(The Before and Beyond) Phase I trials

Pharmacology of drugs targeting the MAPK pathway

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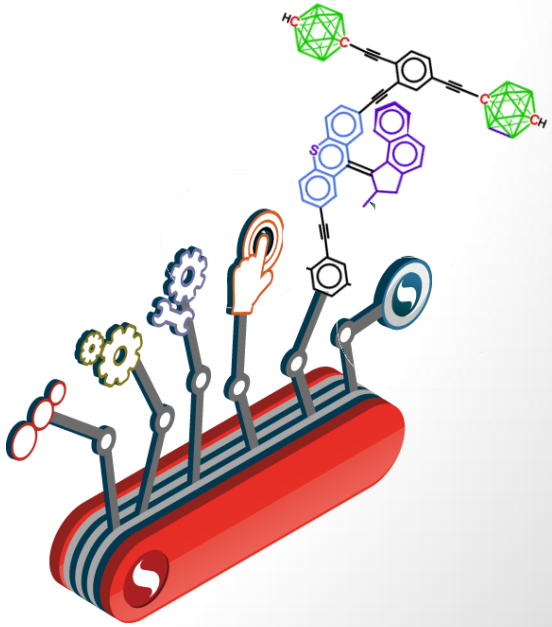
(The Before and Beyond) Phase I trials

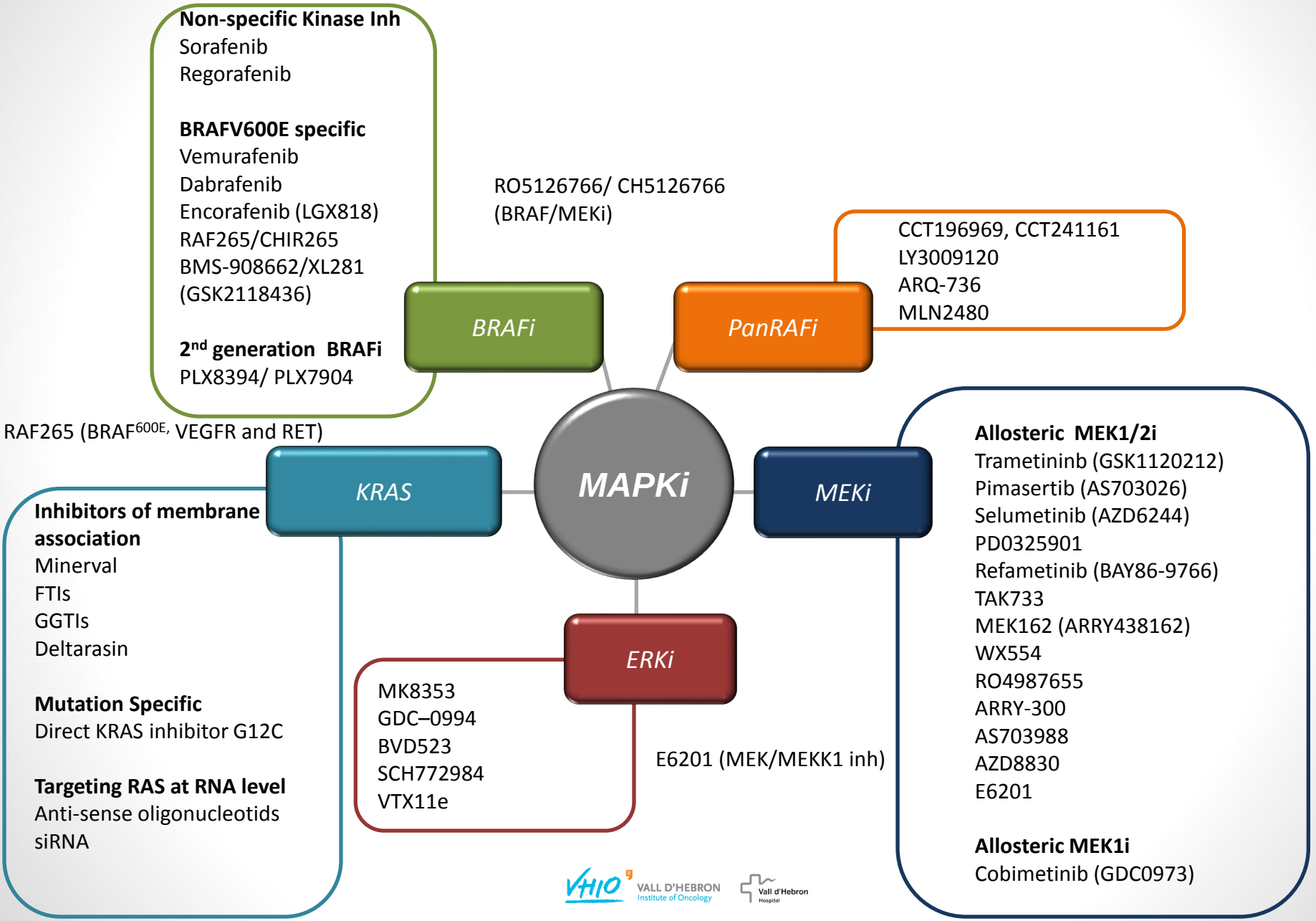
Pharmacology of drugs targeting the MAPK pathway

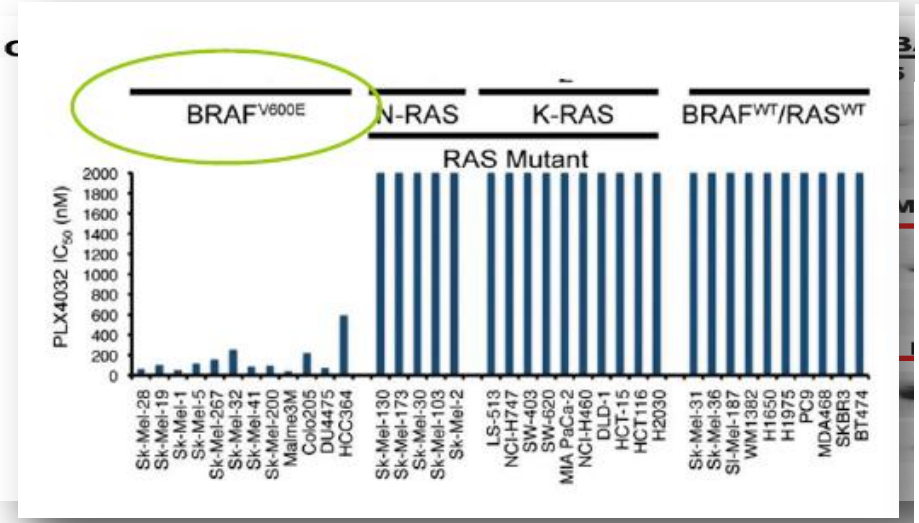
Outline

1. BRAF inhibitors: are they all the same?
   - RAF inhibitors and pharmacological properties
   - 2nd Gen RAFi, “Paradox-breakers”
2. MEK inhibitors
3. Dual… and triple combos
4. New kids on the block:
   - ERKi
   - Drugs targeting KRAS …



The pharmacological landscape of the MAPK pathway





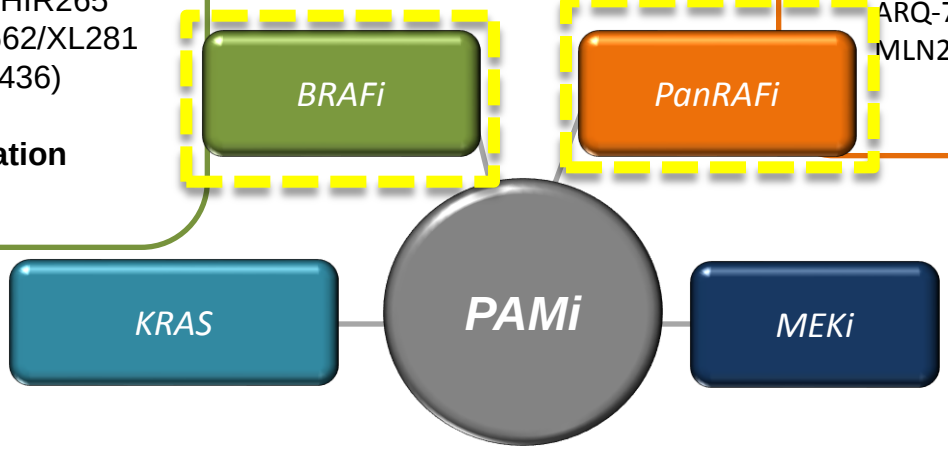
Non-specific
Sorafenib
Regorafenib

BRAFV600E specific
Vemurafenib
Dabrafenib
Encorafenib (LGX818)
RAF265/CHIR265
BMS-908662/XL281
(GSK2118436)

2nd generation
PLX8394

RO5126766/ CH5126766
(BRAF/MEKi)

