

The development of BRAF inhibitors in BRAF mutant melanoma

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MASSACHUSETTS
GENERAL HOSPITAL

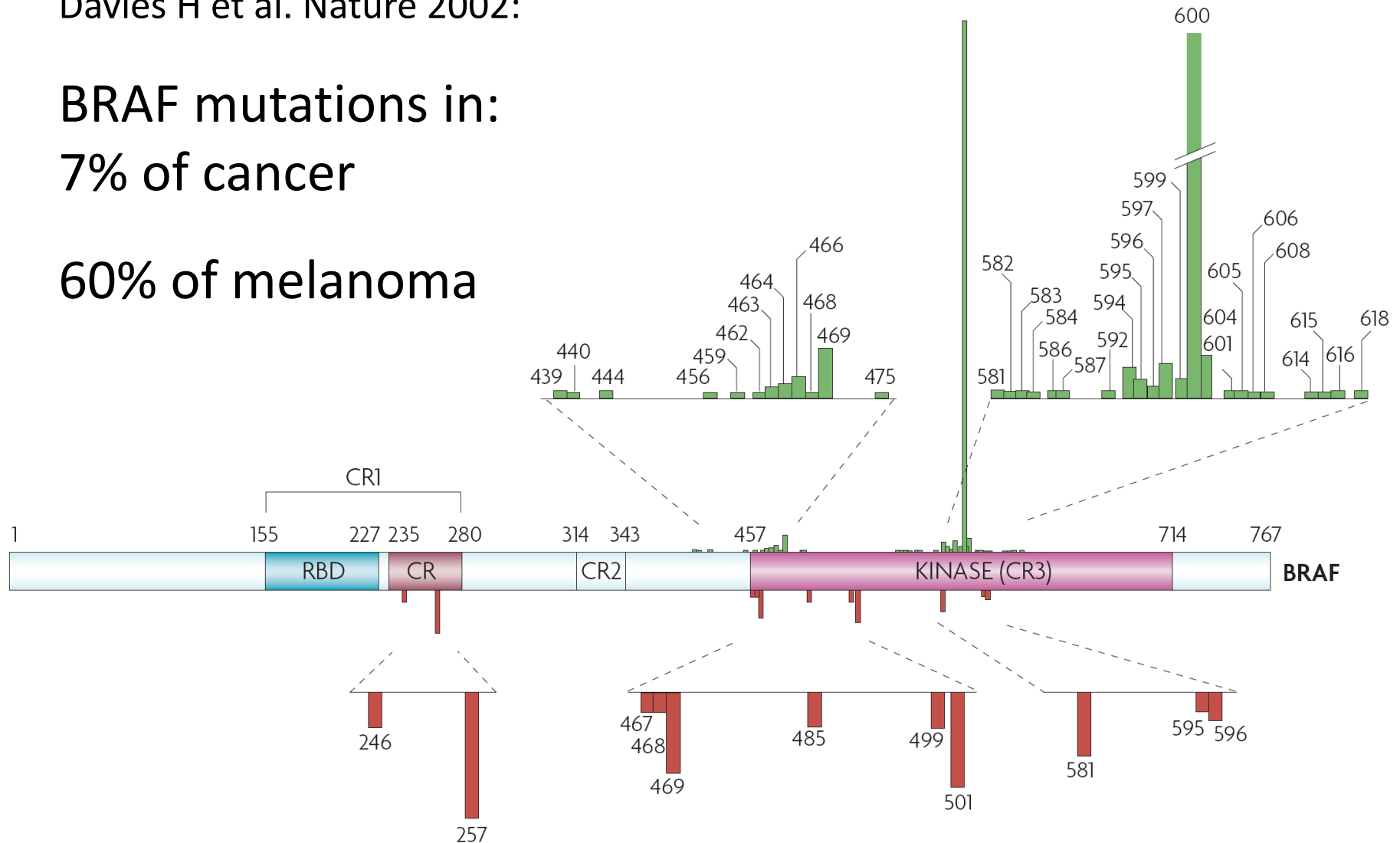
CANCER CENTER

BRAF

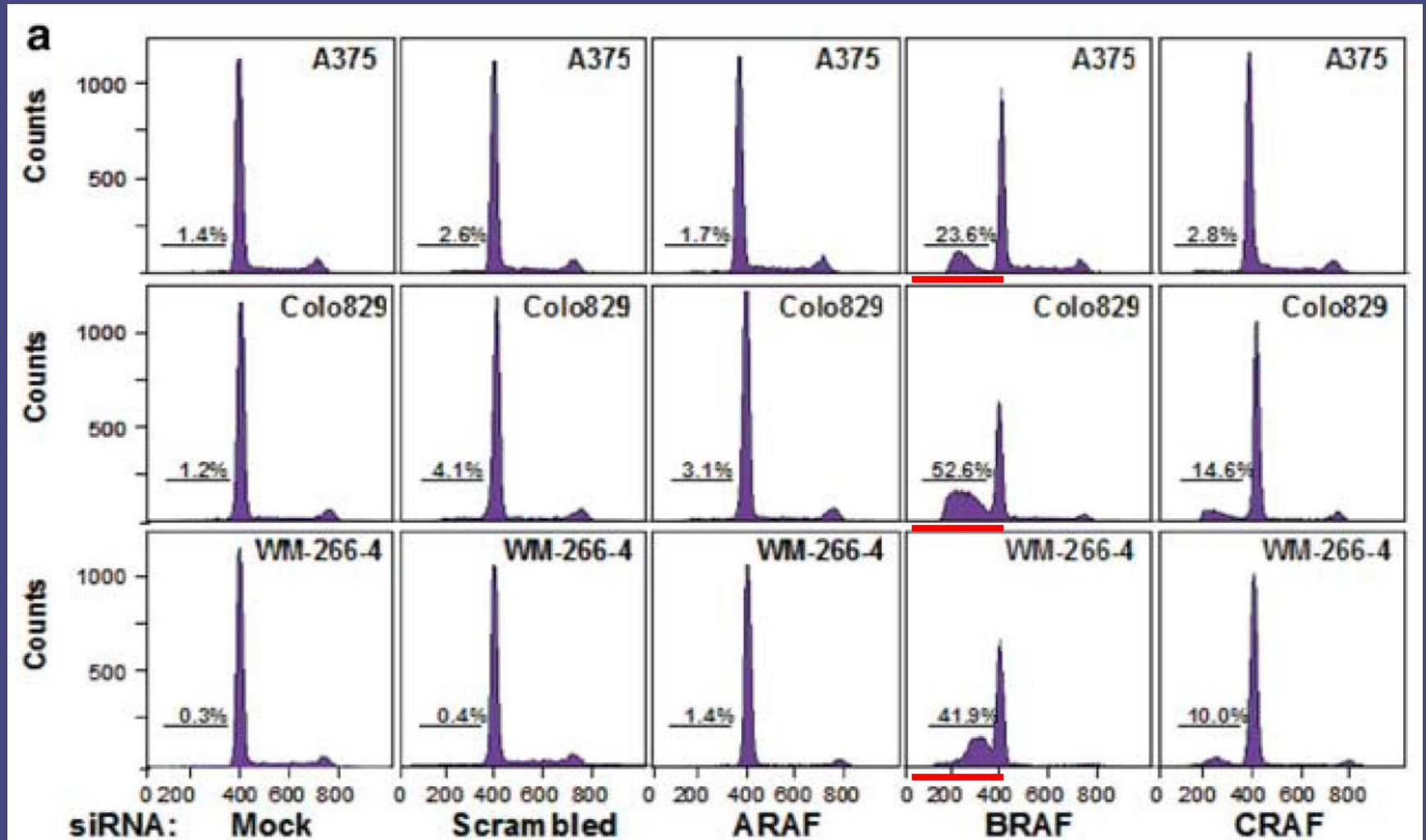
Davies H et al. Nature 2002:

