511)

Progression-free survival: *NRAS or BRAF* mutant



Ascierto P et al. J Clin Oncol 30, 2012 (suppl; abstr 8511)

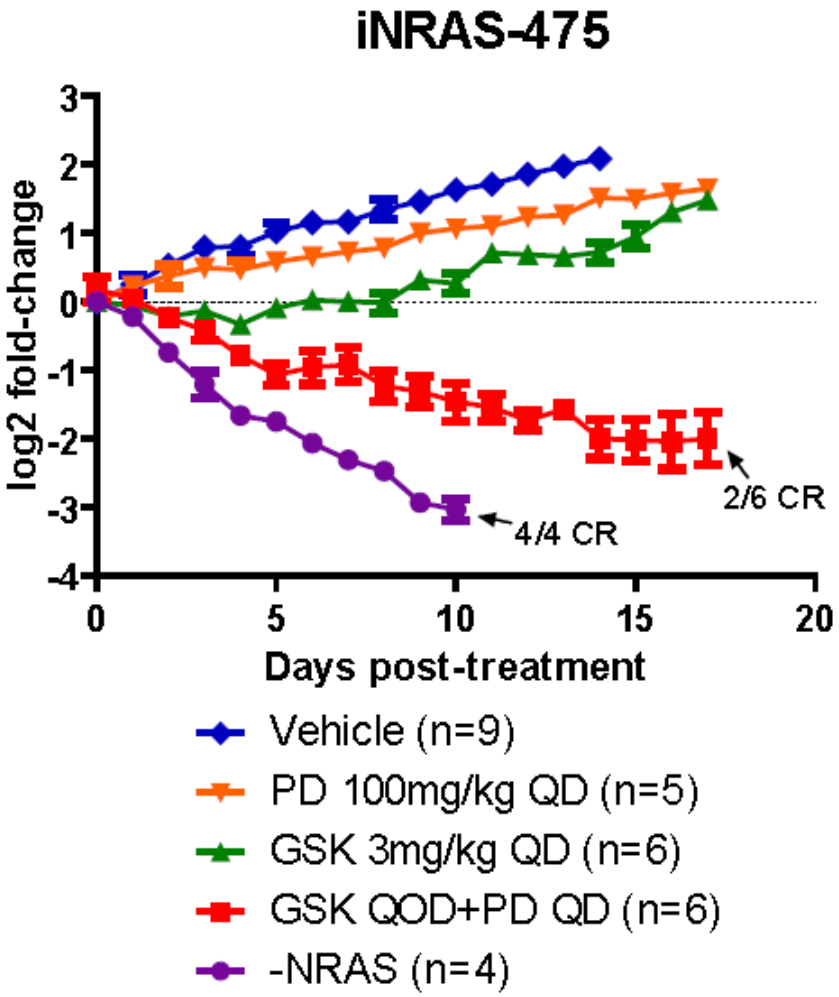
CDK4 identified as the most highly ranged regulator of RAS-specific signaling following MEK inhibition

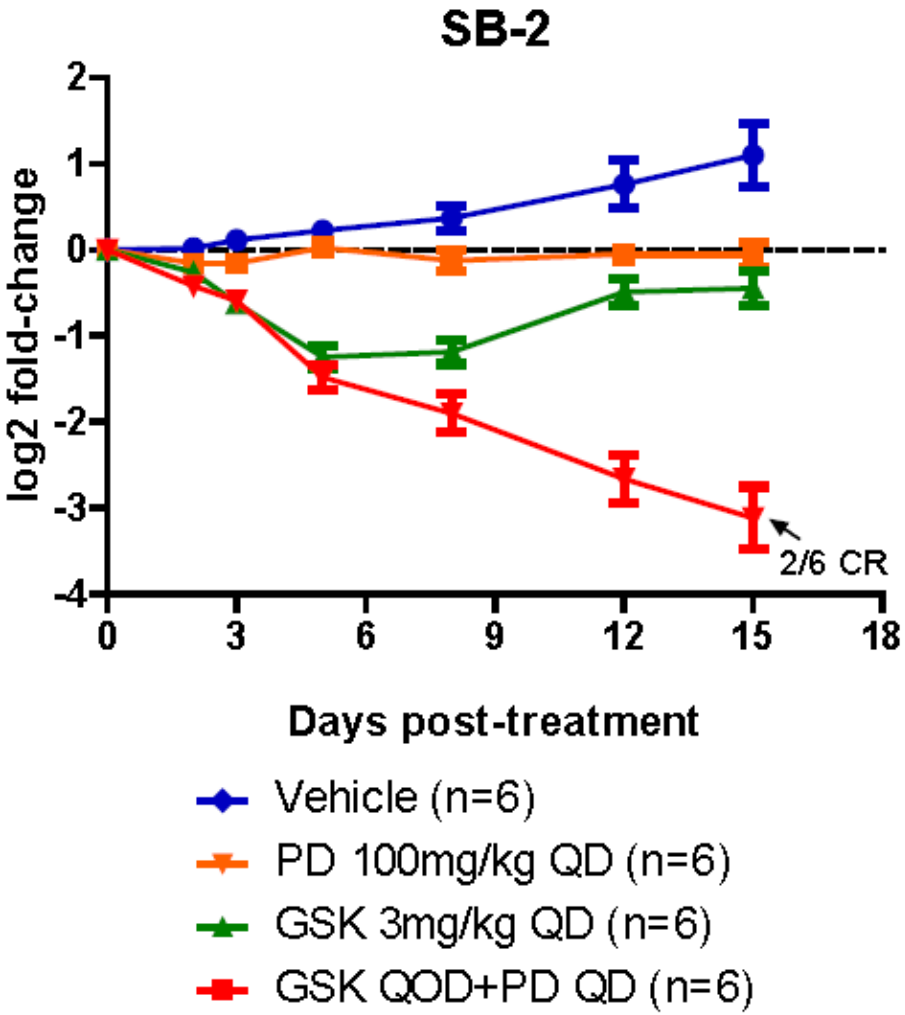


Regulator	Degree Centrality
Cdk4	4.02
Trip13	3.96
Ssrp1	3.89
Xab2	3.75
Psmc3	3.26
Mcm7	3.21
Mcm4	2.76
Mcm8	2.45
Phf5a	2.45
Tcfe3	2.36

Kwong L et al. Nat Med 2012 Sep 16. doi: 10.1038/nm.2941.

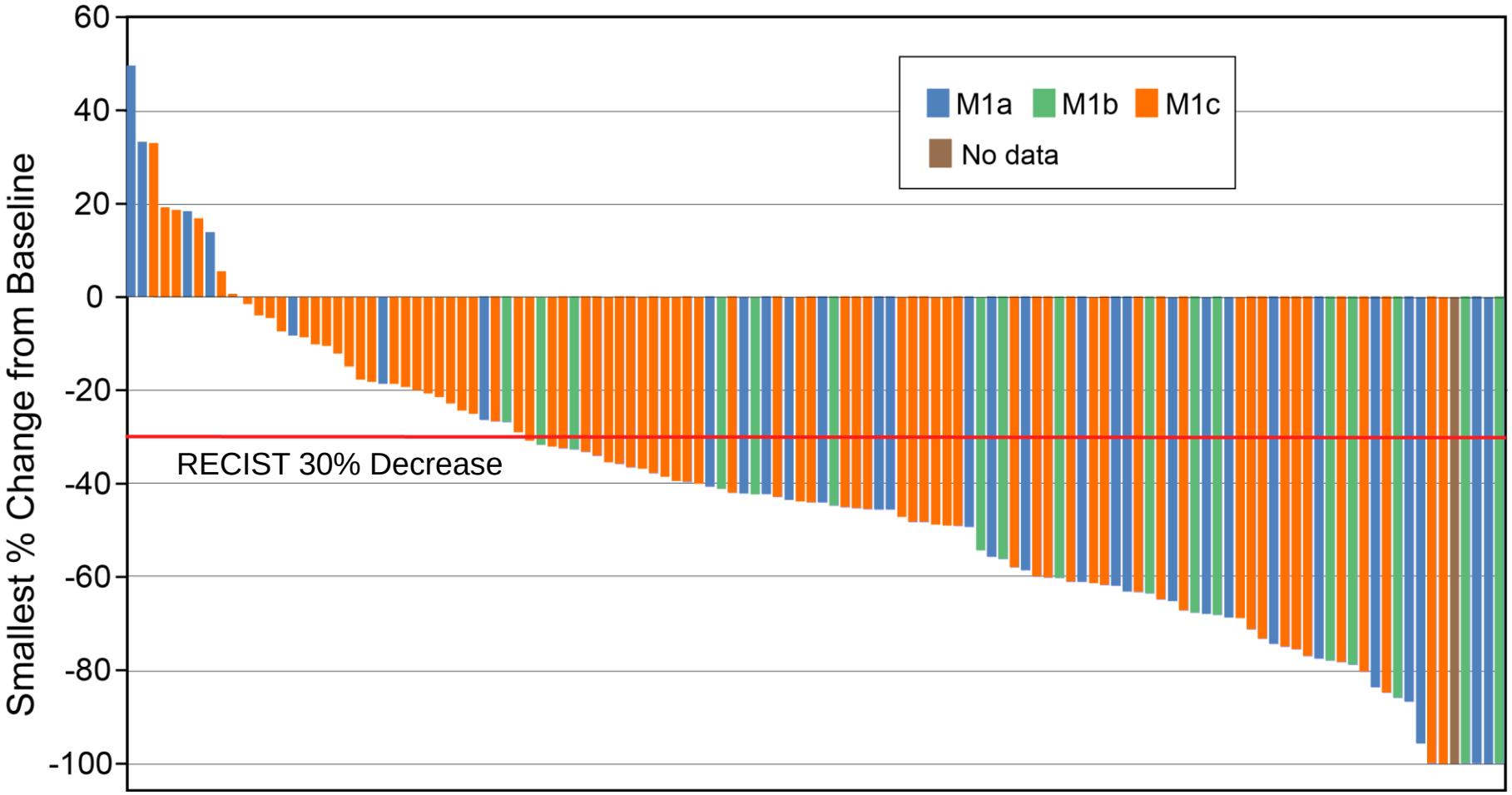
Combined MEK-CDK4 inhibition in inducible NRAS transgenic & xenograft