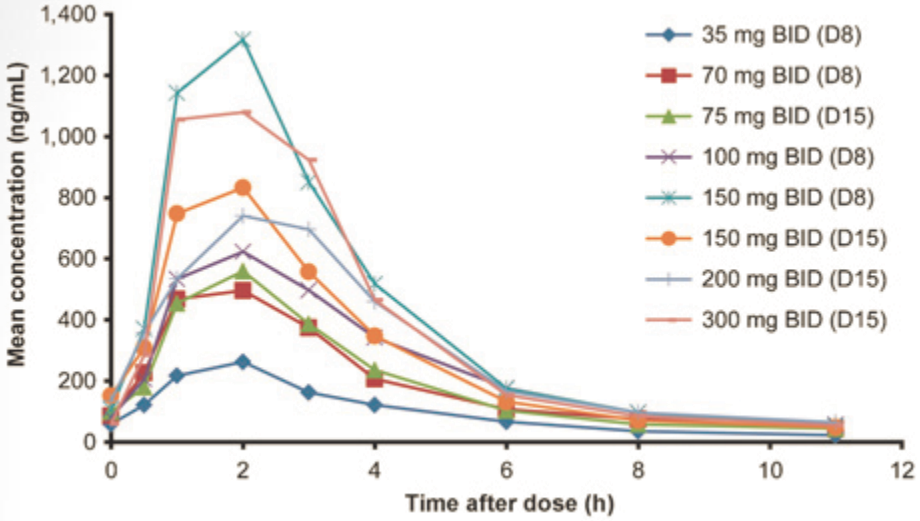
CCT196969, CCT241
LY3009120
ARQ-736
MLN2480



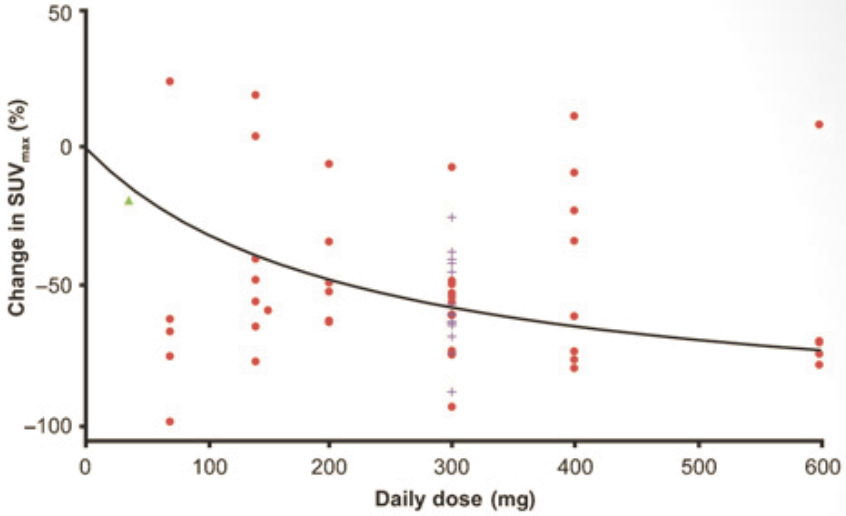
The "Paradox"

PK/PD correlations and dose selection: dabrafenib as a paradigmatic case

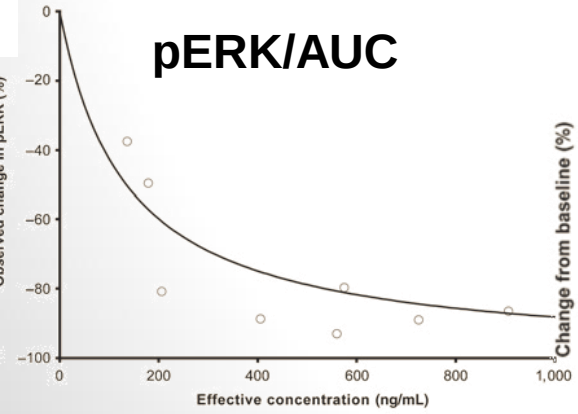
Dabrafenib was administered orally once, twice (BID), or three times daily (TID). No MTD was defined. A recommended phase II dose (RP2D) was chosen based on safety, pharmacokinetic, pharmacodynamic, and response data.

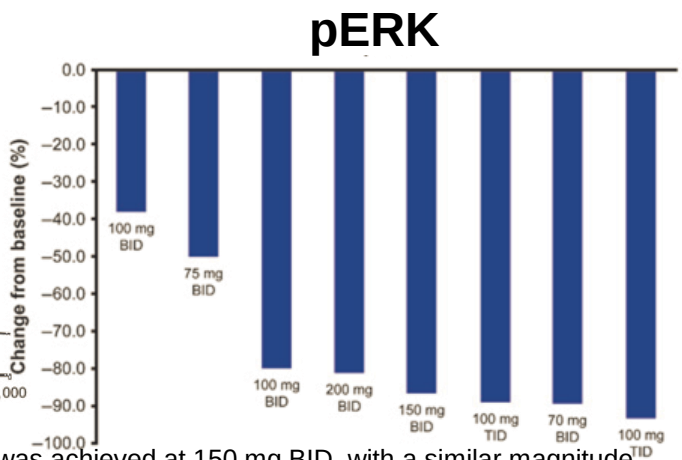


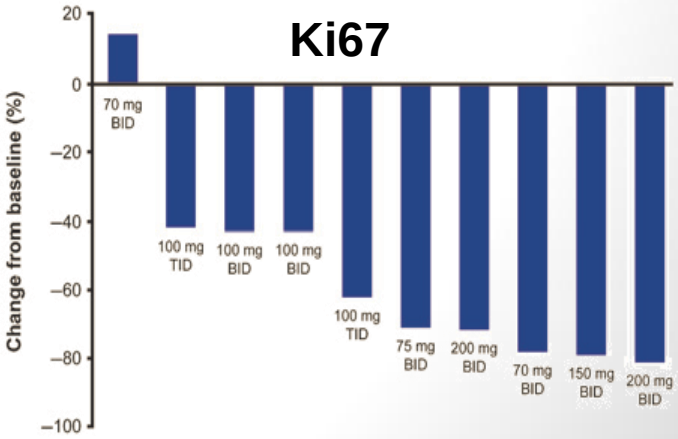
Pharmacokinetic assessment of dabrafenib demonstrated a less than-dose-proportional increase in exposure after repeat dosing above 150 mg BID.



A favorable activity and tolerability profile was demonstrated at 150 mg BID. There was no improvement with TID







Predicted target inhibition of pERK (>80%) was achieved at 150 mg BID, with a similar magnitude of inhibition at higher doses

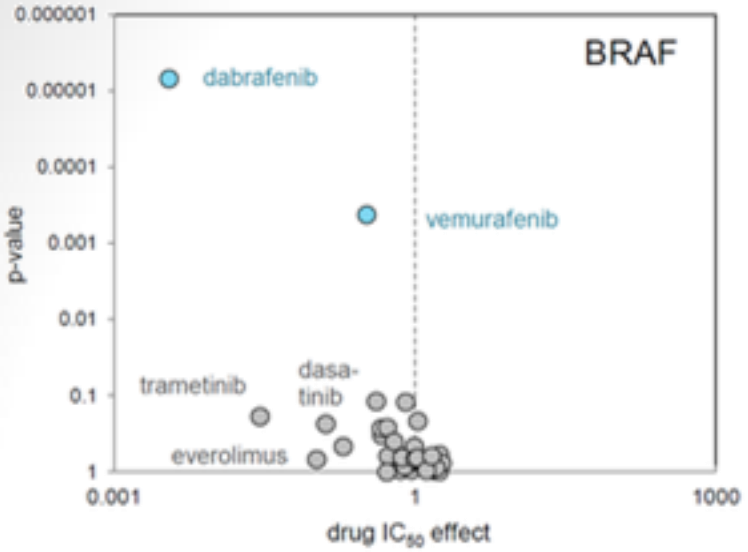
Falchook GS, Clin Cancer Res, 2014

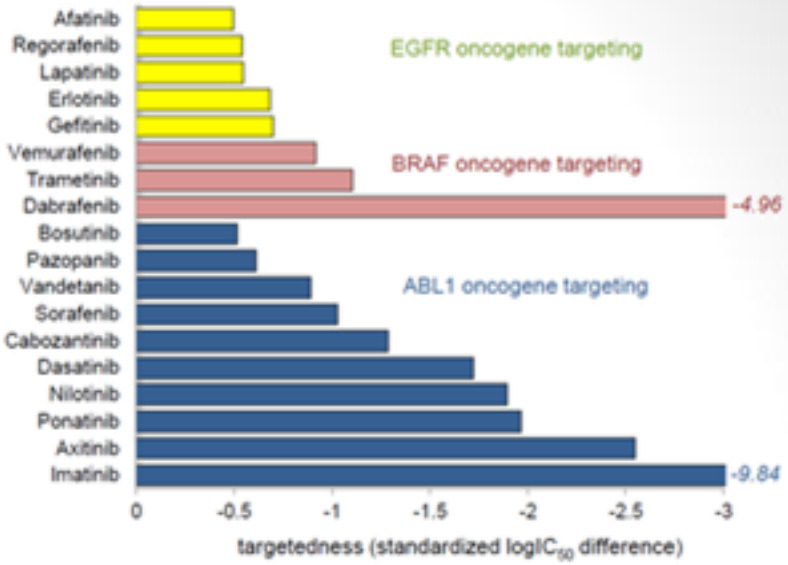
The Devil is in the Details:

RAF inhibitors and Pharmacological properties

Drugs with “unique” properties

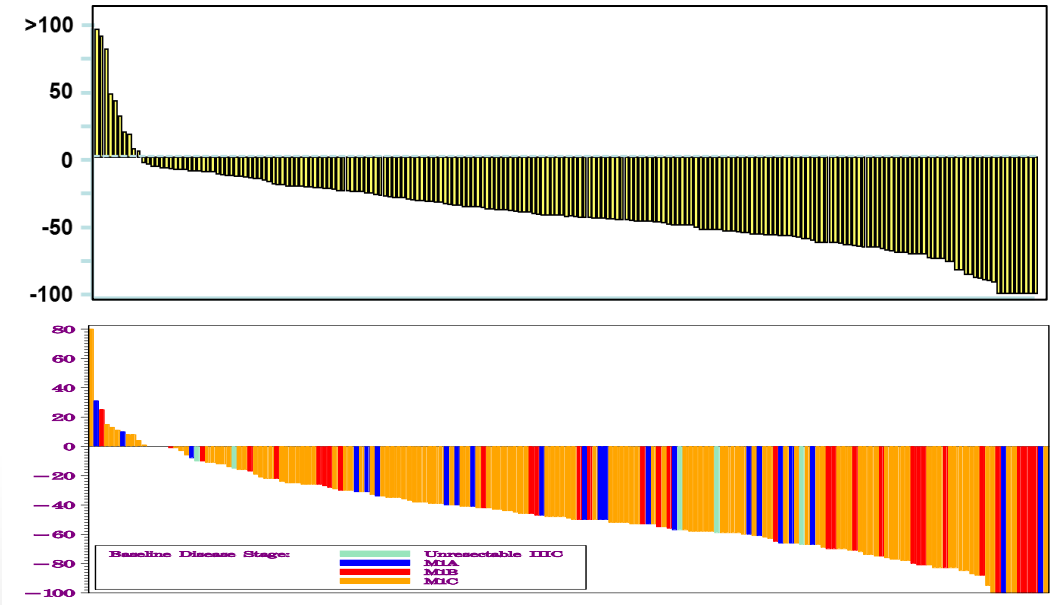
In vitro Comparison of the targeting efficacy of marketed inhibitors.