BRAF mutations in:
7% of cancer

60% of melanoma

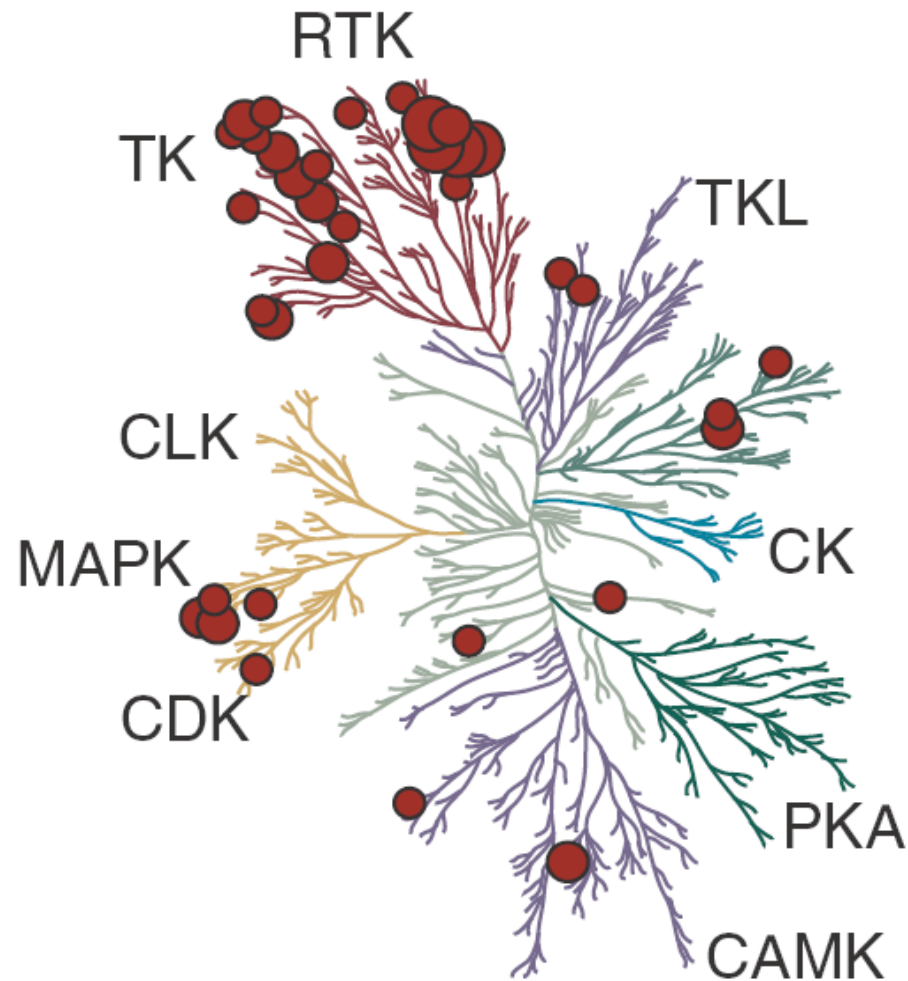


siRNA against BRAF induces apoptosis



Karasarides et al. Oncogene (2004) 23, 6292–6298

Sorafenib selectivity



Sorafenib

Fabian et al. Nat Biotechnol, 2005. 23:329-36.

Single agent BAY 43-9006 in melanoma

39 patients with metastatic melanoma

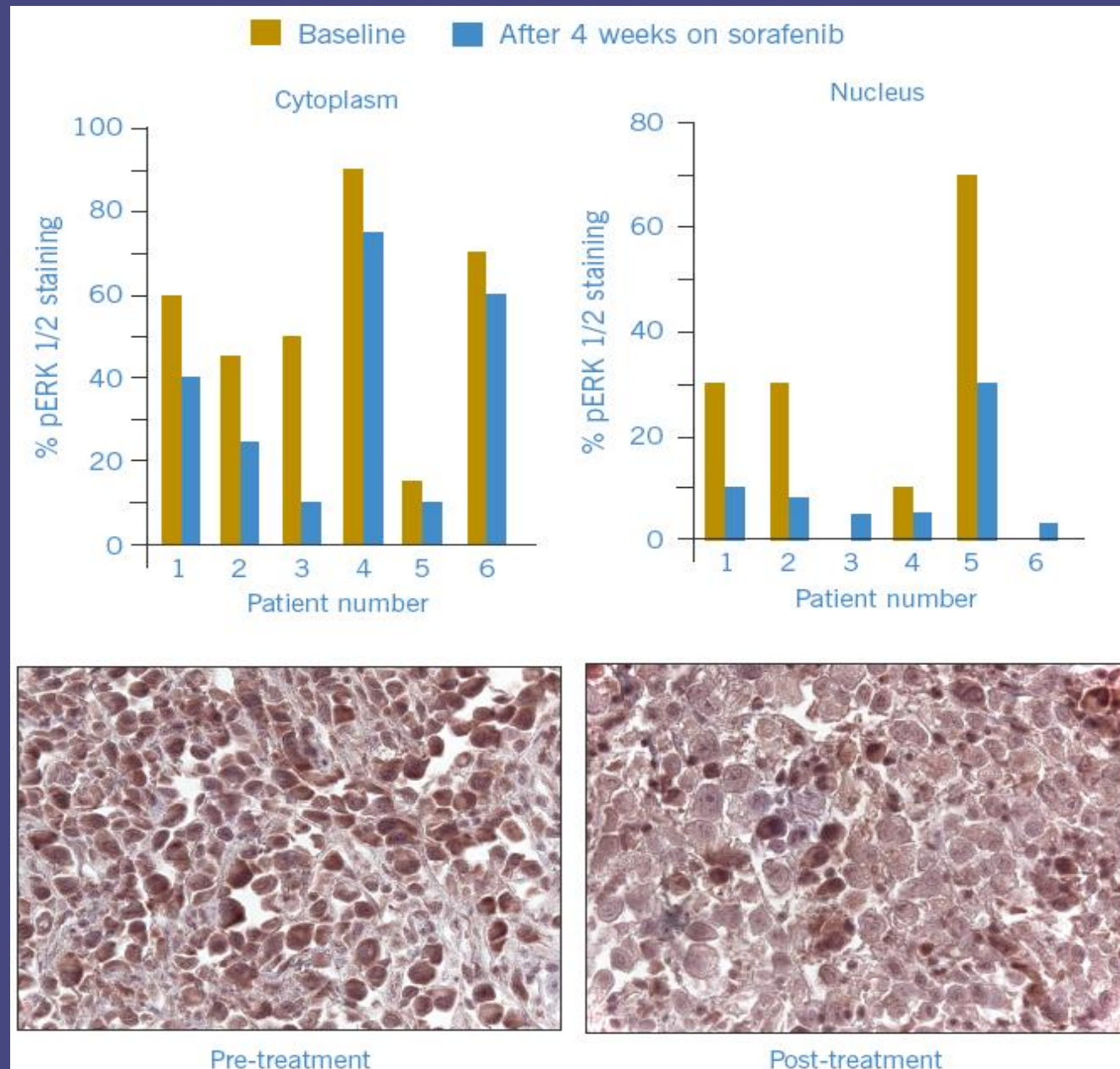
- 1 responder
 - 7 patients with stable disease at 12 weeks
-