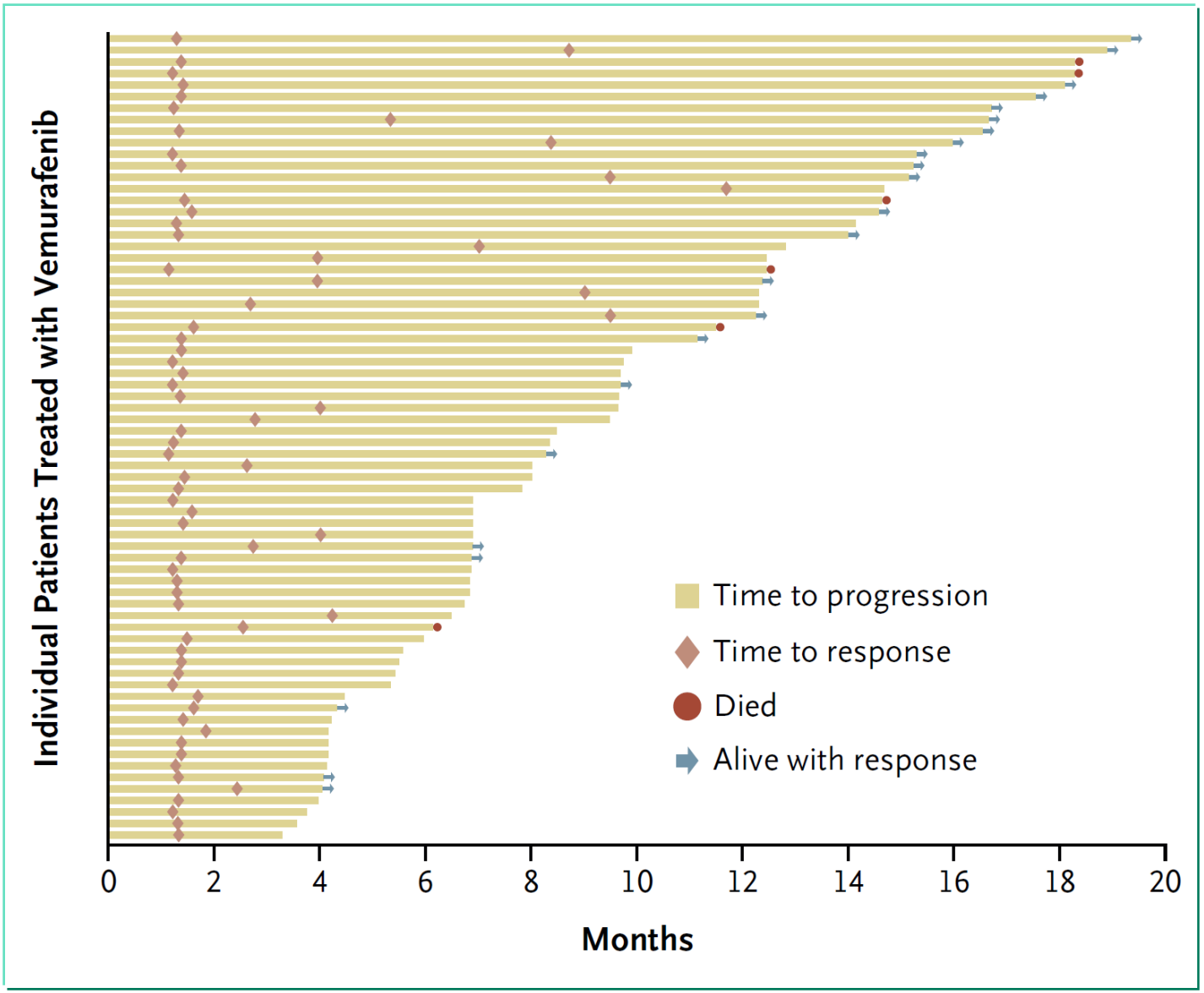
Kwong L et al. Nat Med 2012 Sep 16. doi: 10.1038/nm.2941.

Change in tumor size in 122 ^{V600E}BRAF mutant melanoma patients (vemurafenib)