Uitdehaag JCM, et al. (2014) PLoS ONE 9(3): e92146.

Indirect comparison of vemurafenib and dabrafenib in patients with BRAFV600 mutant metastatic melanoma



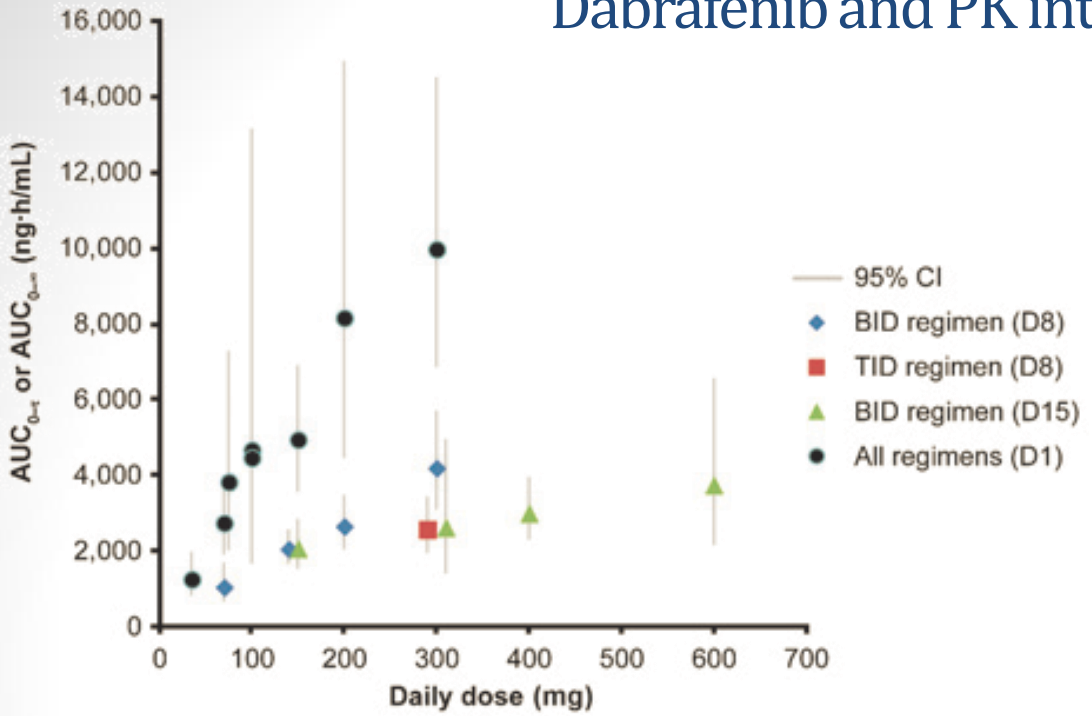
Vemurafenib
(960 mg po bid)

BRIM3
Chapman *et al*.
NEJM 2011

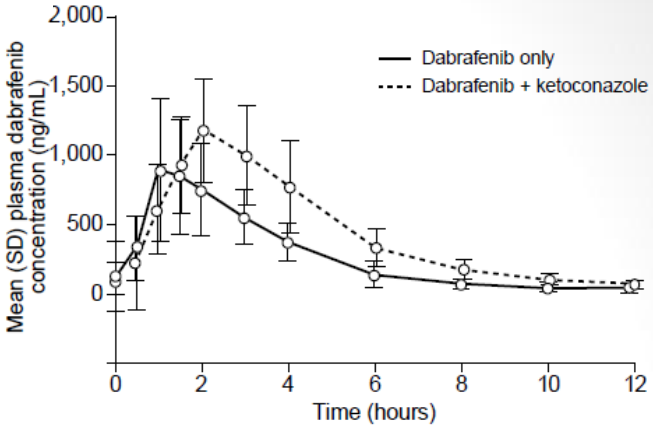
Dabrafenib
(150 mg po bid)

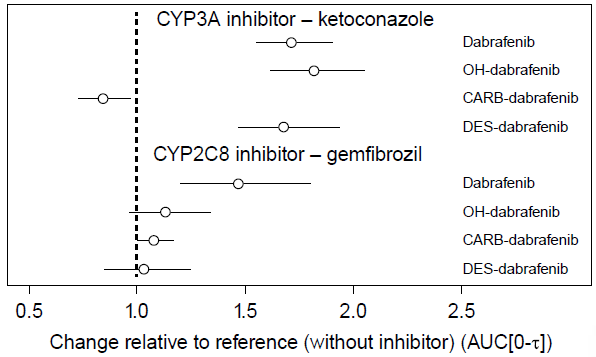
BREAK3
Hauschild *et al*.
Lancet 2012

Dabrafenib and PK interactions



Falchook GS, Clin Cancer Res, 2014

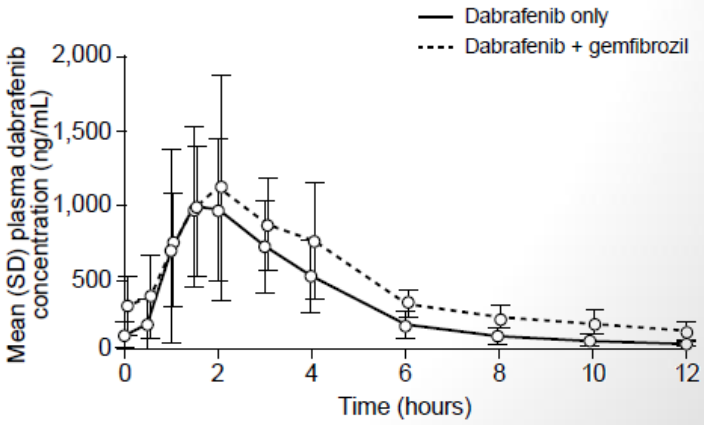




Dabrafenib exposure decrease over time, as a result of induction of its own metabolism (CYP3A).

The major route of elimination is via oxidative metabolism (via CYP2C8 and CYP3A) and biliary excretion.

Dabrafenib could be the victim and the perpetrator of drug-drug interactions with strong inhibitors of CYP2C8 and/or CYP3A4



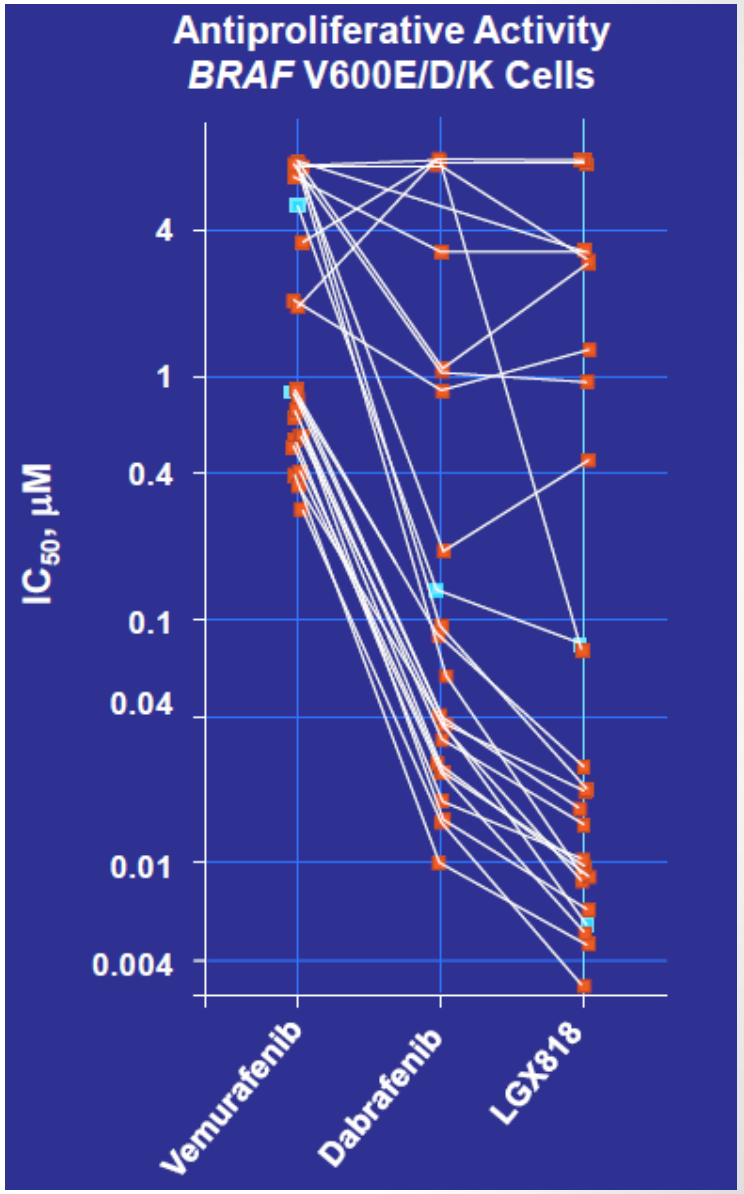
Suttle, AB, The Journal of Clinical Pharmacology, 2014