22 patients with metastatic melanoma

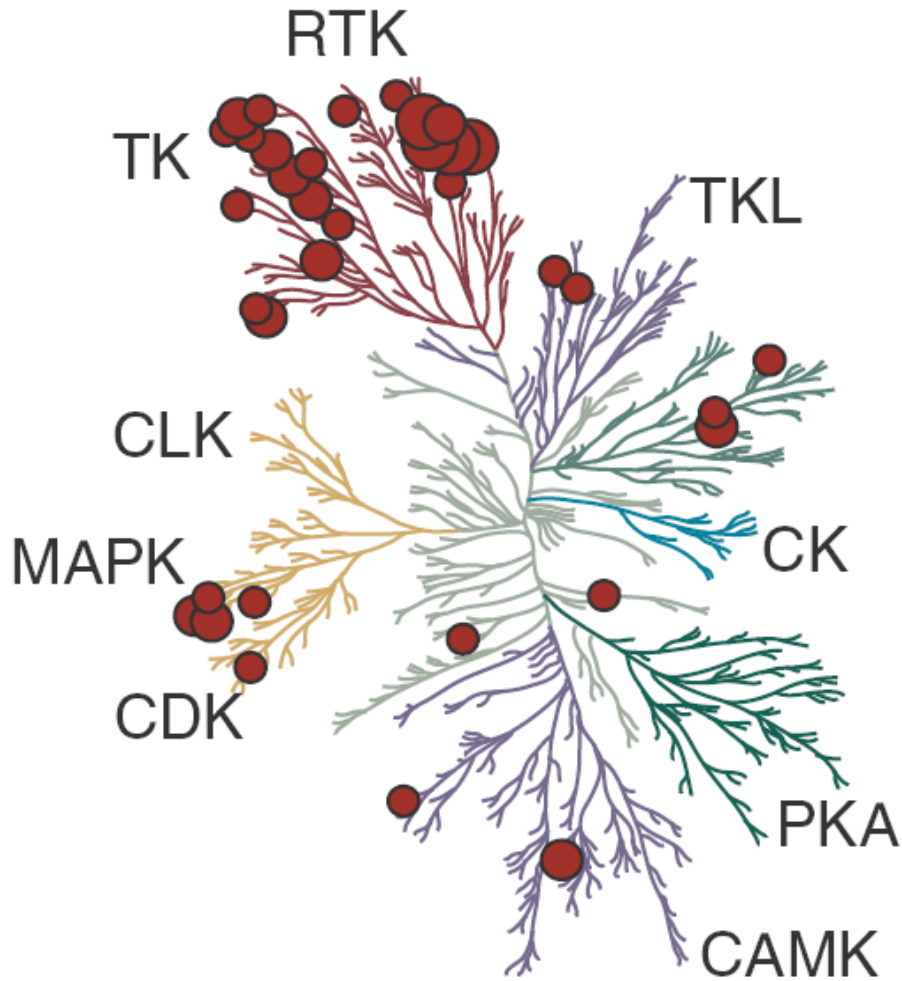
- 1 partial response &
- 12 with stable disease

Median progression-free survival: 3 months

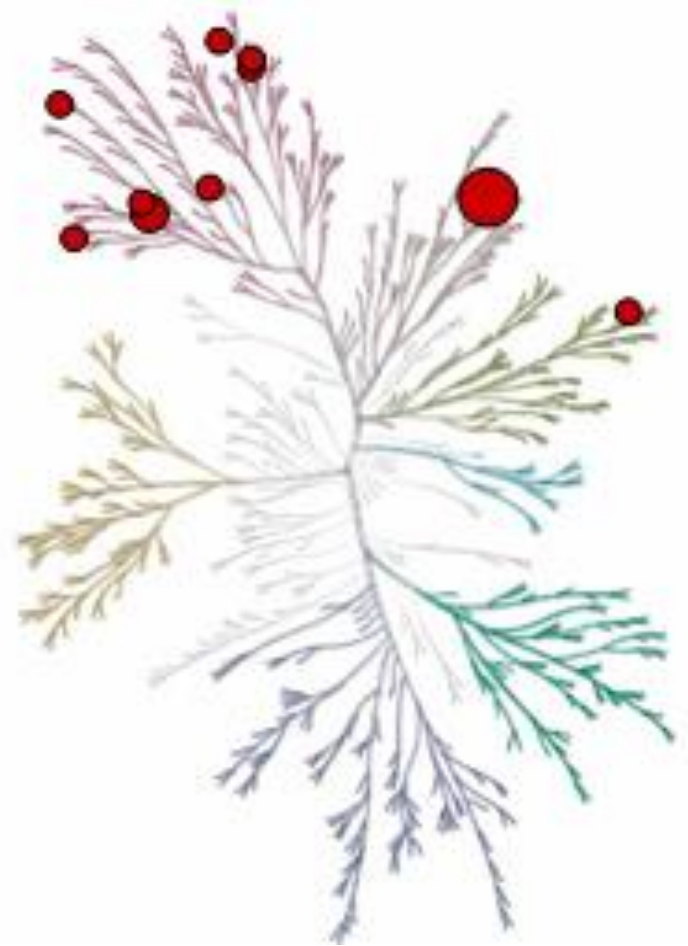
Inhibition of pERK in vivo with sorafenib



Sorafenib & PLX4032 selectivity



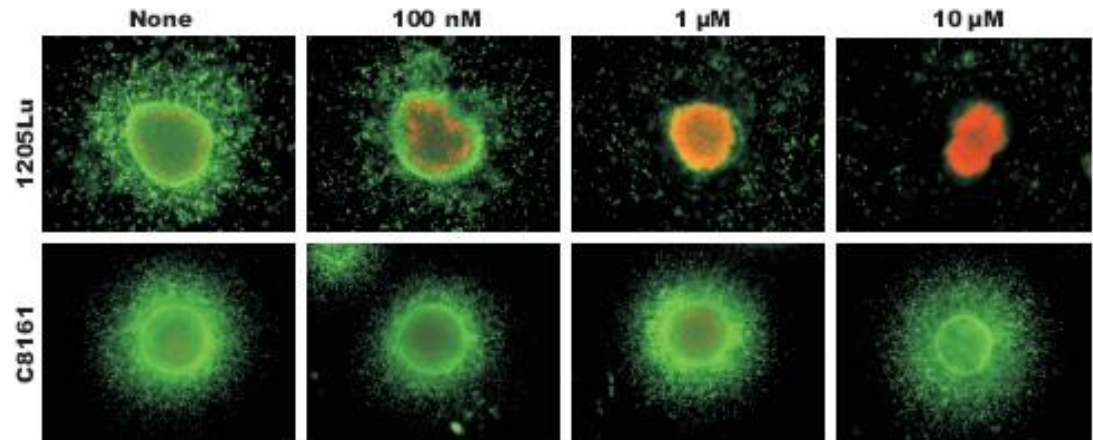
Sorafenib



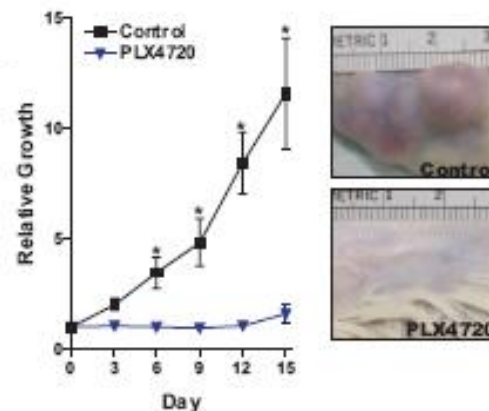
PLX4032

PLX4720: selective BRAF inhibitor is selectively for BRAF mutant melanoma in vitro & in vivo

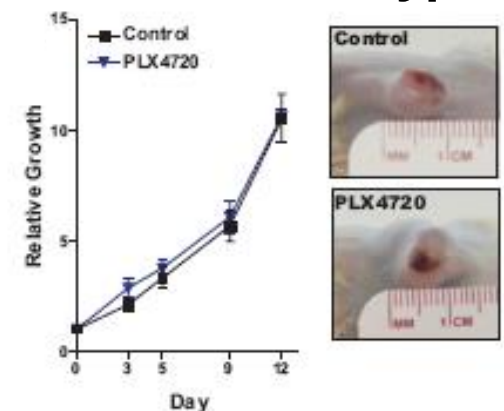
Assay	IC ₅₀ , nM
B-Raf V600E	13
B-Raf	160
BRK	130
FRK	1,300
CSK	1,500
SRC	1,700
FAK	1,700
FGFR	1,900
KDR	2,300
HGK	2,800
CSF1R	3,300
AURORA A	3,400