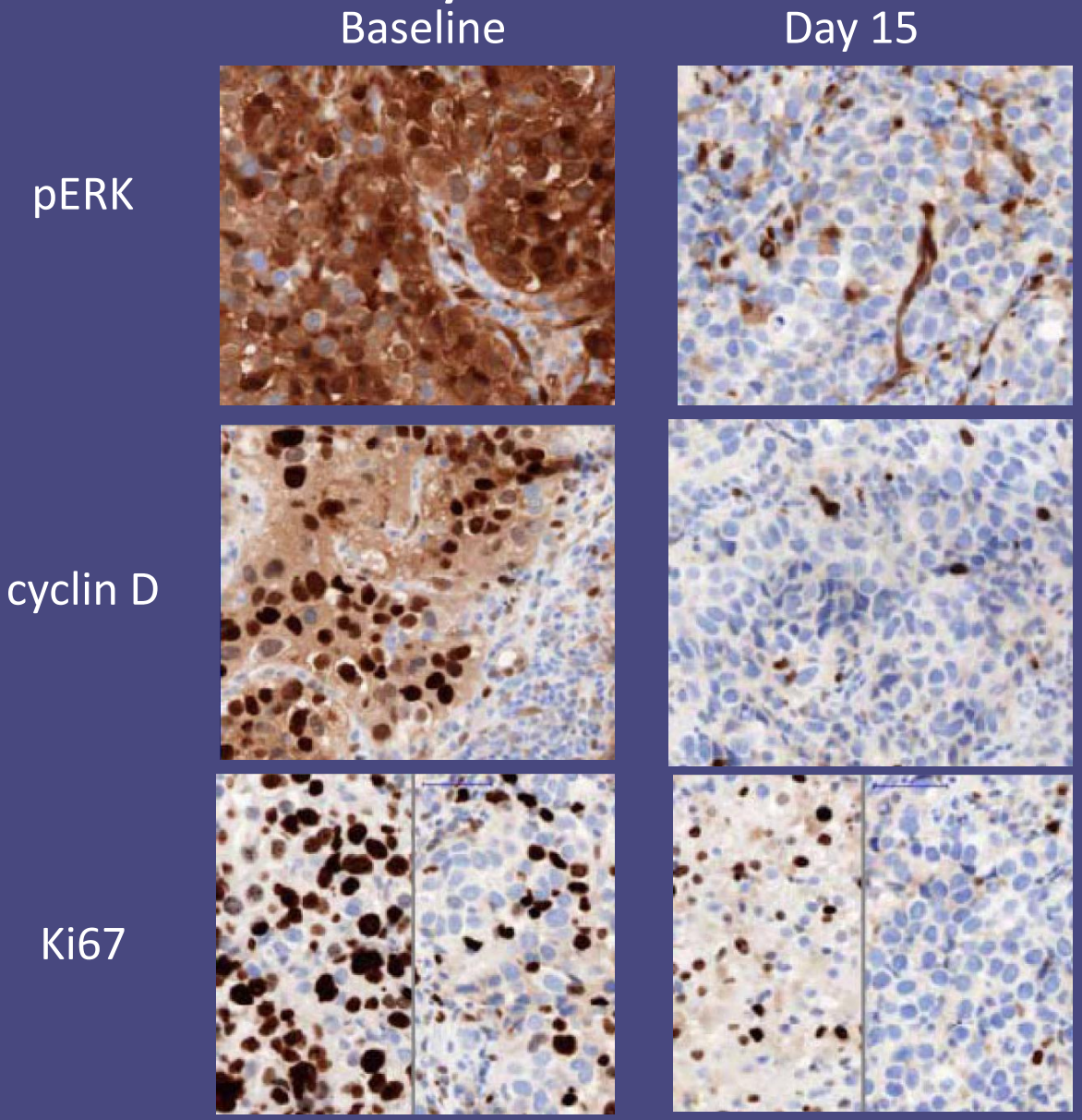
Sosman J et al. NEJM 2012

Progression-free survival in vemurafenib phase II trial



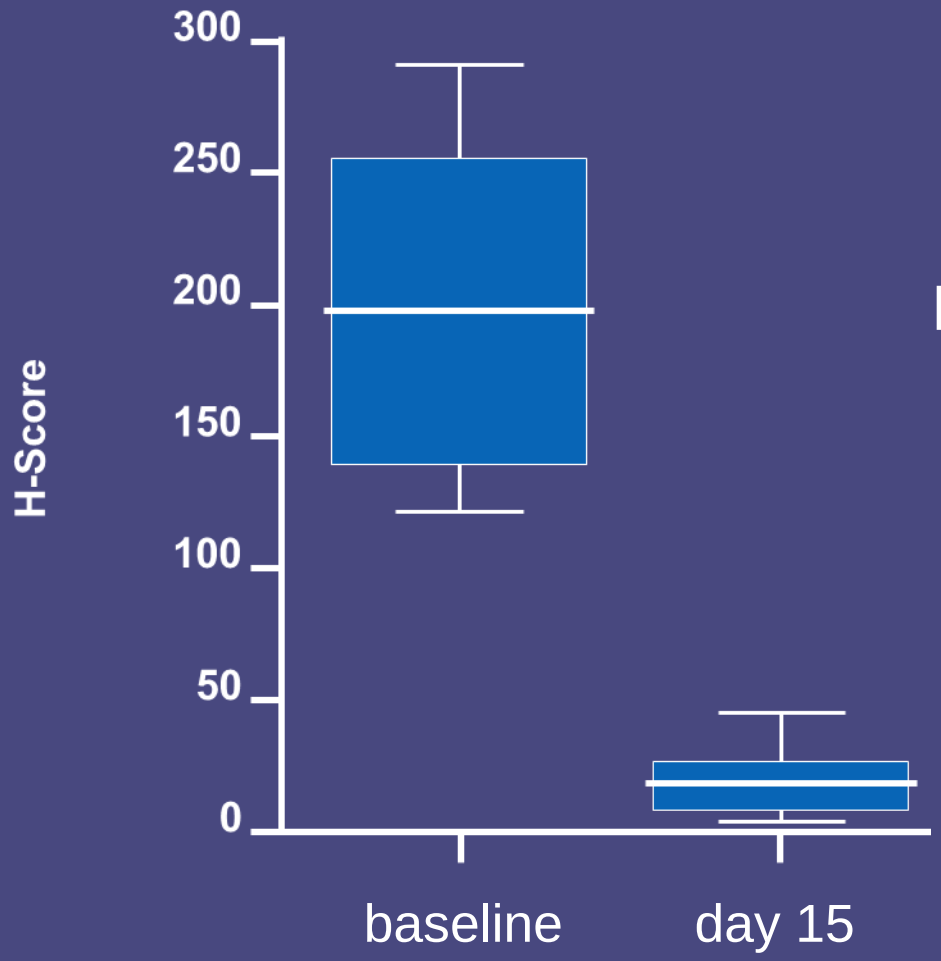
Sosman J et al. NEJM 2012

Changes in MAP kinase signaling and markers of cell cycle on vemurafenib



Flaherty KT et al.
NEJM 2012

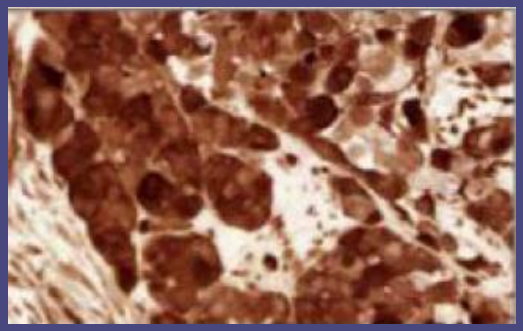
Cytoplasmic pERK on vemurafenib



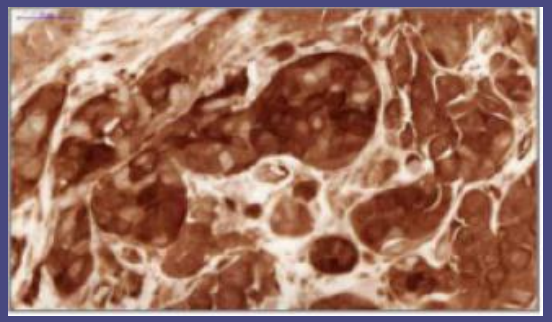
N = 23

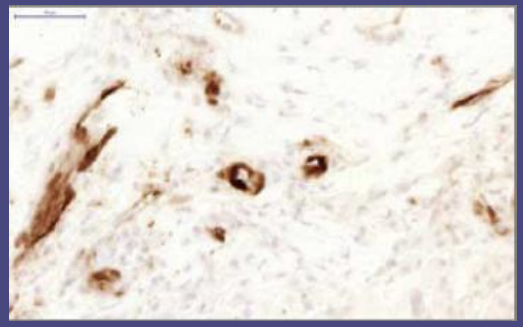
McArthur G et al.