Encorafenib. A BRAFi with special pharmacological properties

Selectivity… Potency and a long dissociation t 1/2

		B-Raf	B-Raf (V600E)	C-Raf
Multikinase inhibitor	**Sorafenib**	22 nM	38 nM	6 nM
Multikinase inhibitor	**Regorafenib**	28 nM	19 nM	2.5 nM
BRAF (V600E selective)	**Vemurafenib**	100 nM	31 nM	48 nM
BRAF (V600E selective)	**Dabrafenib**	3.2 nM	0.8 nM	5.0 nM
BRAF (V600E selective)	**Encorafenib (LGX818)**	0.5 nM	0.4 nM	0.3 nM

Compound	Dissociation $t_{1/2}$, h
LGX818	> 30
Vemurafenib	0.5
Dabrafenib	2

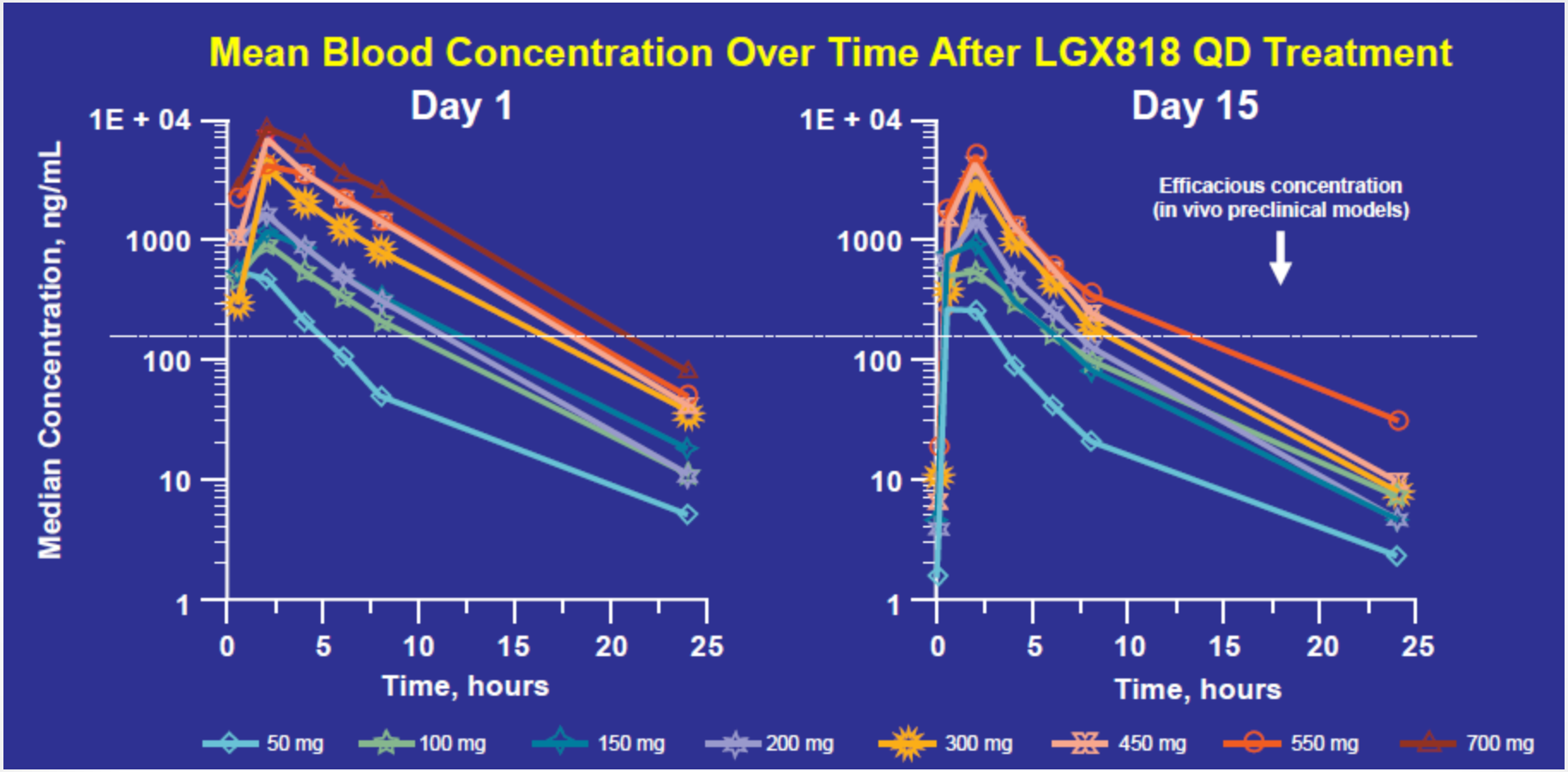


The dissociation half-time represents the time needed for half the ligands to dissociate from the receptor to which they were initially bound.