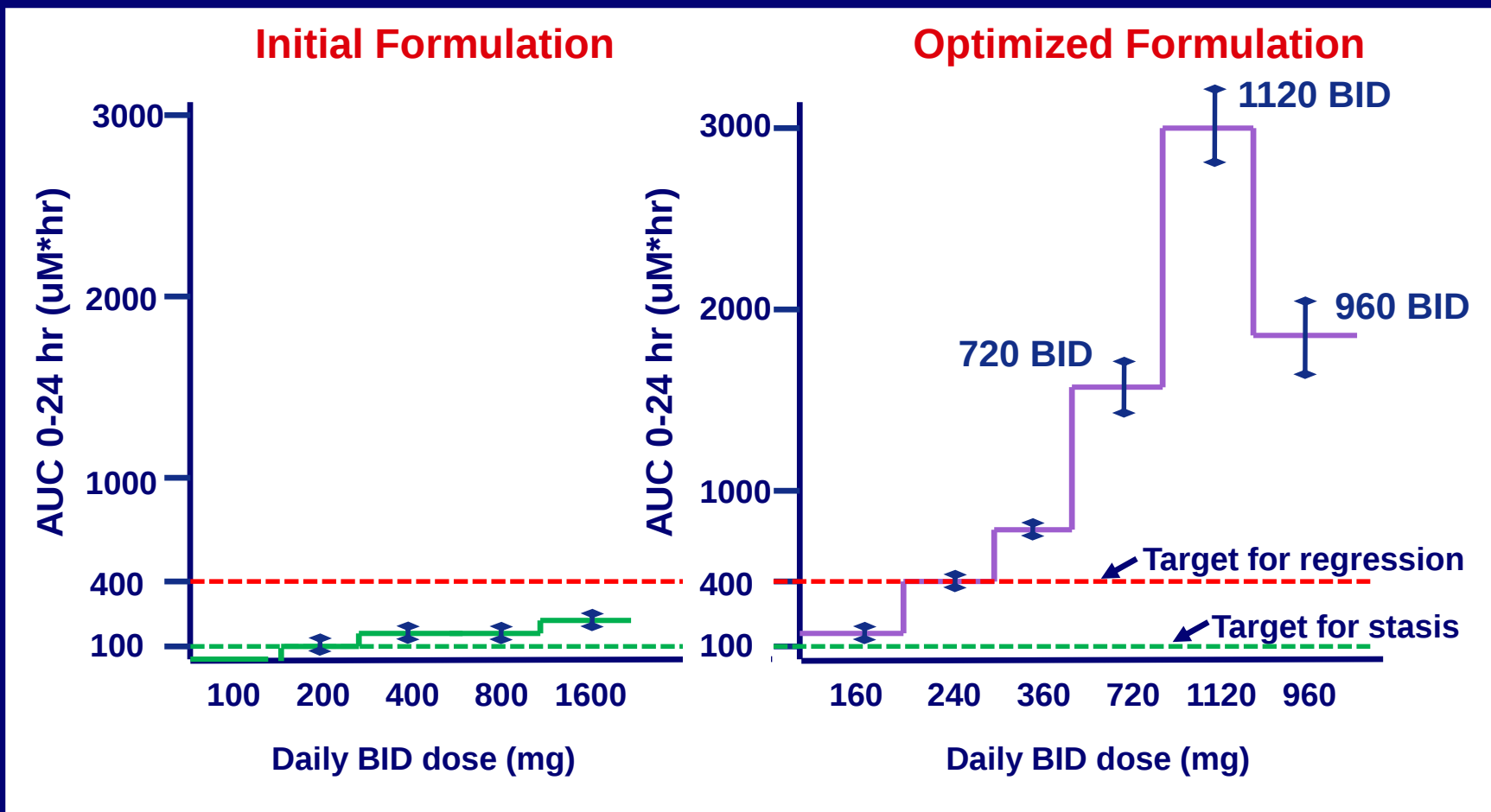
BRAF mutant



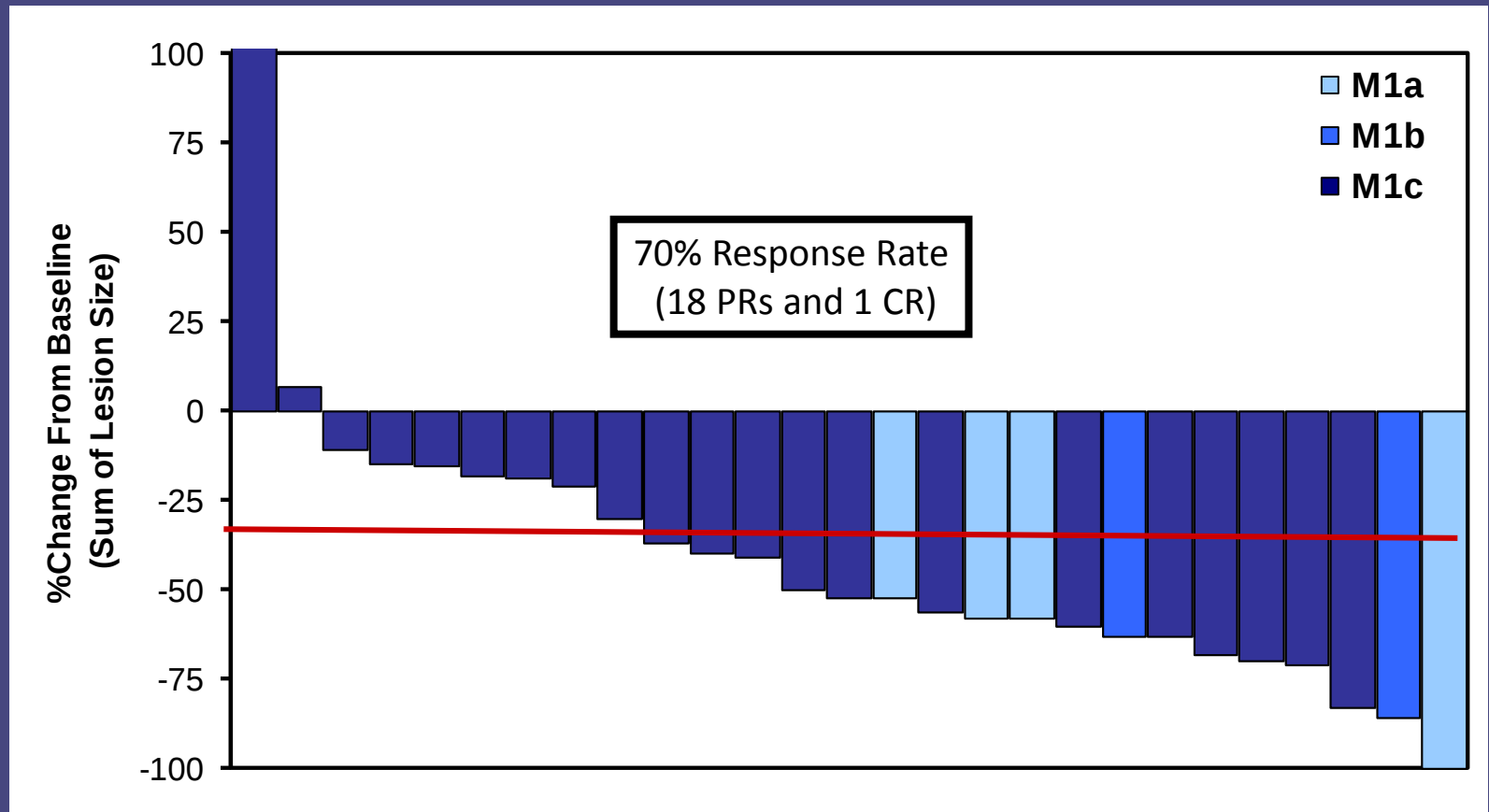
BRAF wild-type



PLX4032 optimized formulation achieves preclinical target exposure for tumor regression