ASCO 2011

pERK through response & progression

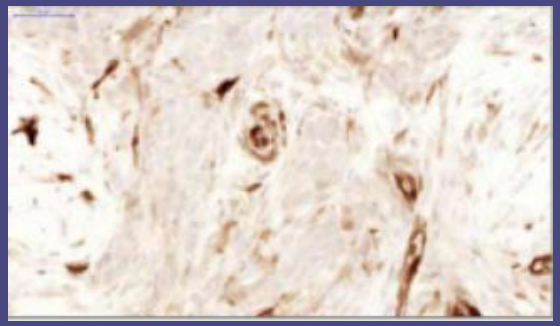


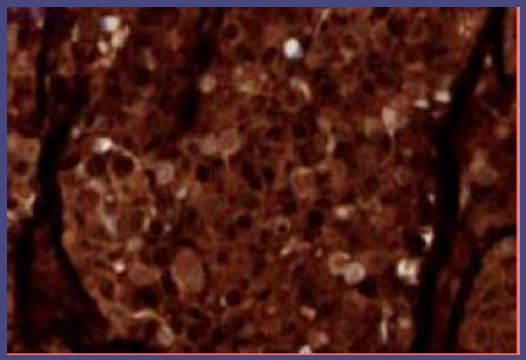
Baseline



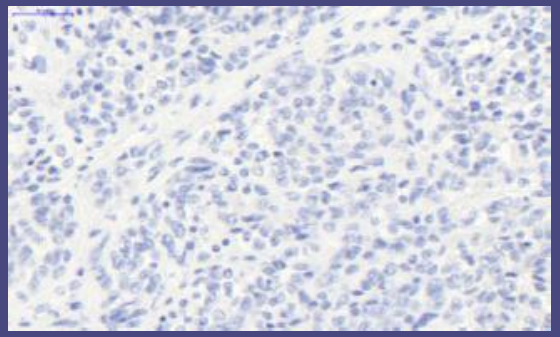


Day 15

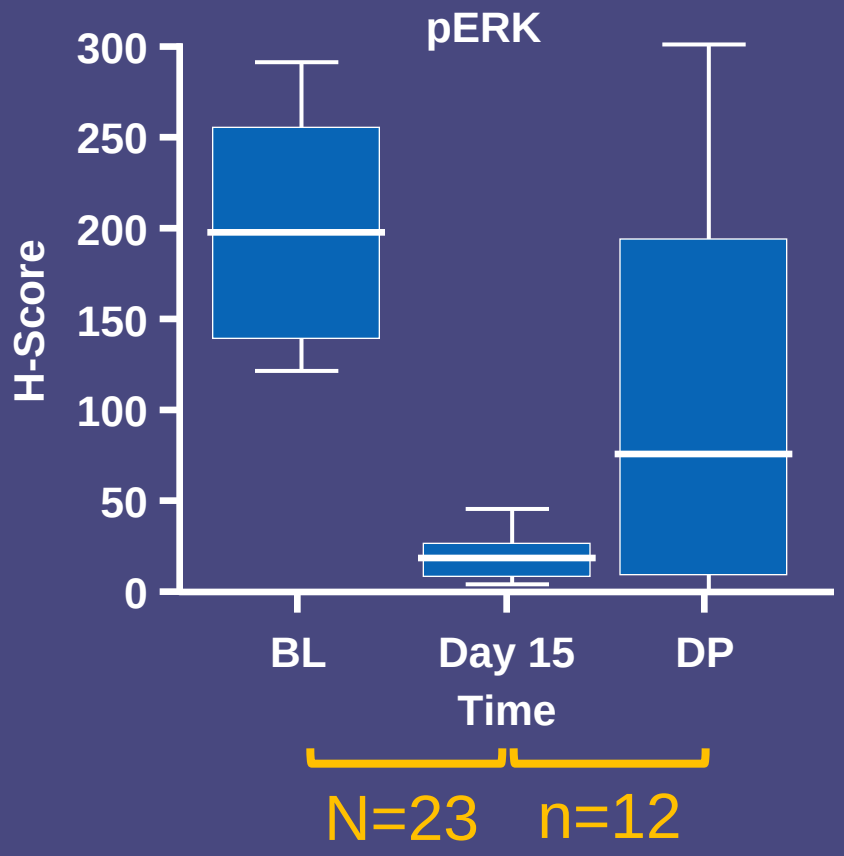


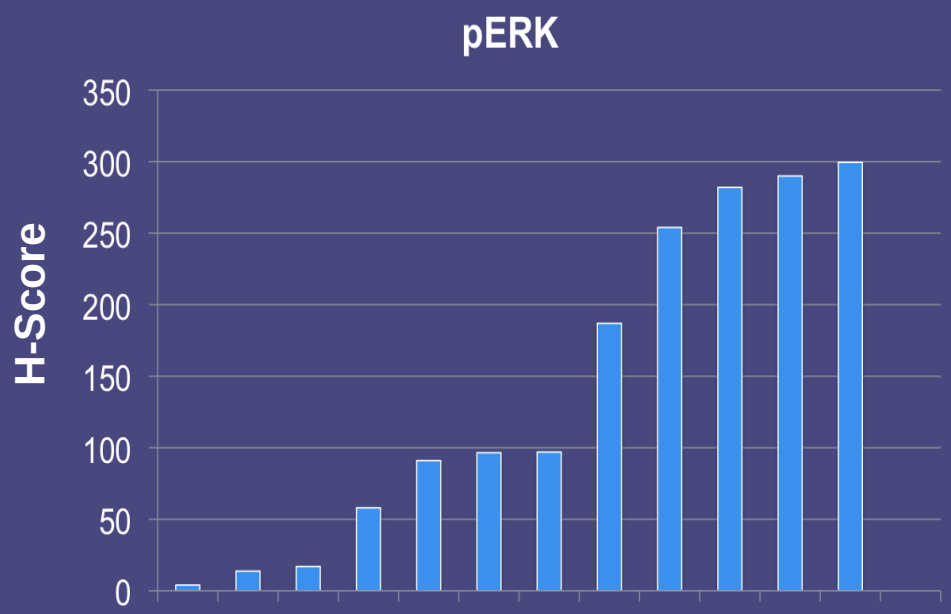


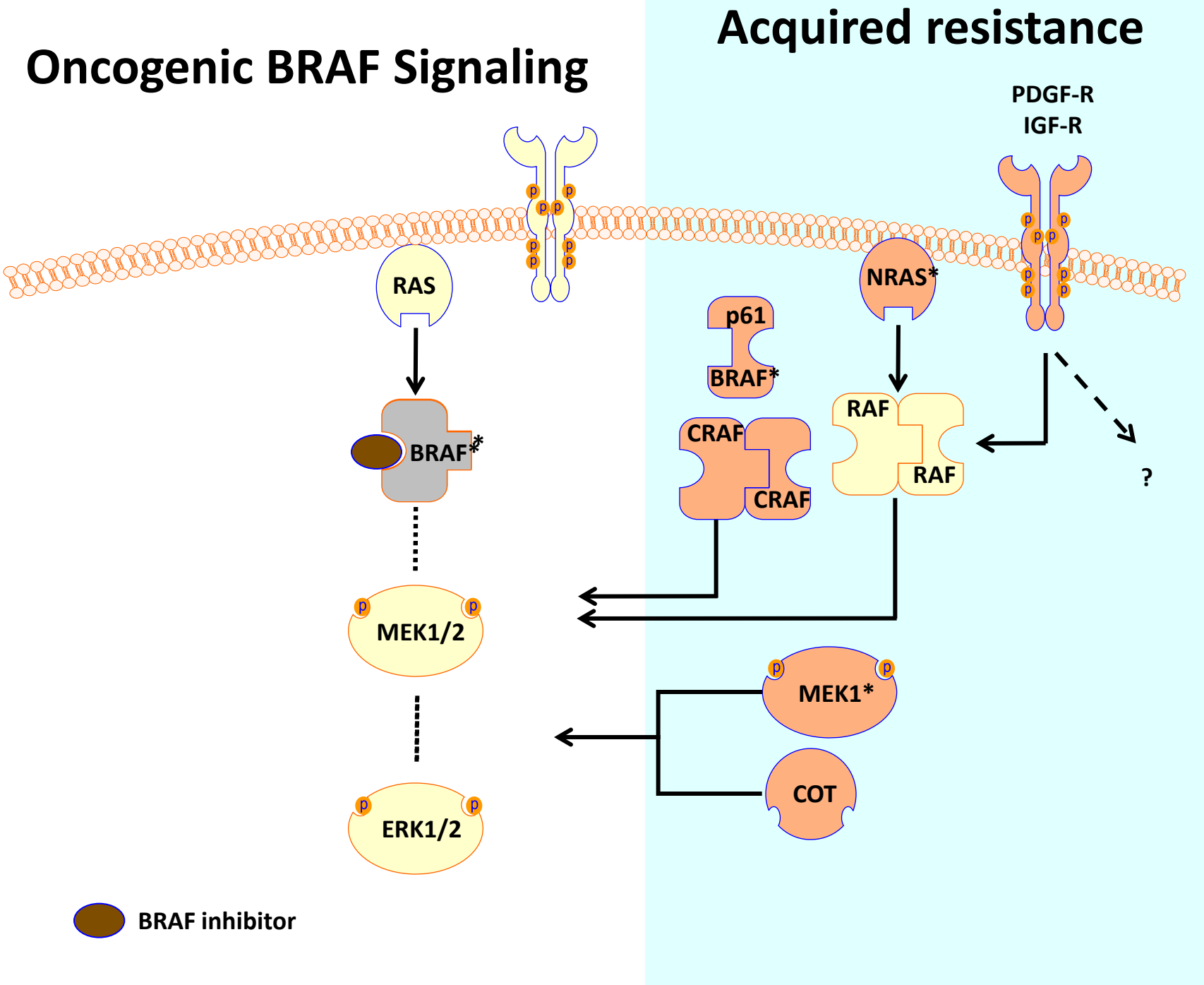
Disease progression



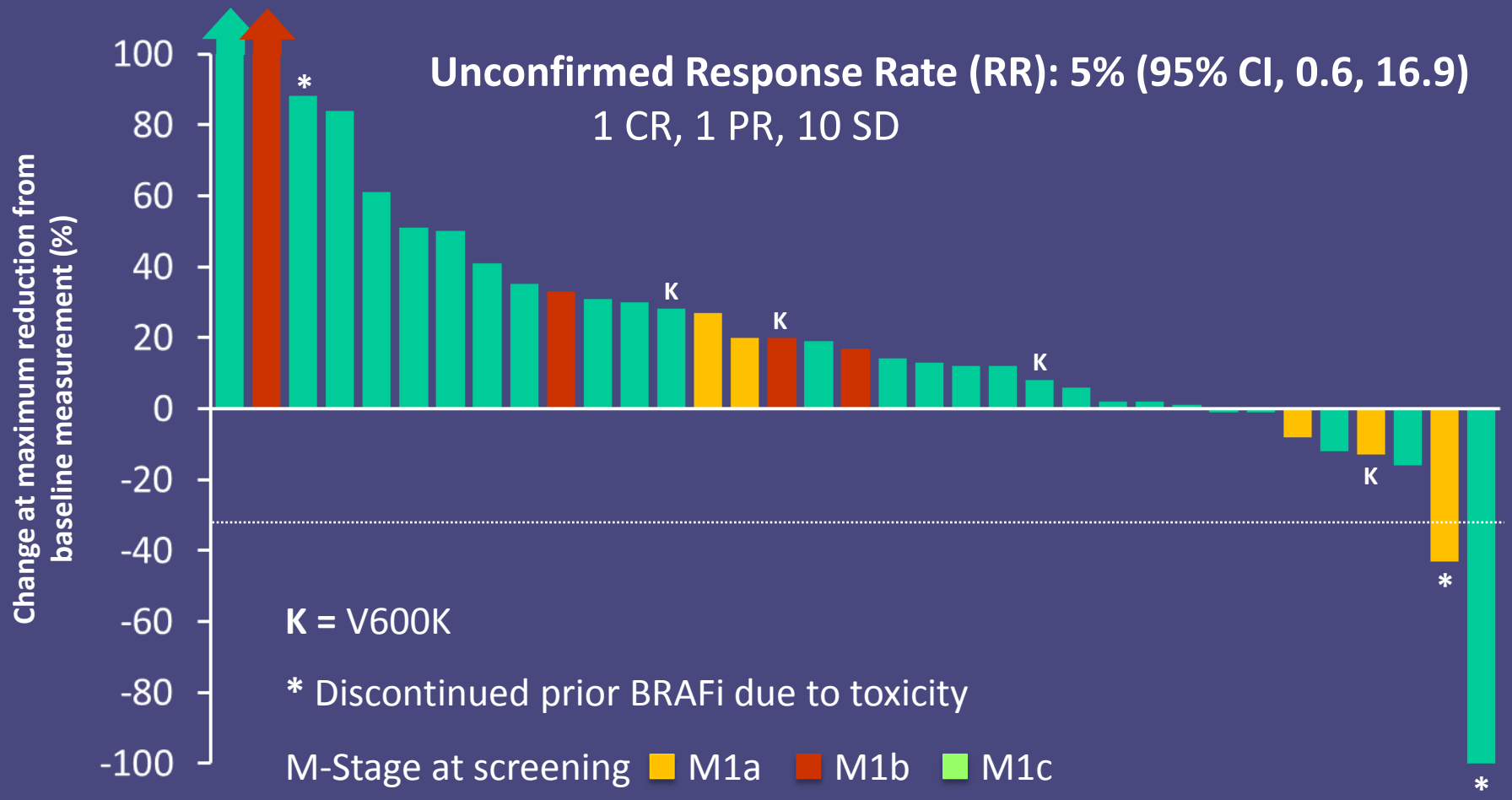
ERK phosphorylation is restored variably at progression





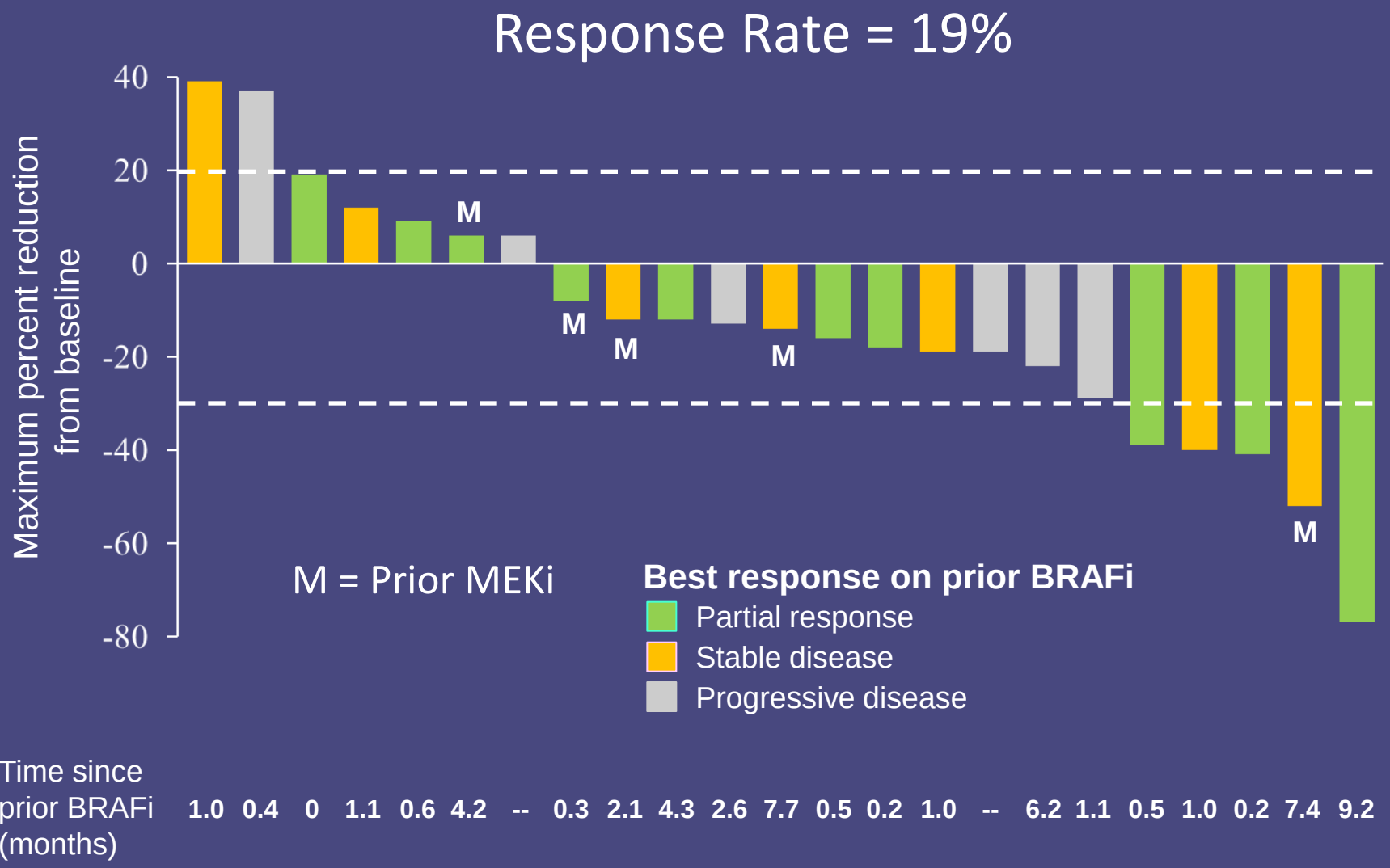