Dummer R, ASCO 2013

Encorafenib. A BRAFi with special pharmacological properties

Metabolic induction

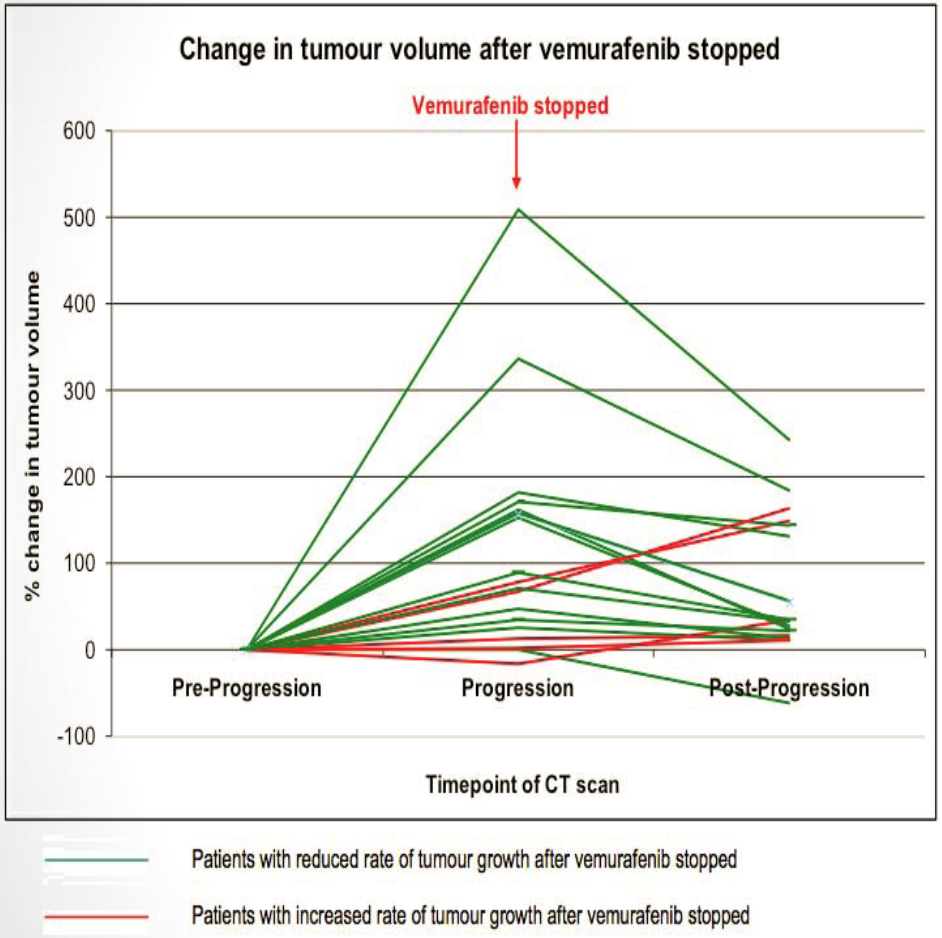


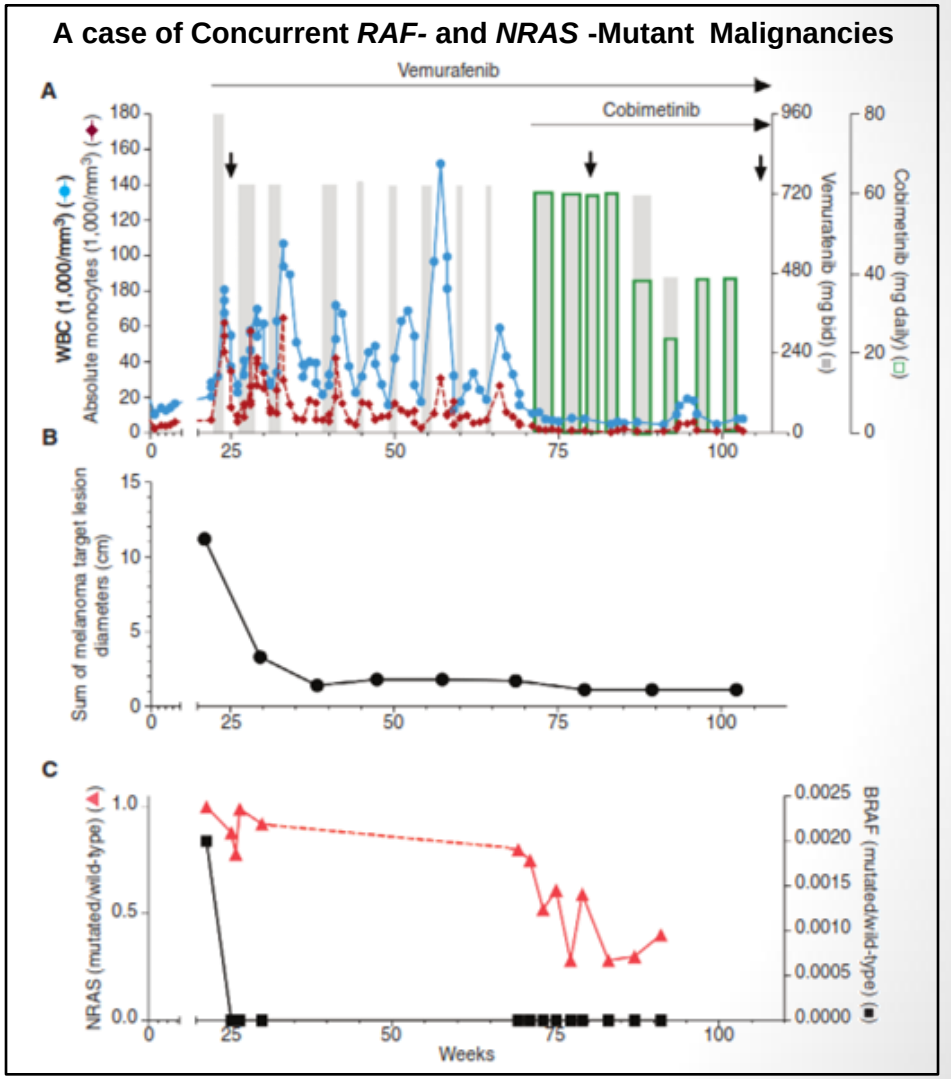
Day 15 exposures were consistently lower (30%-60%) than those on day 1, probably due to induction of CYP enzymes

A case for pulsatile therapy?

Pulsatile therapy with BRAFi?

Clinical observations



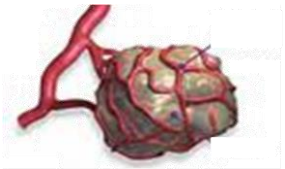


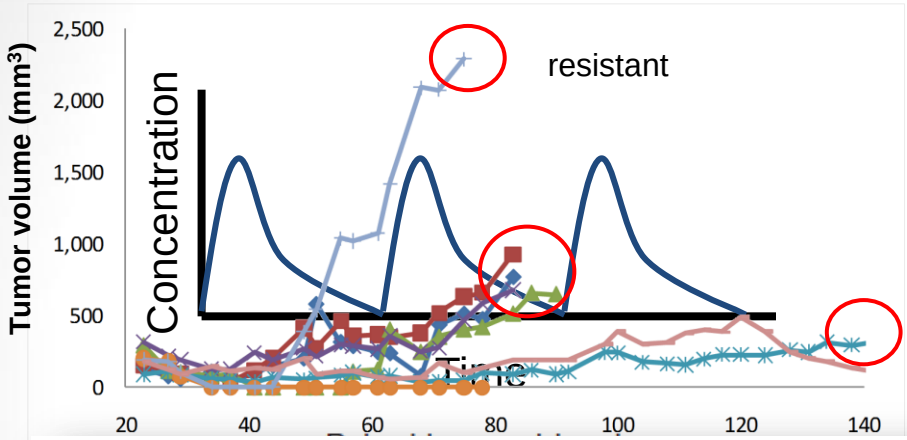
Fisher et al, SMR Annual Meeting, 2012
Stuart et al, AACR 2013

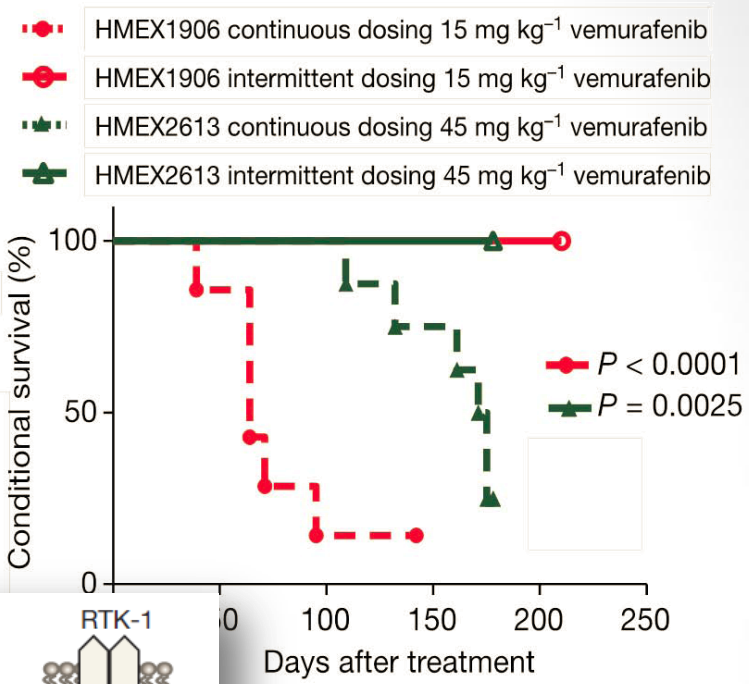
Abdel-Whab O. et al. Cancer discovery, 2014

Pulsatile therapy with BRAFi?