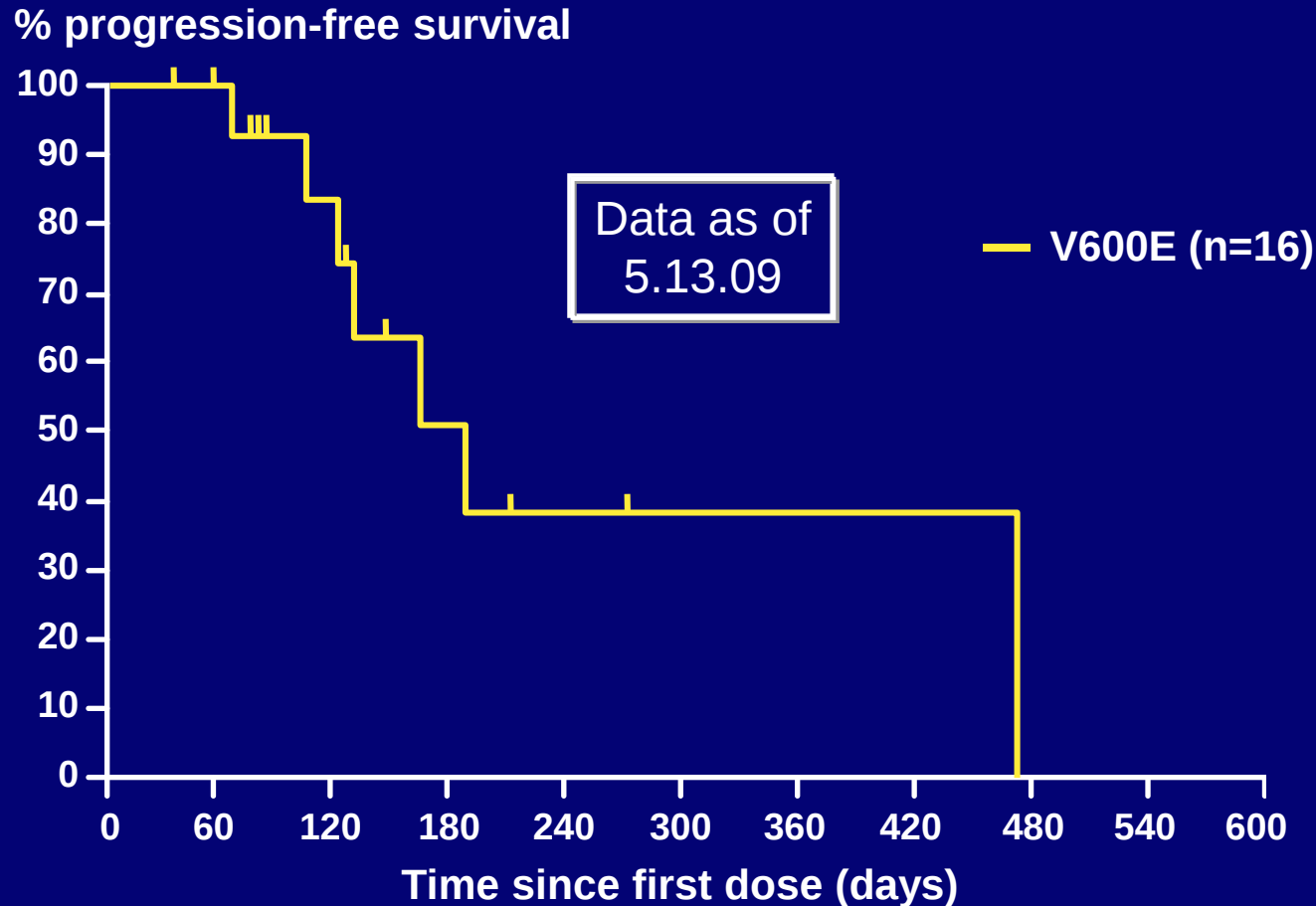
Interim best overall response in extension cohort patients



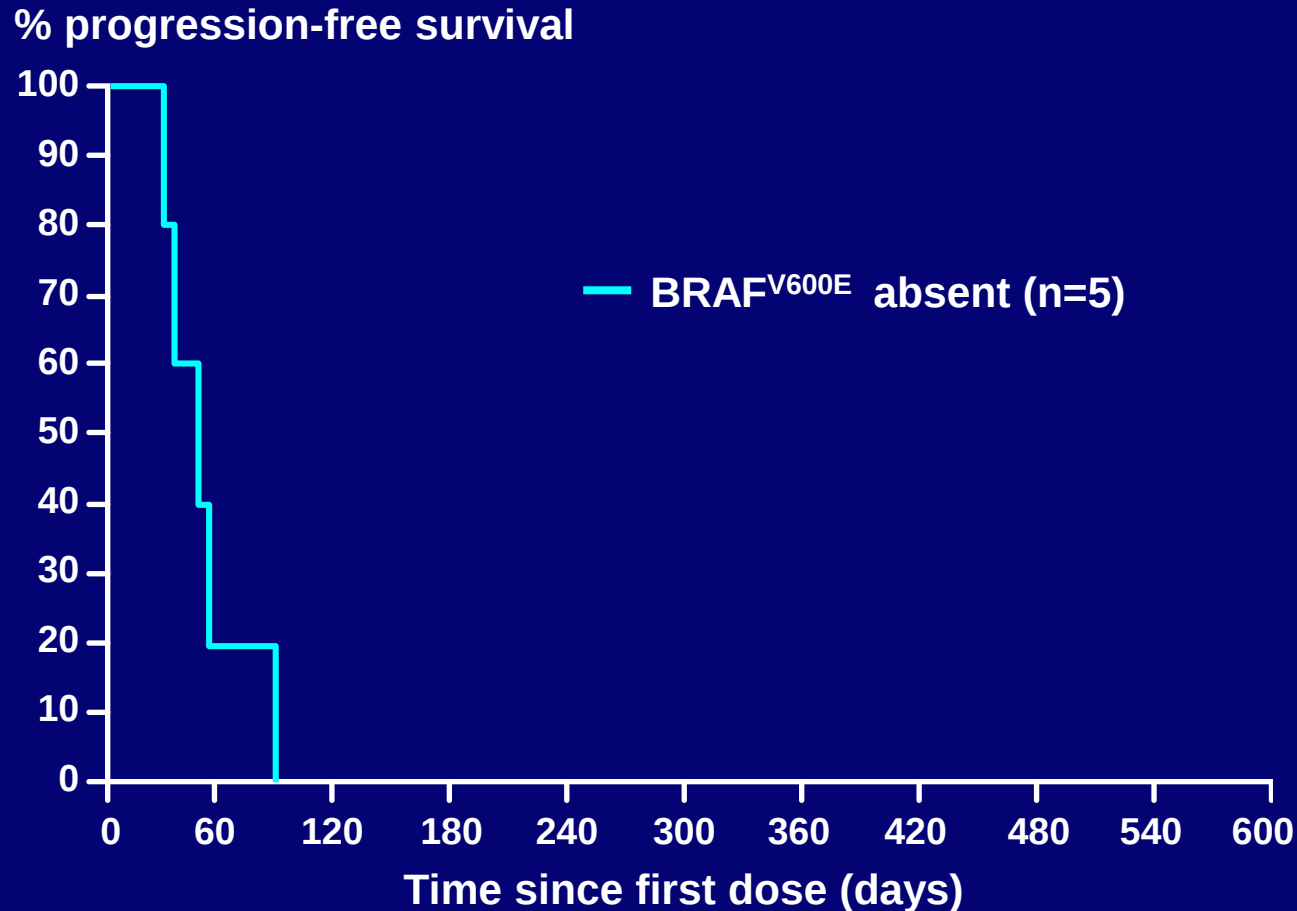
n=27 Evaluable Patients

As of 8/21/09

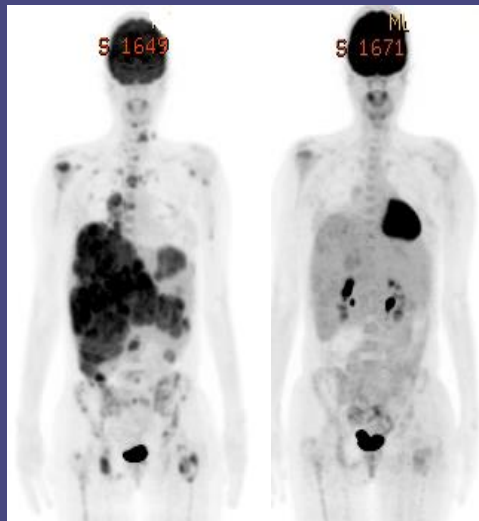
Interim PLX4032 phase I Kaplan-Meier plot: BRAF^{V600E} melanoma patients ($\geq 240\text{mg BID}$)