Oncogenic BRAF Signaling
Acquired resistance
PDGF-R
IGF-R
RAS
NRAS*
p61
BRAF*
BRAF*
CRAF
CRAF
RAF
RAF
?
MEK1/2
MEK1*
COT
ERK1/2
BRAF inhibitor

Single-agent MEK inhibitor has minimal activity in BRAFi refractory patients



Kim KB et al. SMR 2011

Tumor regression on BRAF/MEK combination in BRAF inhibitor refractory patients



Flaherty KT et al. SMR 2011

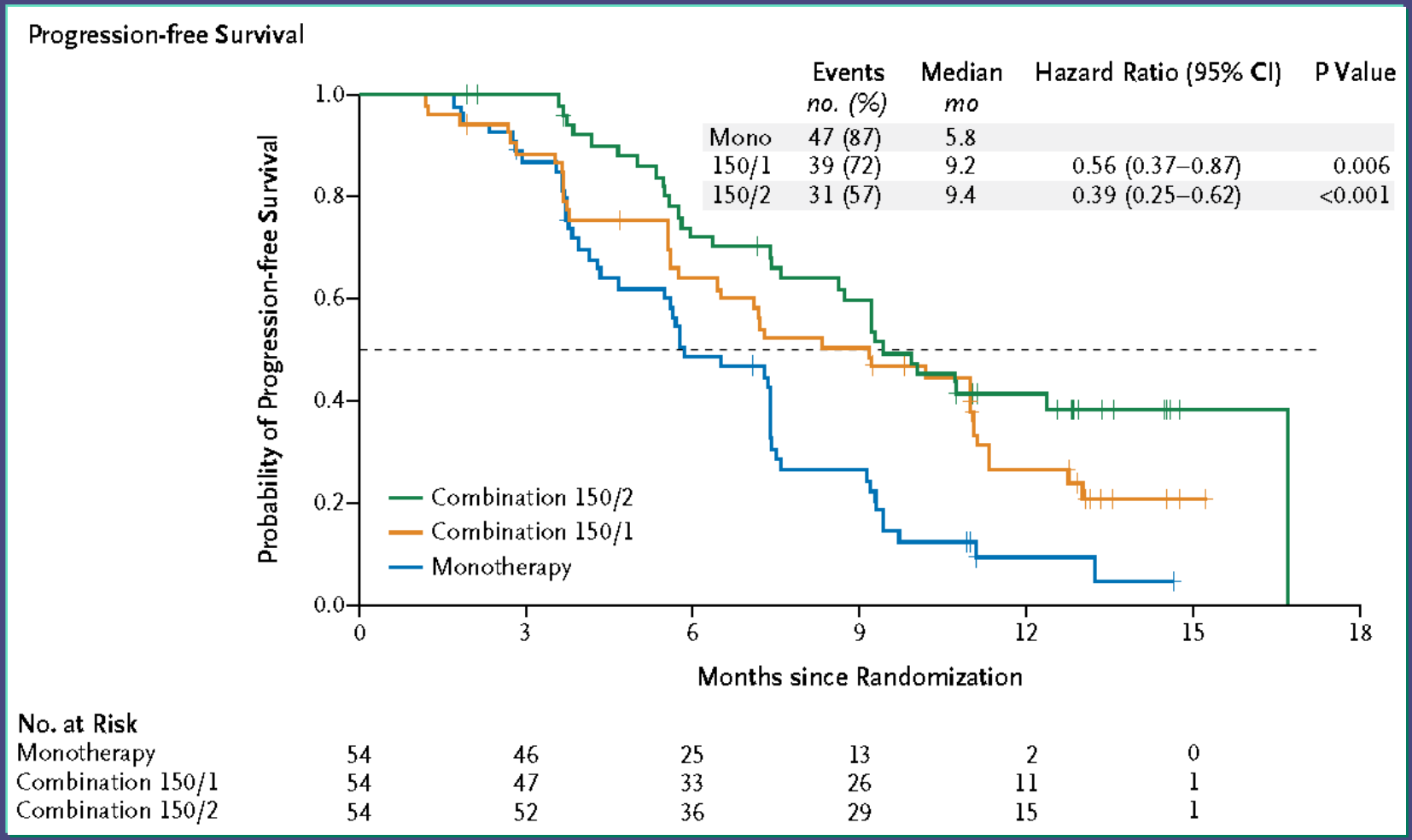
Dabrafenib/trametinib vs. dabrafenib: Confirmed Response Rate