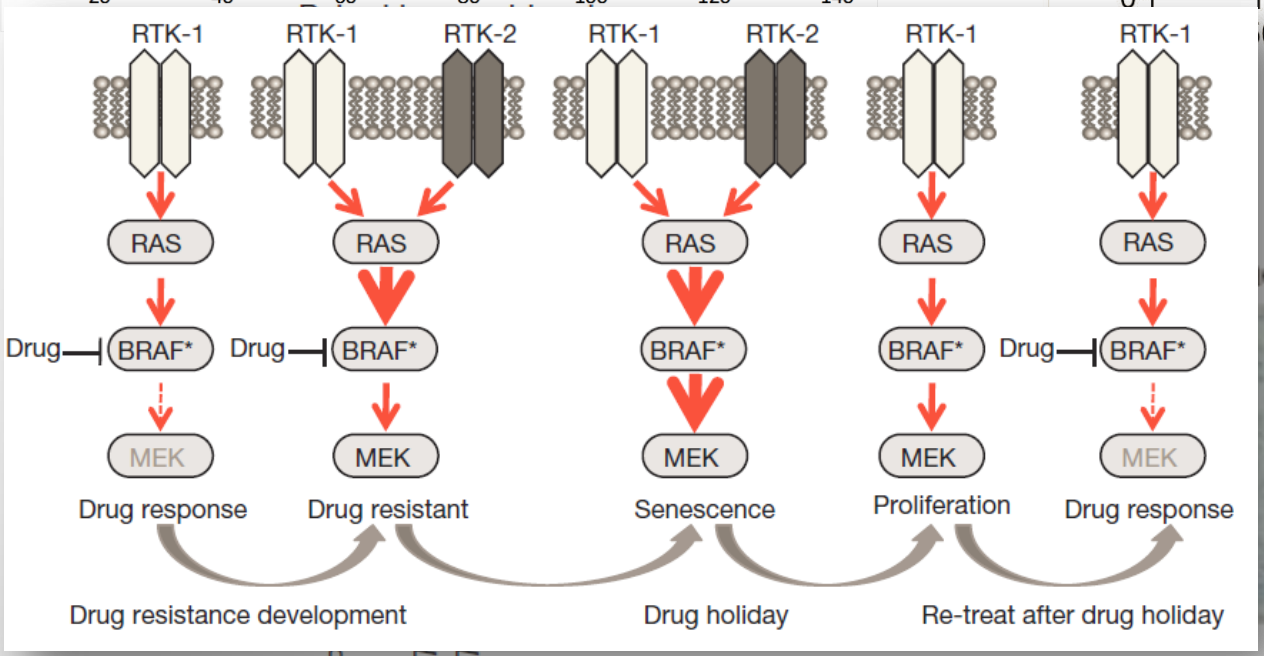
Preclinical observations

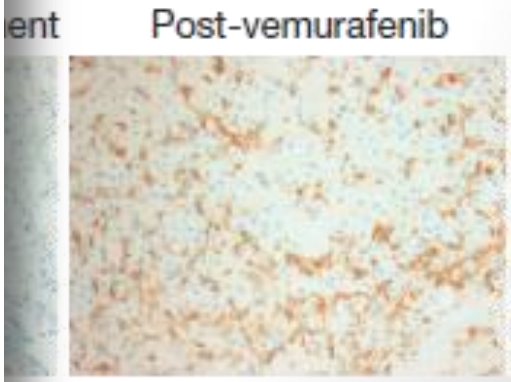






Das Thakur, M Nature, 2013

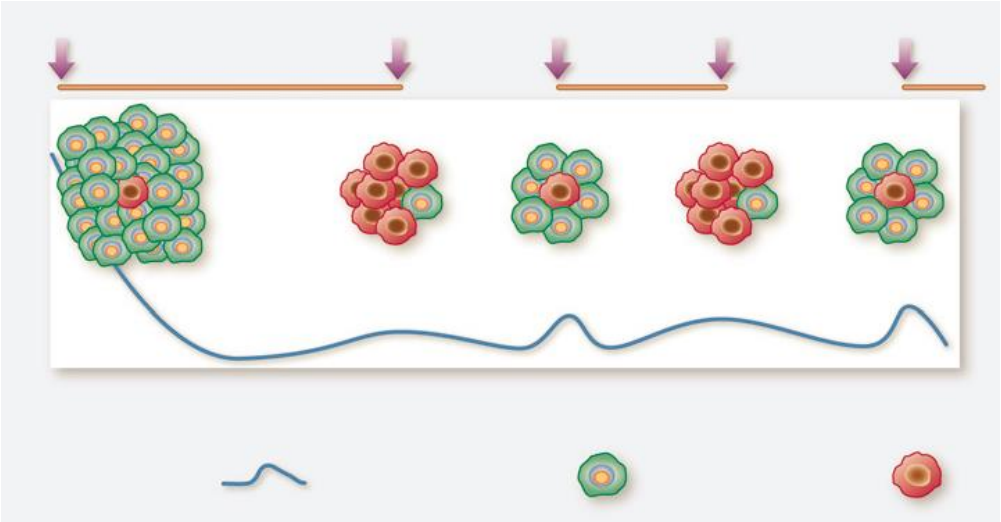




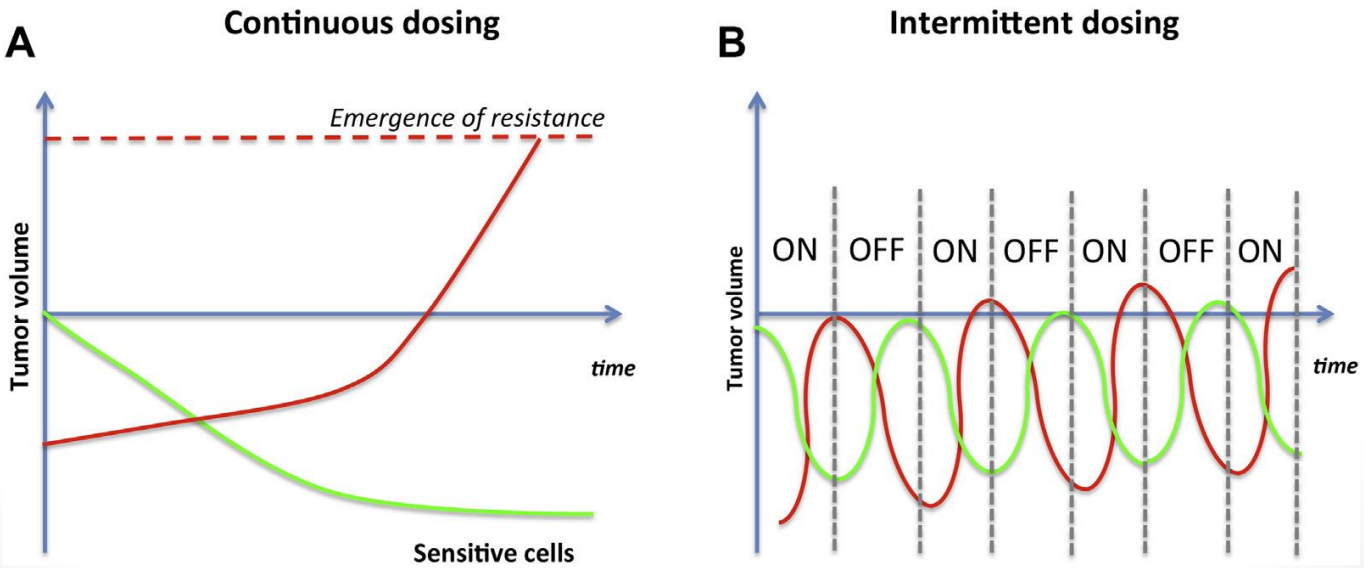
Sun et al. Nature April 2014

Pulsatile therapy with BRAFi?

The hypothesis

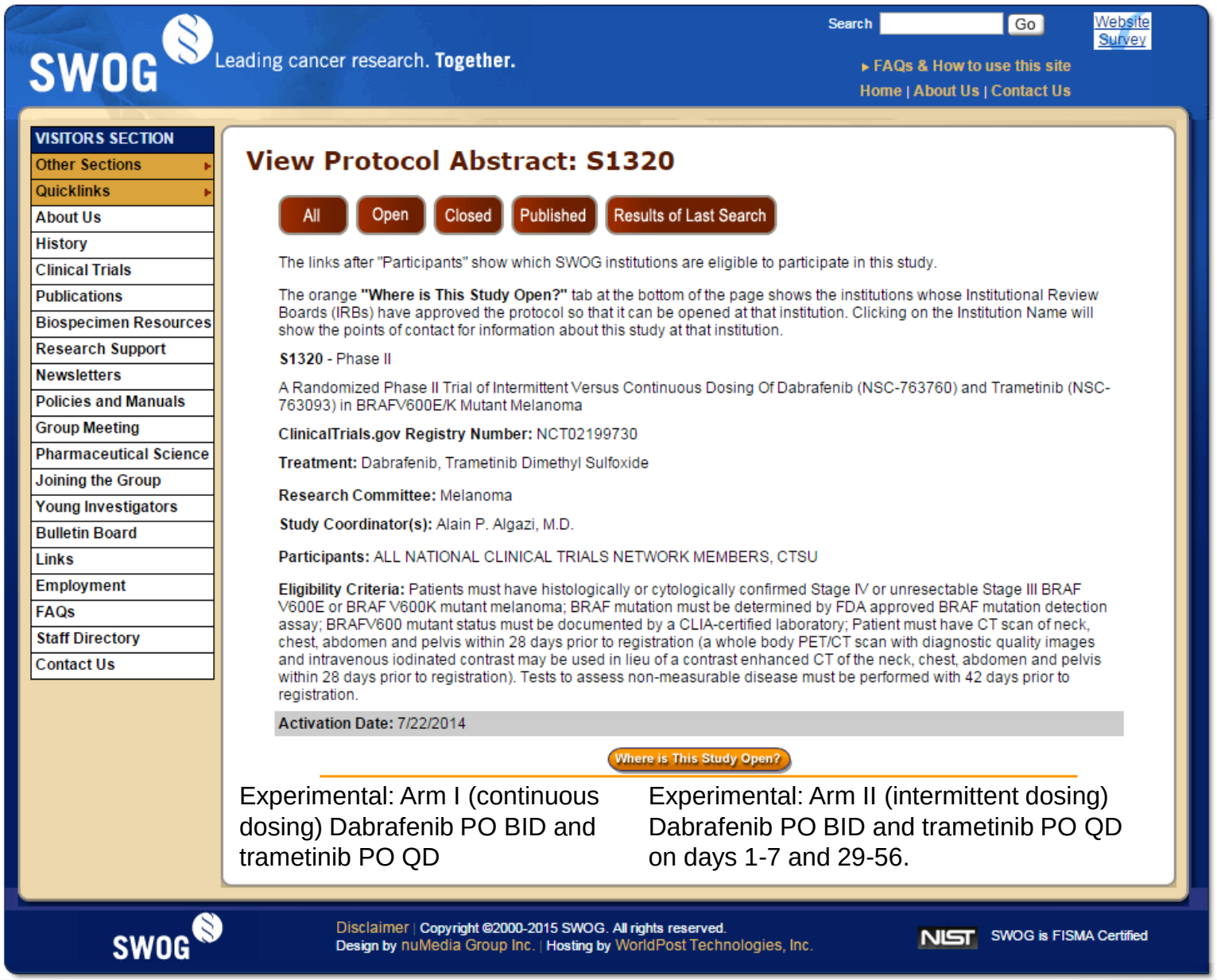


Das Thakur MD Cancer Res. 2013



Girotti, M.R., et al., Molecular Oncology (2014)

Pulsatile therapy with BRAFi?



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View Protocol Abstract: S1320

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The links after "Participants" show which SWOG institutions are eligible to participate in this study.

The orange **"Where is This Study Open?"** tab at the bottom of the page shows the institutions whose Institutional Review Boards (IRBs) have approved the protocol so that it can be opened at that institution. Clicking on the Institution Name will show the points of contact for information about this study at that institution.

S1320 - Phase II

A Randomized Phase II Trial of Intermittent Versus Continuous Dosing Of Dabrafenib (NSC-763760) and Trametinib (NSC-763093) in BRAFV600E/K Mutant Melanoma

ClinicalTrials.gov Registry Number: NCT02199730

Treatment: Dabrafenib, Trametinib Dimethyl Sulfoxide

Research Committee: Melanoma

Study Coordinator(s): Alain P. Algazi, M.D.

Participants: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS, CTSU

Eligibility Criteria: Patients must have histologically or cytologically confirmed Stage IV or unresectable Stage III BRAF V600E or BRAF V600K mutant melanoma; BRAF mutation must be determined by FDA approved BRAF mutation detection assay; BRAFV600 mutant status must be documented by a CLIA-certified laboratory; Patient must have CT scan of neck, chest, abdomen and pelvis within 28 days prior to registration (a whole body PET/CT scan with diagnostic quality images and intravenous iodinated contrast may be used in lieu of a contrast enhanced CT of the neck, chest, abdomen and pelvis within 28 days prior to registration). Tests to assess non-measurable disease must be performed with 42 days prior to registration.

Activation Date: 7/22/2014

Where is This Study Open?

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Experimental: Arm I (continuous dosing) Dabrafenib PO BID and trametinib PO QD

Experimental: Arm II (intermittent dosing) Dabrafenib PO BID and trametinib PO QD on days 1-7 and 29-56.