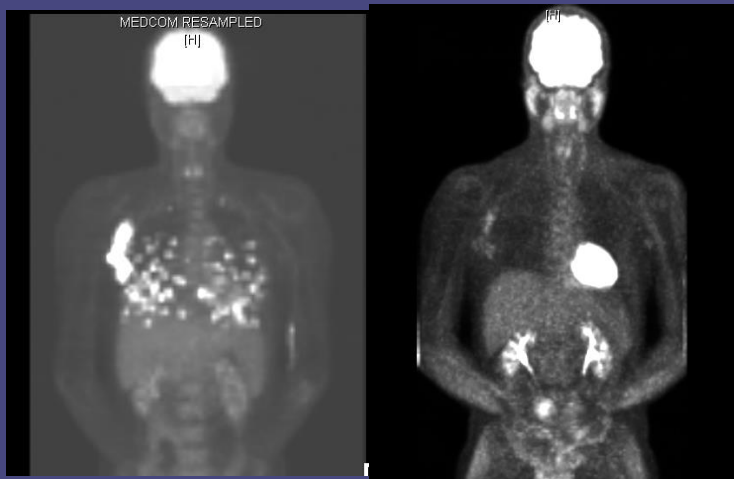
Interim PLX4032 phase I Kaplan-Meier plot: non- BRAF^{V600E} melanoma patients (≥ 240mg BID)



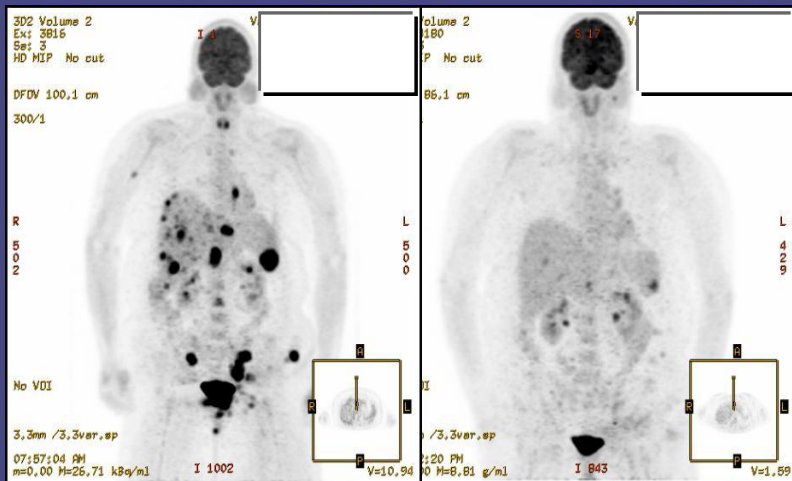
PET Scans at Baseline and Day 15 after PLX4032