	Mono D (N=54)	Combination D+T 150/1 (N=54)*	Combination D+T 150/2 (N=54)
CR	2 (4)	3 (6)	5 (9)
PR	27 (50)	24 (44)	36 (67)
SD	22 (41)	24 (44)	13 (24)
PD	3 (6)	2 (4)	0
Response Rate†	29 (54%)	27 (50%) p=0.77	41 (76%) p=0.026
Duration of Response Months (95% CI)	5.6 (4.5, 7.4)	9.5 (7.4, NA)	10.5 (7.4, 14.9)

*1 patient in 150/1 group was not evaluable

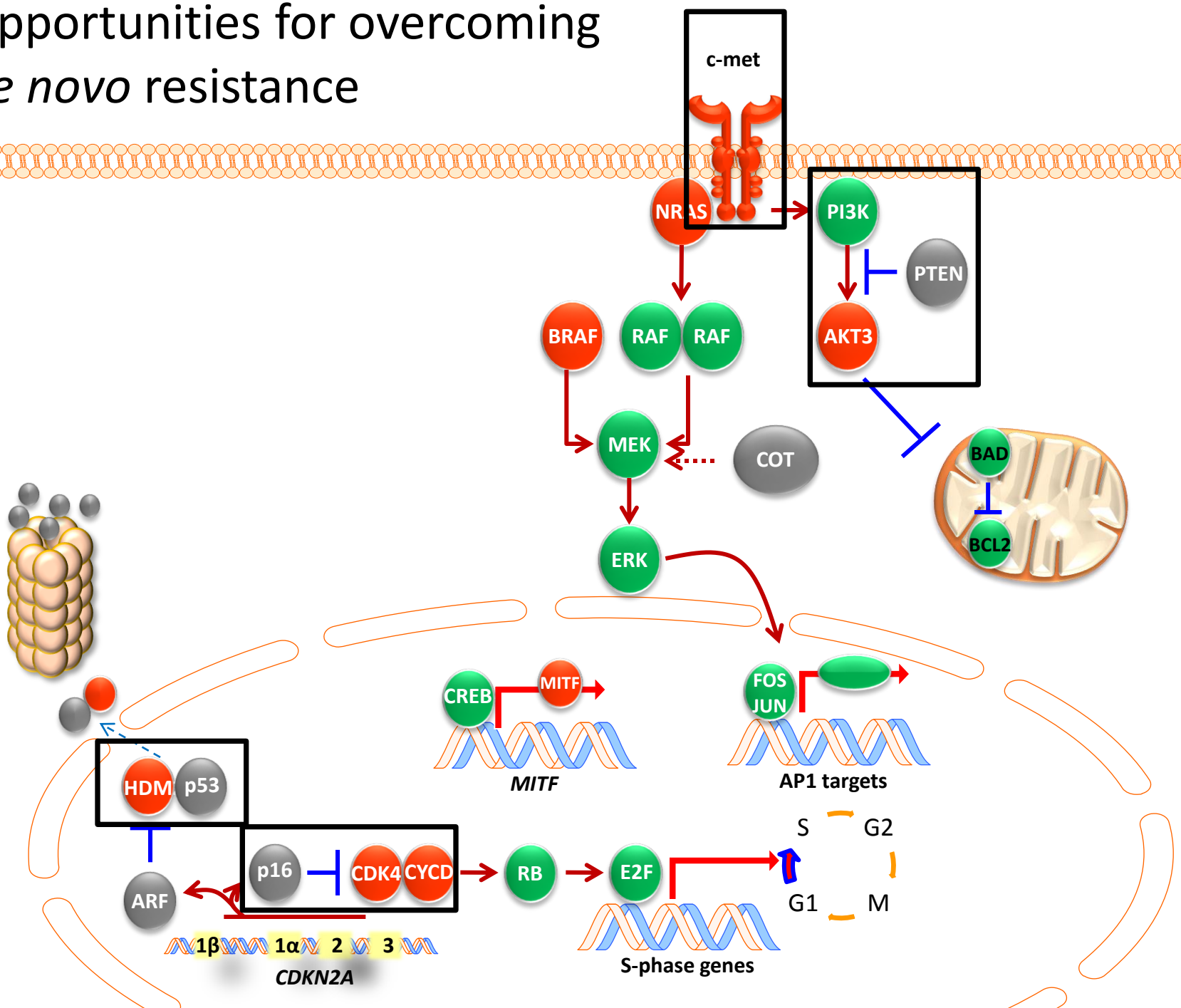
Long G et al. ESMO 2012