2nd Gen RAFi, "Paradox-breakers": PLX8394/ PLX7904

ClinicalTrials.gov

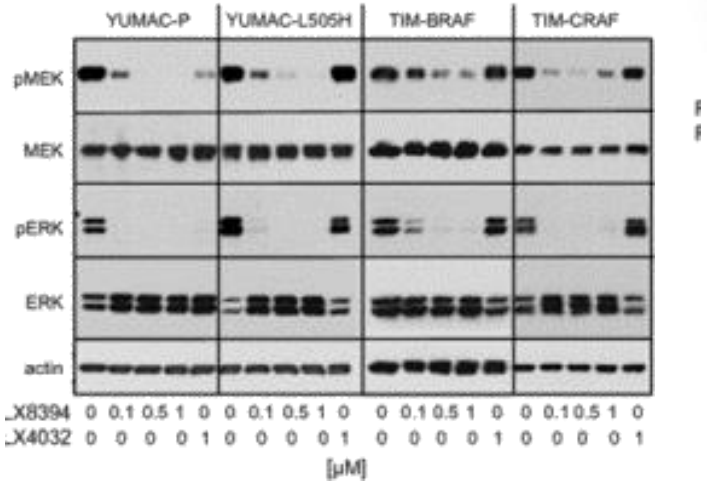
A service of the U.S. National Institutes of Health

ClinicalTrials.gov Identifier: NCT02012231

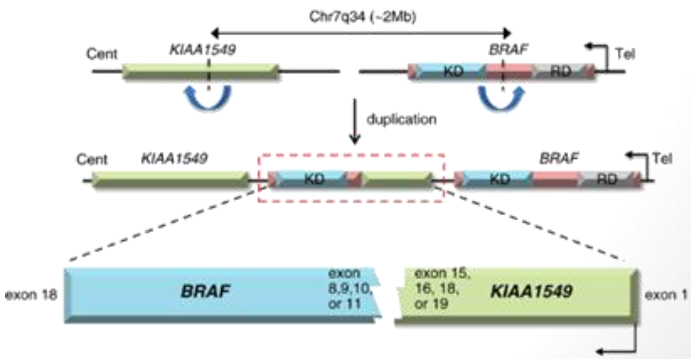
Phase I/IIa Study to Evaluate the Safety, PK, PD, and Preliminary Efficacy of PLX8394 in Patients With Advanced Cancers.

- Melanoma
- Thyroid Cancer
- Colorectal Cancer
- Non-small Cell Lung Cancer
- Cholangiocarcinoma
- Histiocytosis
- Hairy Cell Leukemia

Cells / Inhibitor	PLX4032	PLX7904	PLX8394
YUMAC-TIM-BRAF	4.5	1.5	0.177
YUMAC-TIM-CRAF	9	0.092	0.024
YUMAC-BRAF^{L505H}	3.4	0.389	0.095
YUGEN8	0.092	0.064	0.033
YUGEN8-BRAF^{L505H}	1.0	0.377	0.035



- Inhibit RAF signaling in BRAF(V600E) without paradoxical effects in wild-type cells.
- Block the growth of vemurafenib-resistant BRAF(V600E) cells that express mutant BRAF(L505H), NRAS or BRAF splice variants



Chen YH, Oncogene 2013

"Paradox-breaking" BRAFi: PanRAFi

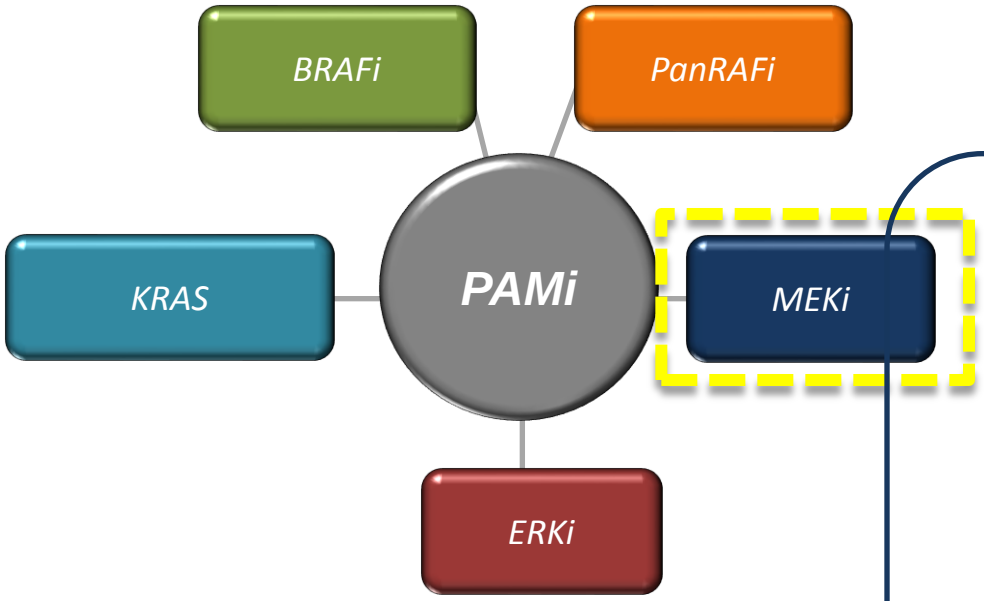
CCT196969
CCT241161
PLX7904
LY3009120

- **2nd generation pan-Raf inhibitors inhibit A-, B-, and C-Raf**
- **Minimal paradoxical pathway activation in B-Raf wild type background,** avoiding skin side effects (such SCC)
- **Being active against monomers,** inhibit BRAF V600E cells and nonV600E/K mutant tumor cells
- **May be active against vemurafenib- or dabrafenib-resistant cells:**
  - **Being active against Raf homodimers**, inhibit p61BRaf and KIAA1549-BRAF splice variants
  - **Being active against Raf heterodimers, inhibit Nras & Kras mutant cells.**

Chen YH, Oncogene 2013
Peng SB, AACR 2014
Girotti MR et al. Cancer Cell 2015

MEK inhibitors

BRAF/MEKI:
RO5126766/CH5126766

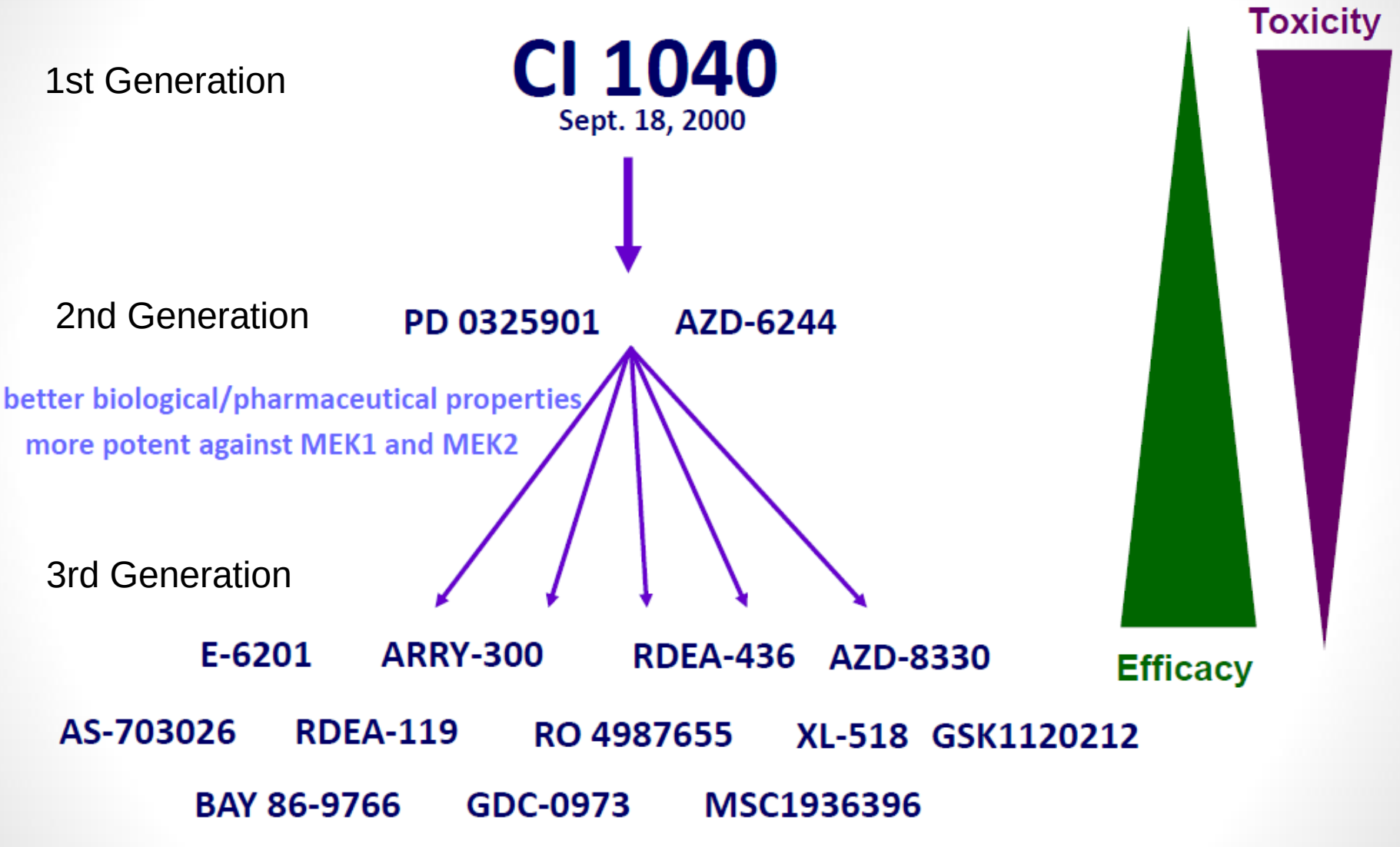


E6201 (MEK/MEKK1 inh)