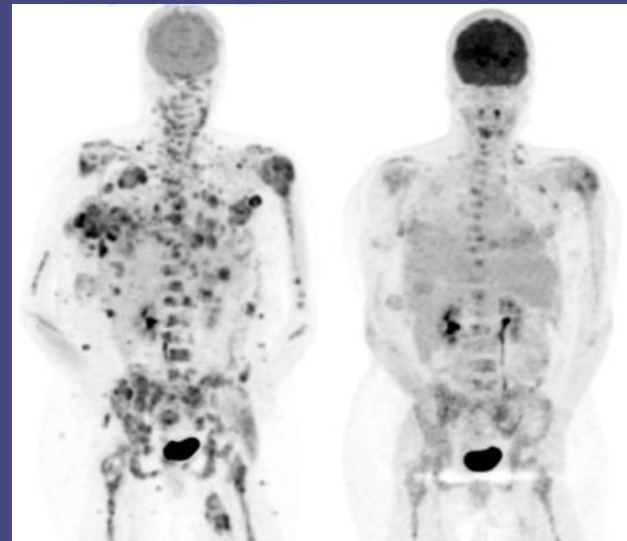
#69 MDA



#63 MSKCC

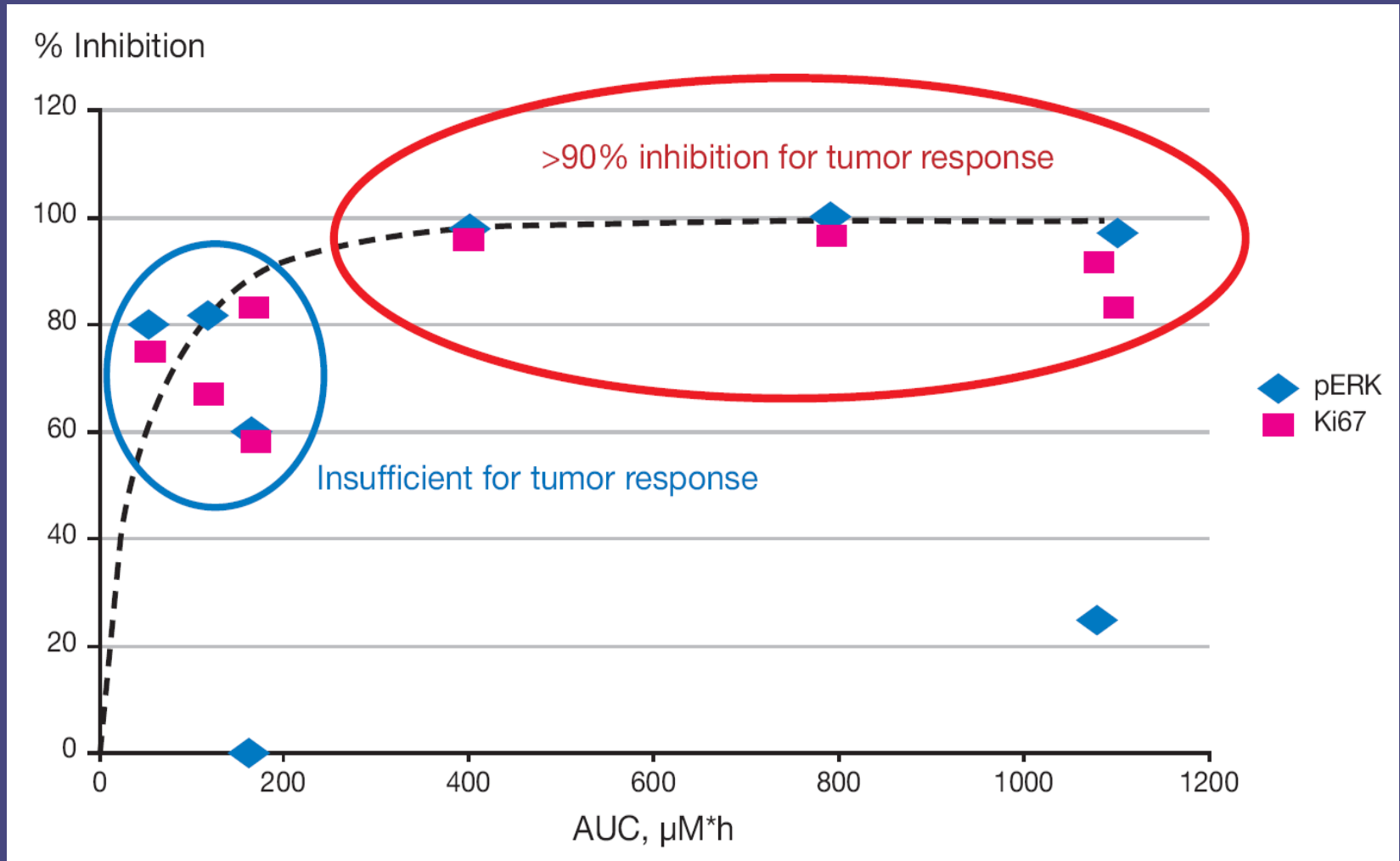


#56 Vanderbilt

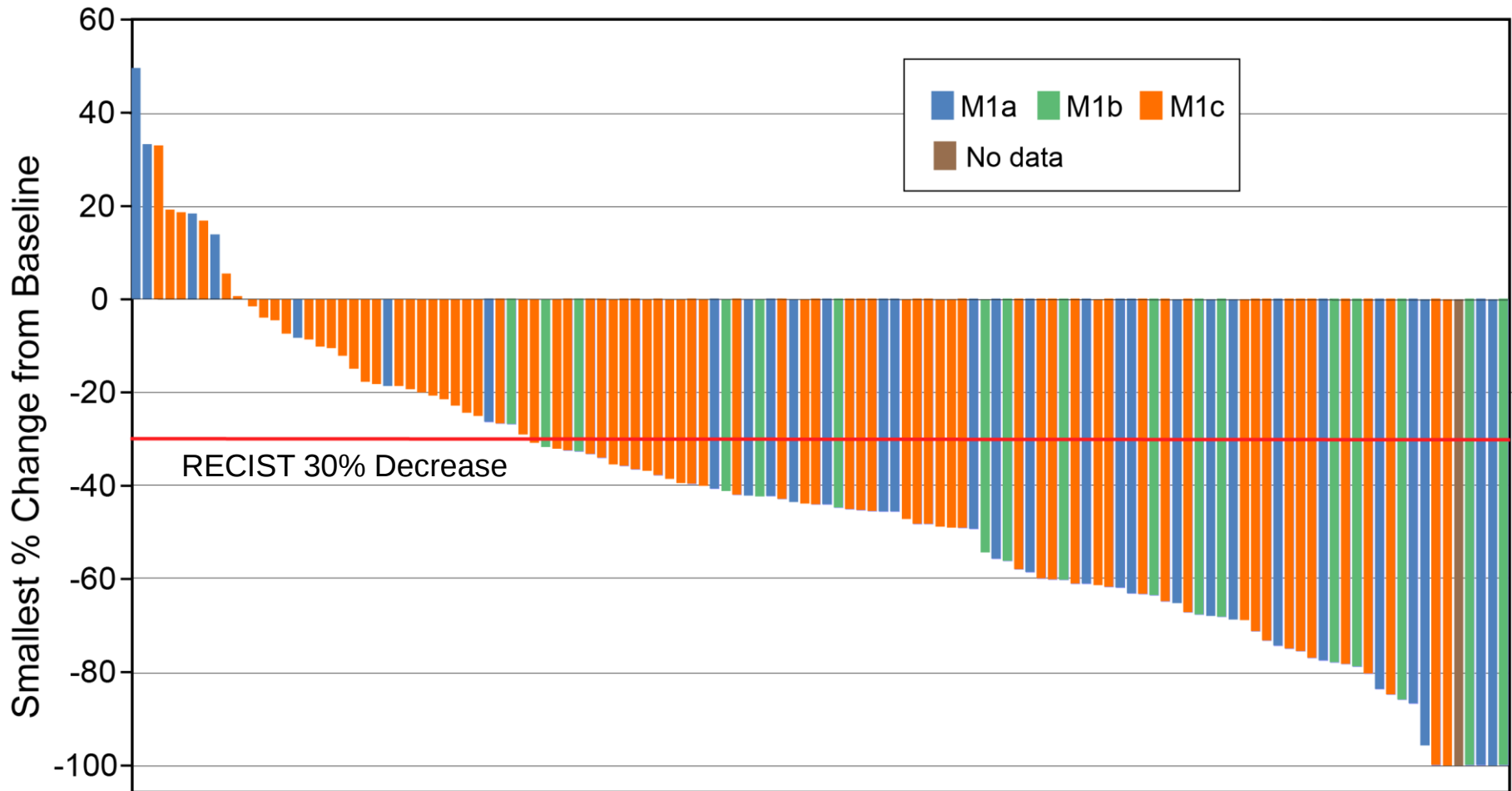


#59 Peter MacCallum

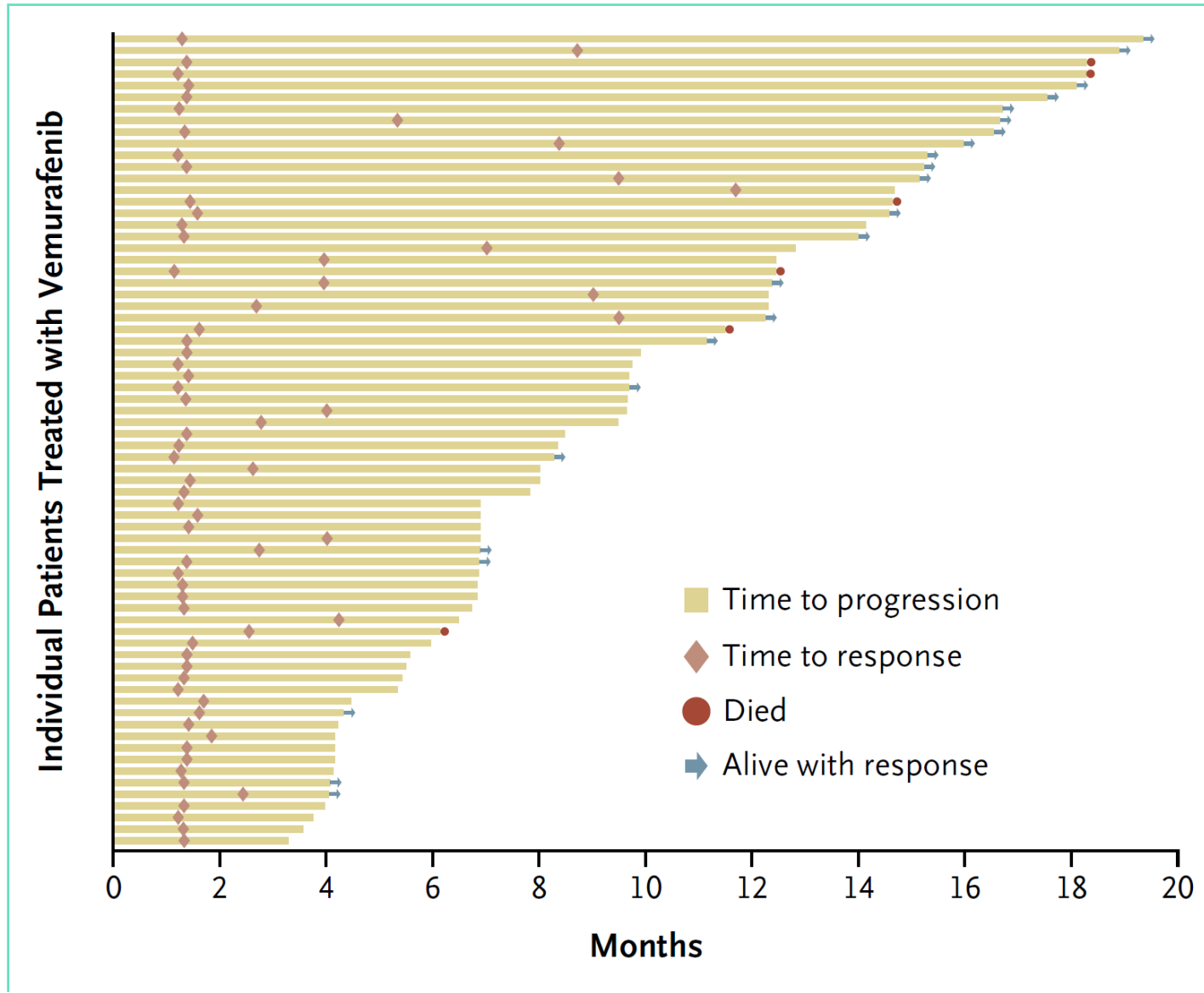
Dose-response in pharmacodynamic markers



Change in tumor size in 122 V^{600E} BRAF mutant melanoma patients (vemurafenib phase II trial)