Delayed resistance with BRAF/MEK combination versus single-agent BRAF inhibition

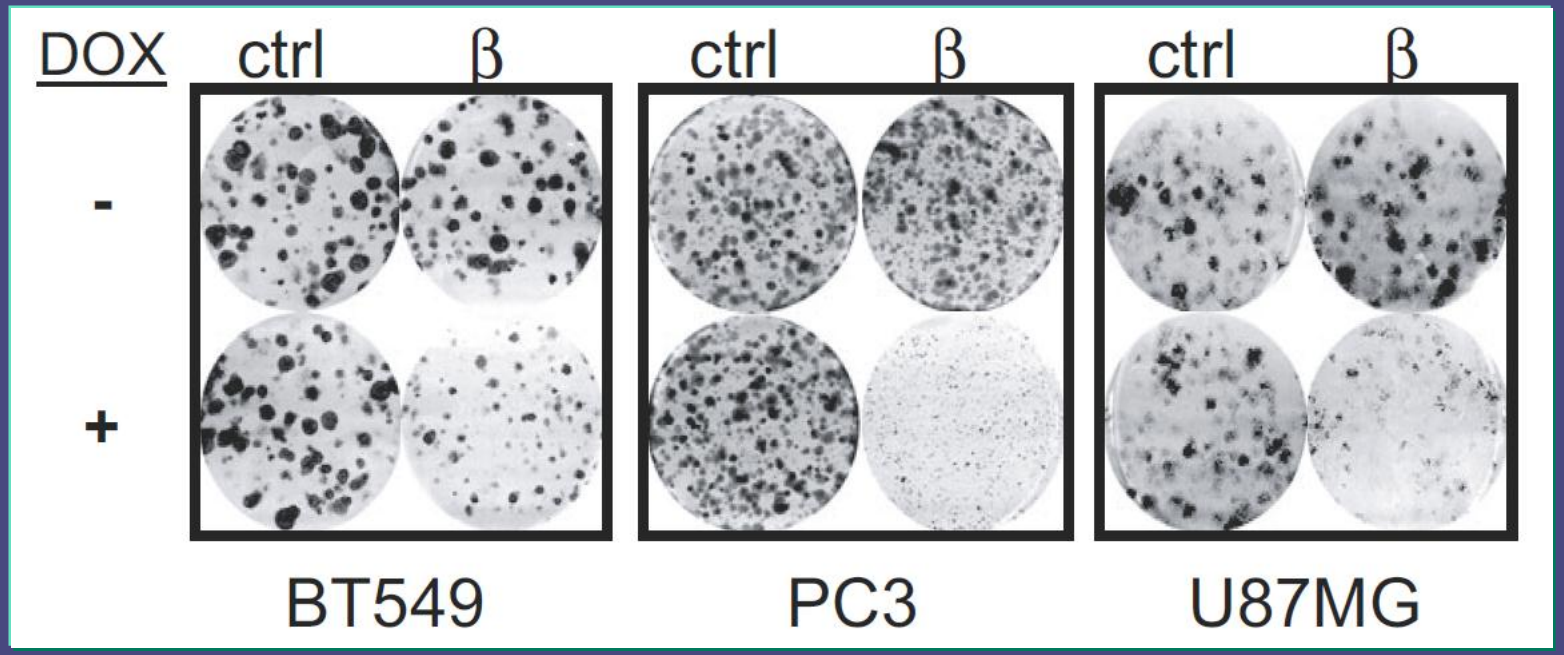


Flaherty KT et al. NEJM DOI: 10.1056/NEJMoa1210093

Opportunities for overcoming *de novo* resistance

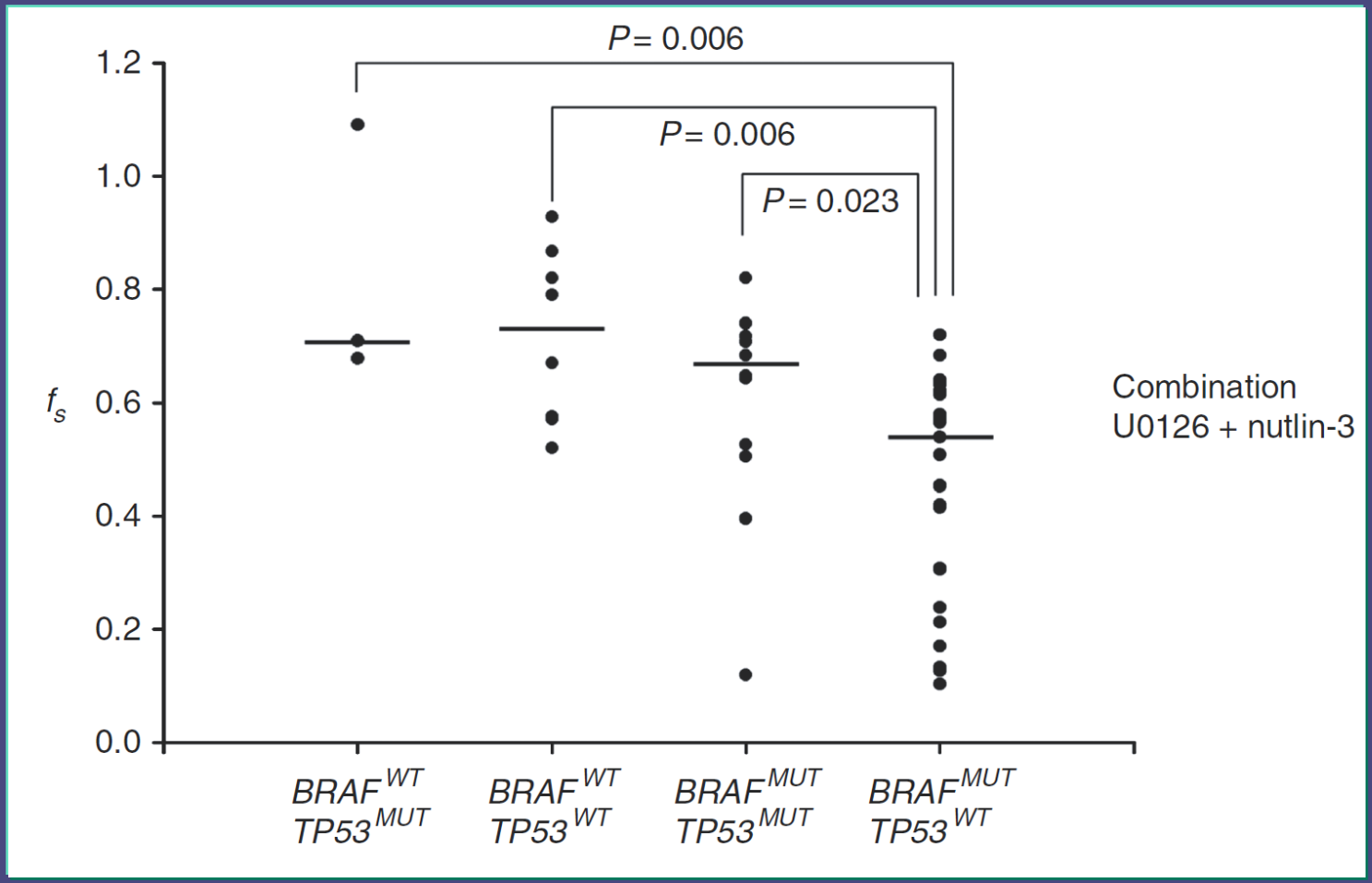


Inducible expression of PI3Kβ shRNA in PTEN deleted cell lines inhibits growth



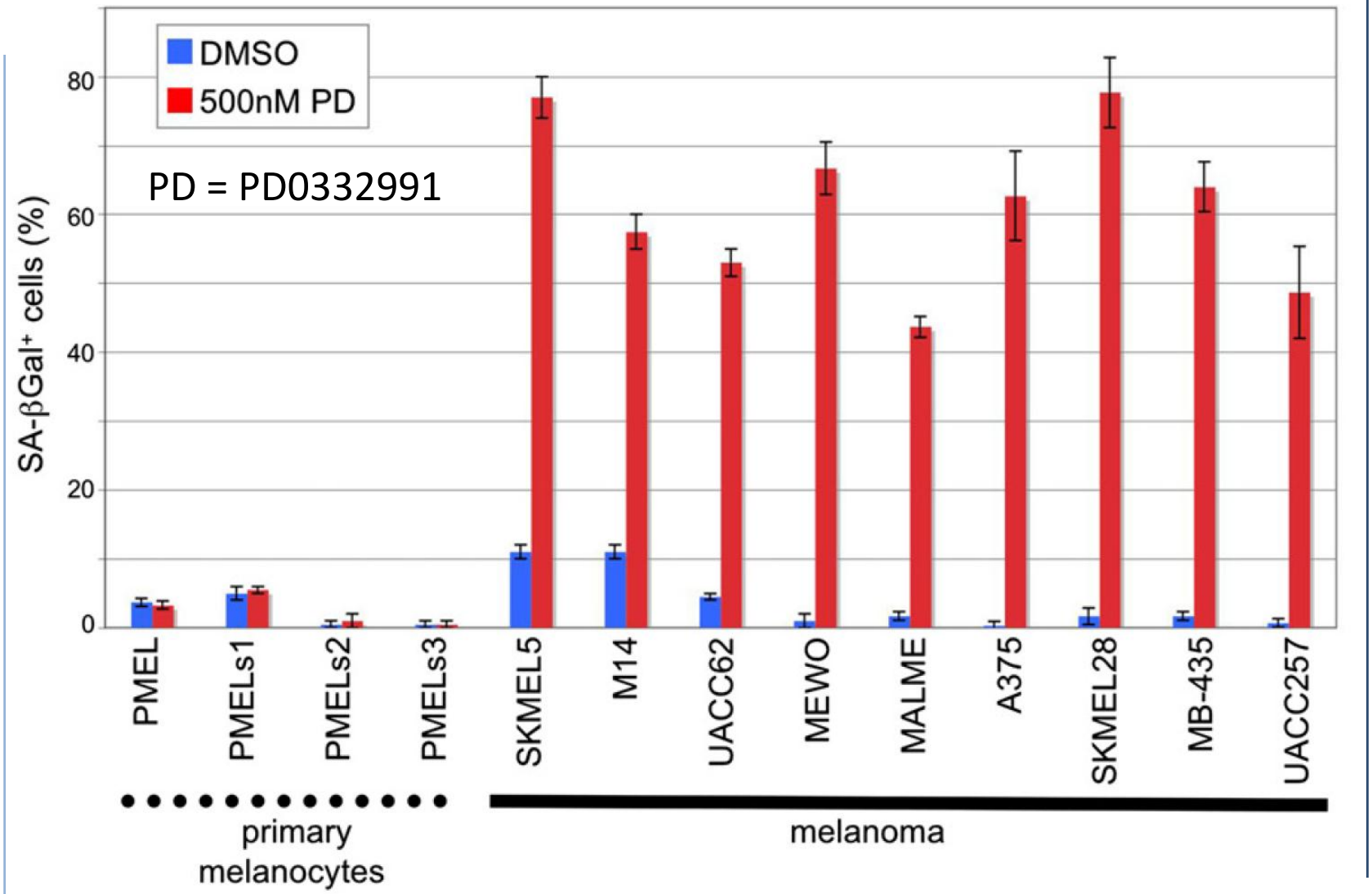
Wee S et al. Proc Natl Acad Sci U S A. 2008 ;105(35):13057-62.

Synergy between MEK inhibitor & nutlin-3 in BRAF mutant/p53 WT melanoma



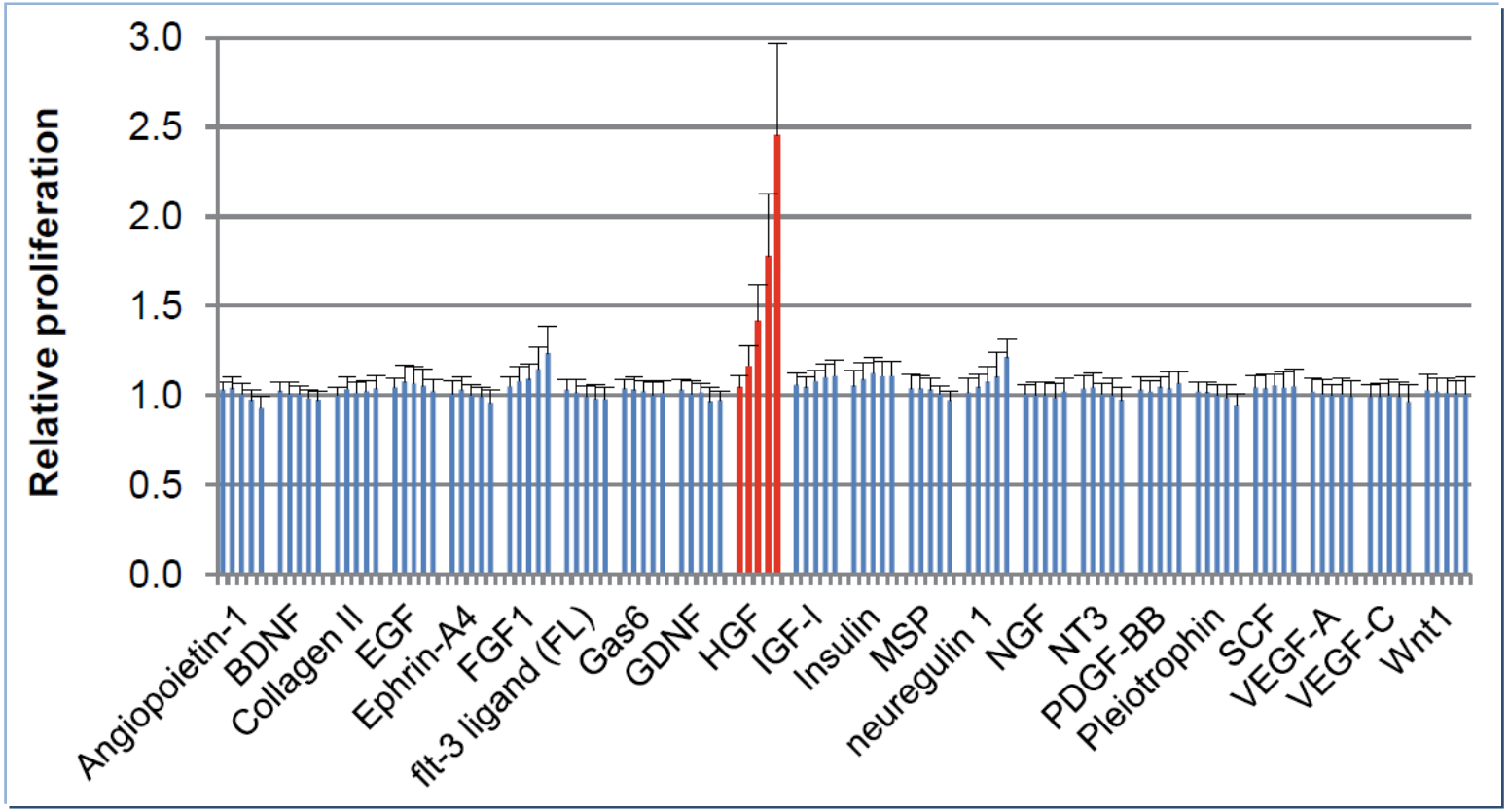
Ji Z et al. J Invest Dermatol. 2012

CDK4 inhibitor induces senescence



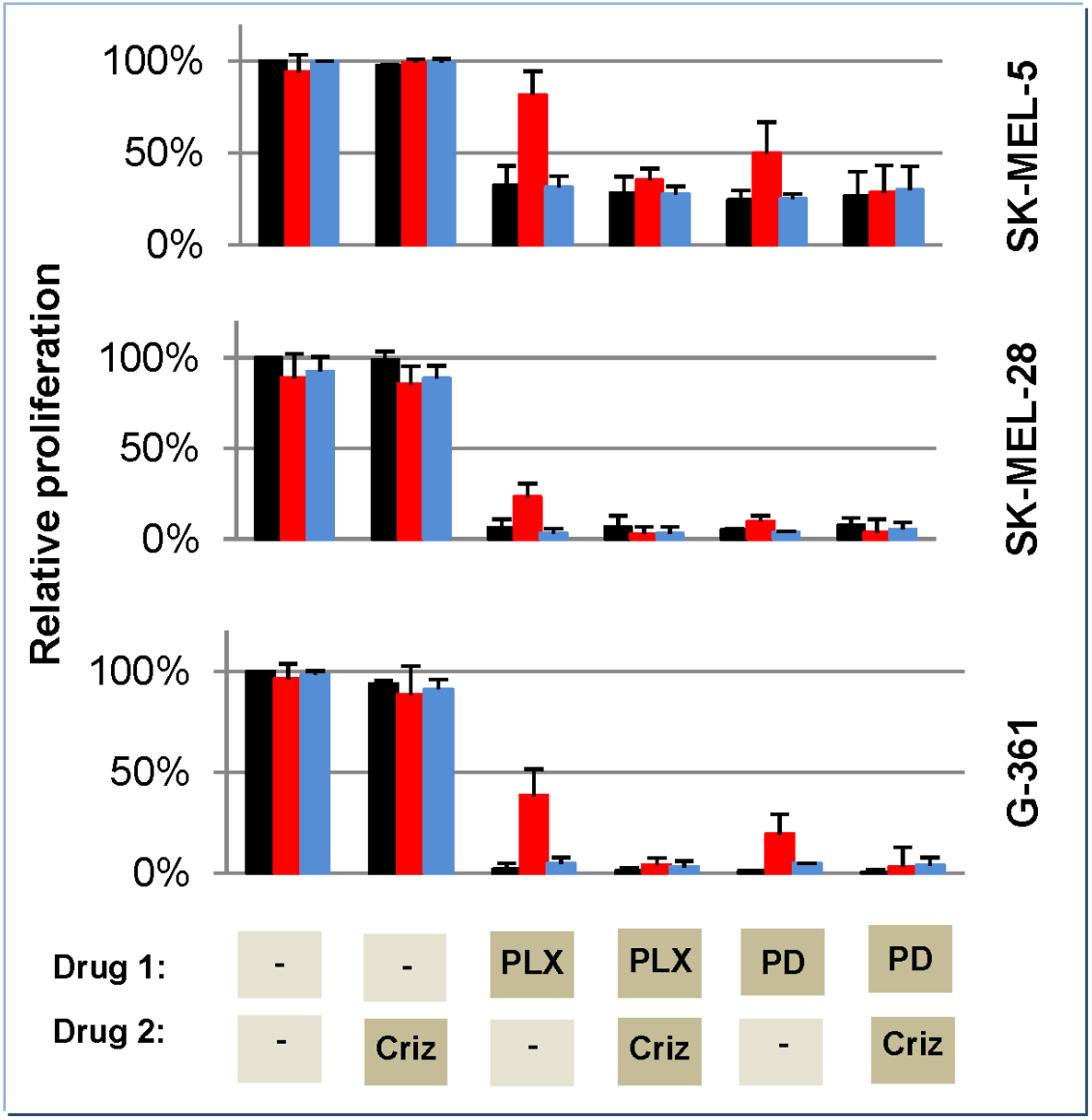
Cancer Cell 2011;20: 620–634

HGF uniquely conferred resistance among 576 cytokines, growth factors, soluble cell adhesion molecules



Straussman R et al. Nature. 2012 Jul 26;487(7408):500-4.

Combined effect BRAFi & c-meti



Straussman R et al. Nature. 2012 Jul 26;487(7408):500-4.

Conclusions

- CKIT inhibitors in CKIT mutant melanoma is effective in a minority
  - AKT reactivation may underlie resistance
- In NRAS mutant melanoma, single-agent MEK inhibition has activity
  - A combination with CDK4 inhibition appears promising
- In BRAF mutant melanoma, MAPK reactivation is common and BRAF/MEK dual inhibition suppresses resistance
  - Need to ascertain if BRAF/MEK resistance is MAPK dependent or not