Progression-free survival in vemurafenib phase II trial

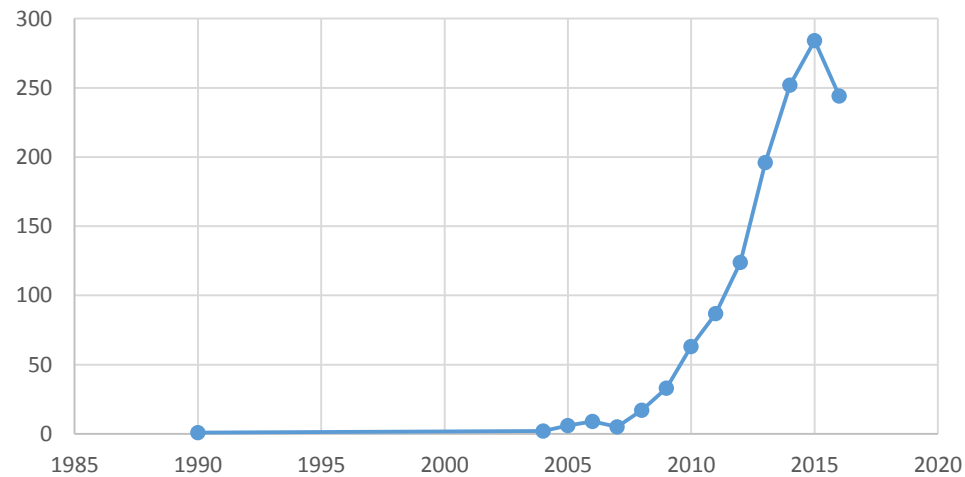


Pharmacodynamics & acquired resistance

MAPKi

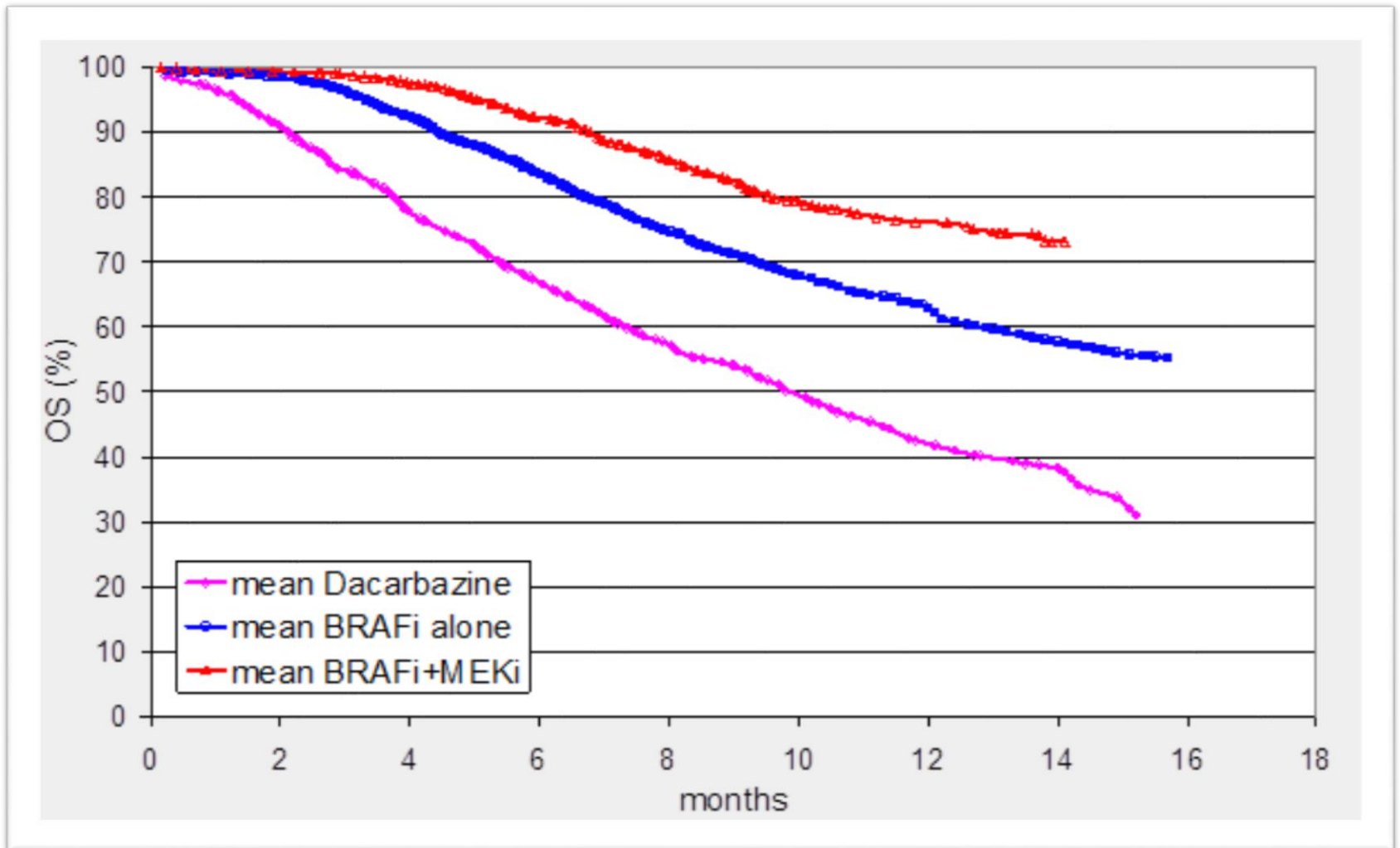


pubmed - BRAF resistance count



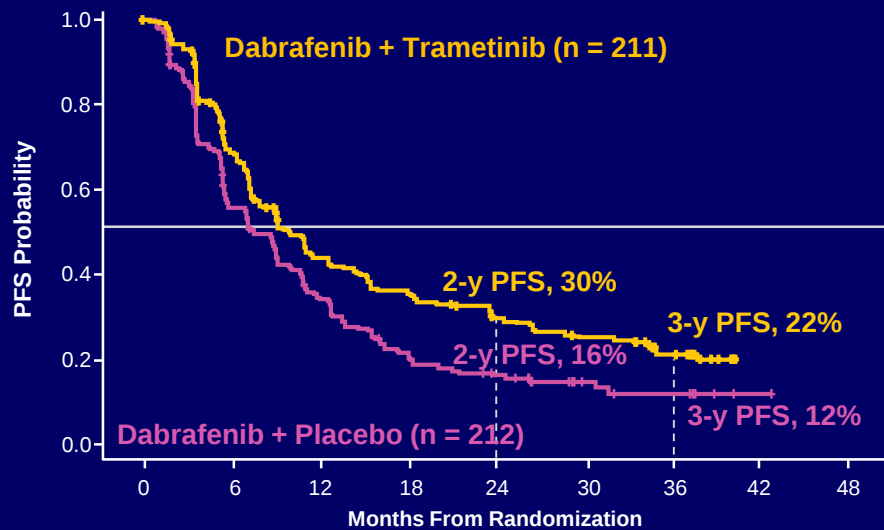
Wagle N et al JCO 2011; Shi et al. Nature 2012; Poulikakos et al. Nature 2012; Straussman R et al. Nature 2012; Whittaker S et al. Cancer Discovery 2013; Maertens O et al. Cancer Discovery 2013

Meta-analysis of randomized phase II and III trials with BRAF and BRAF/MEK inhibition: overall survival



PFS and OS

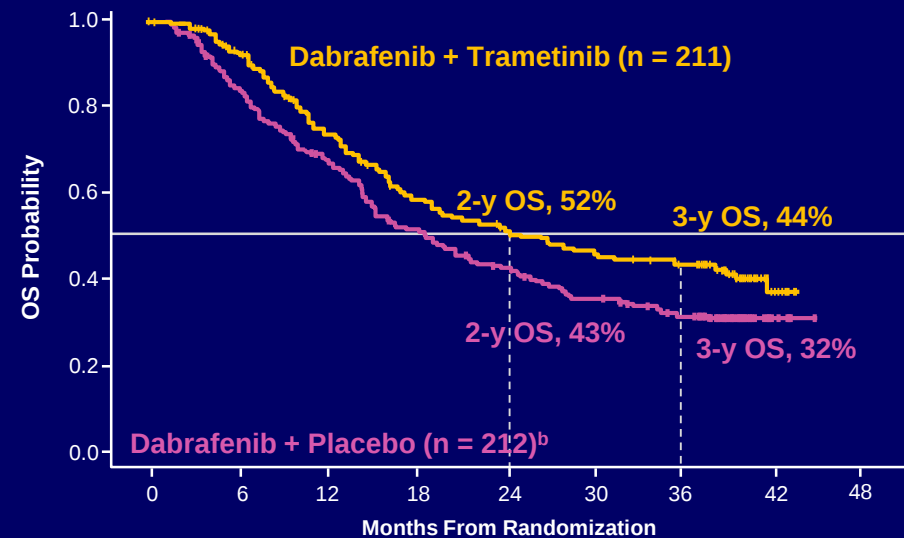
Progression-Free Survival



Number at risk

D+T	211	137	84	69	54	45	31	0	
D+Pbo	212	110	67	41	29	11	7	1	0

Overall Survival



Number at risk

D+T	211	187	143	111	96	86	76	13	0
D+Pbo	212	175	138	104	84	69	57	7	0

Flaherty et al. ASCO 2016