Allosteric MEK1/2i
Trametininb (GSK1120212)
Pimasertib (AS703026)
Selumetinib (AZD6244)
PD0325901
Refametinib (BAY86-9766)
TAK733
MEK162 (ARRY438162)
WX554
RO4987655
ARRY-300
AS703988
AZD8830
E6201

Allosteric MEK1i
Cobimetinib (GDC0973)

Family tree of MEK inhibitors



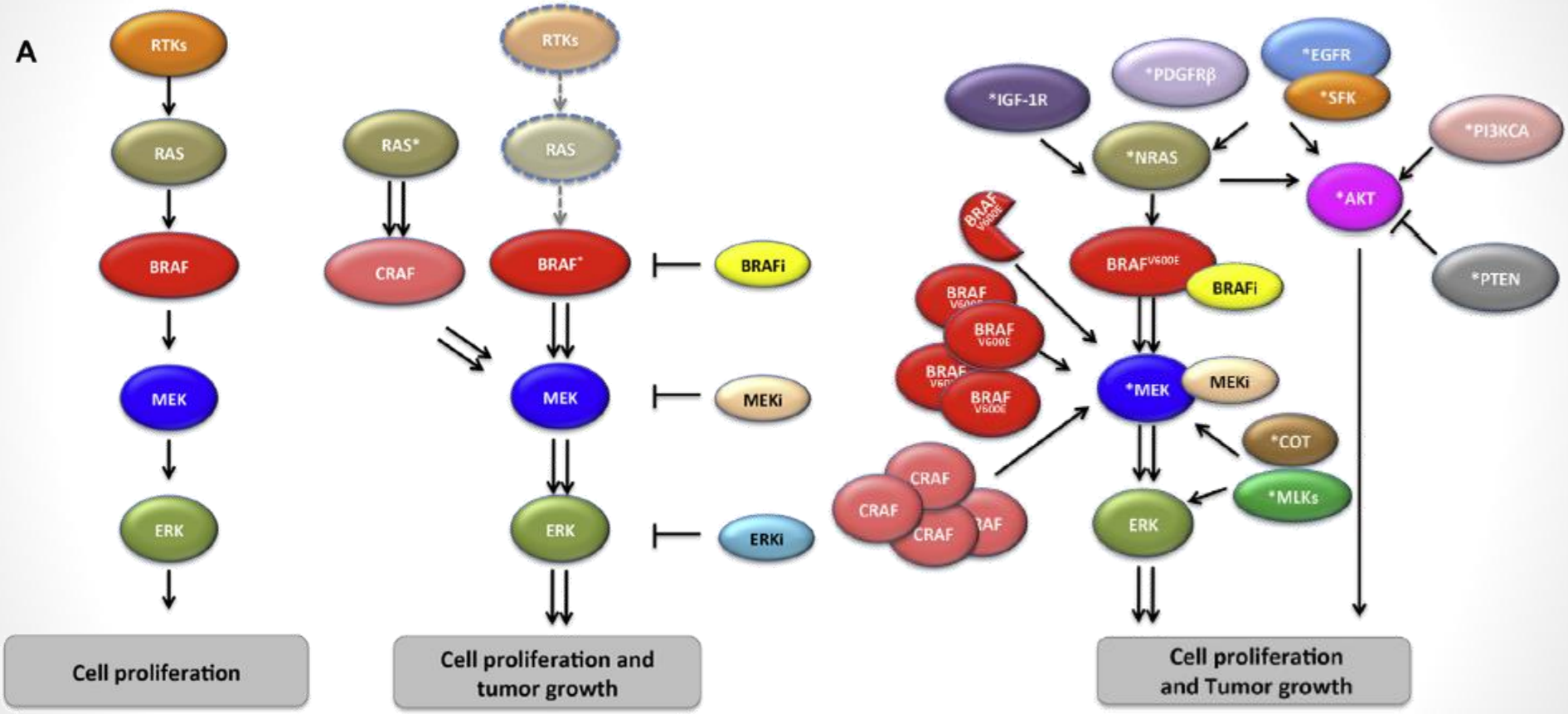
From Pat Lorusso

Pharmacology meets combination strategies

…Dual combinations

…triple combinations

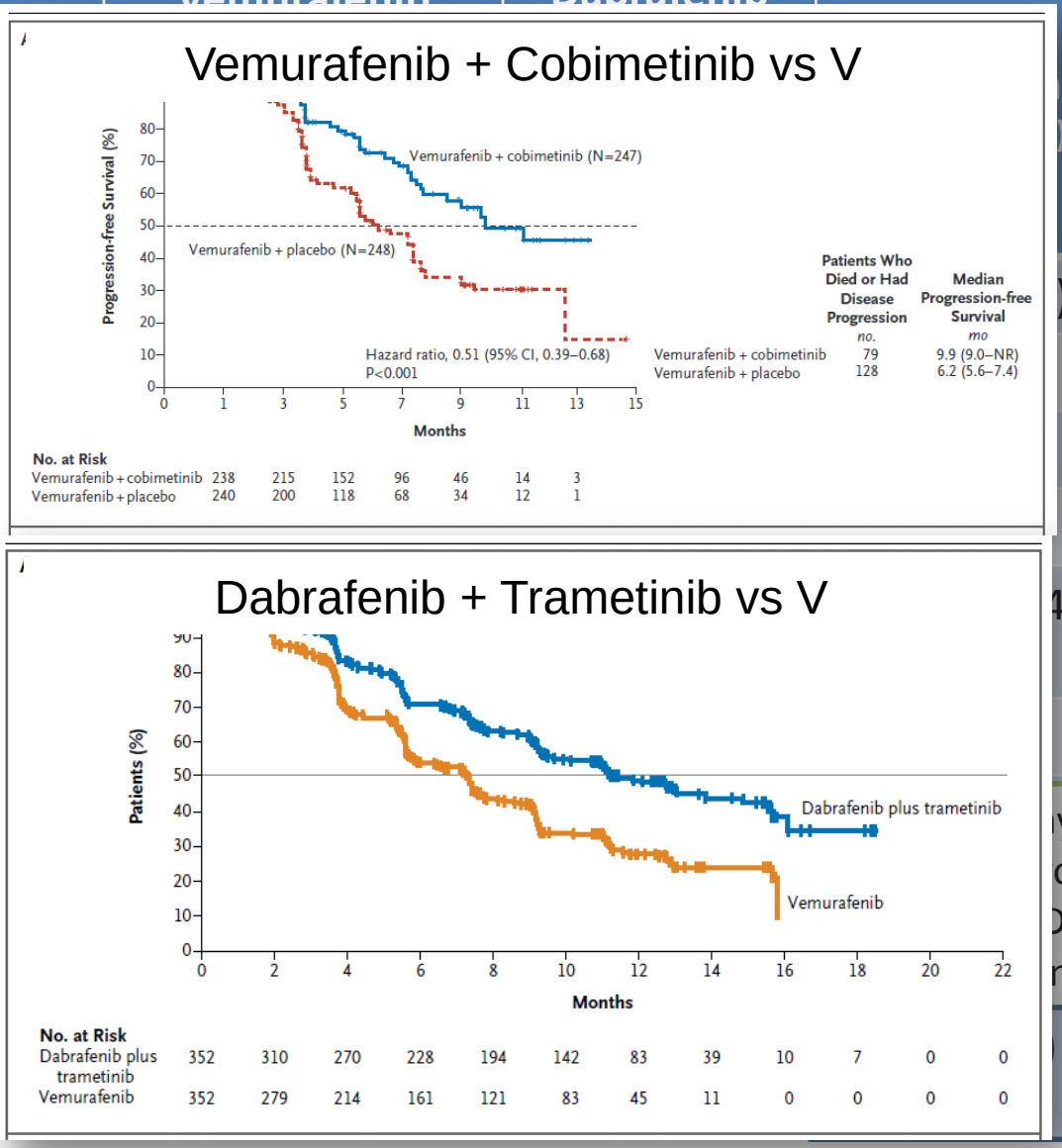
Mechanisms of resistance to BRAFi and potential combos



Girotti, M.R., et al., Molecular Oncology (2014)

Dual combinations BRAFi+ MEKi: Comparison of G3 toxicity

	Vemurafenib	Dabrafenib		Dabrafenib (150 mg BID)
Any G3				198 (57%)
Diarrhea				0
Rash				0
Photosensitivity				NA
AST / ALT elevate				NA
CreatinKinase eleva				NA
Pyrexia				
Decreased EF				
Hypertension				
Cutan ce	grade 3 pro			9 (17%)

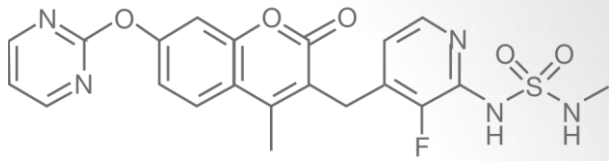


y grade: pyrexia,
omiting.
Dose reduction:
nuation: 13%

Flaherty, K et al. NEJM 2012; Robert, C et al. N Engl J Med 2015; Ribas, A et al. Lancet Oncol 2014; Larkin, J, NEJM 2014

RAF/MEK inhibitor, RO5126766

	V600E BRAF	WT BRAF	CRAF	MEK1
IC50 (nM)	8.2	19	56	160

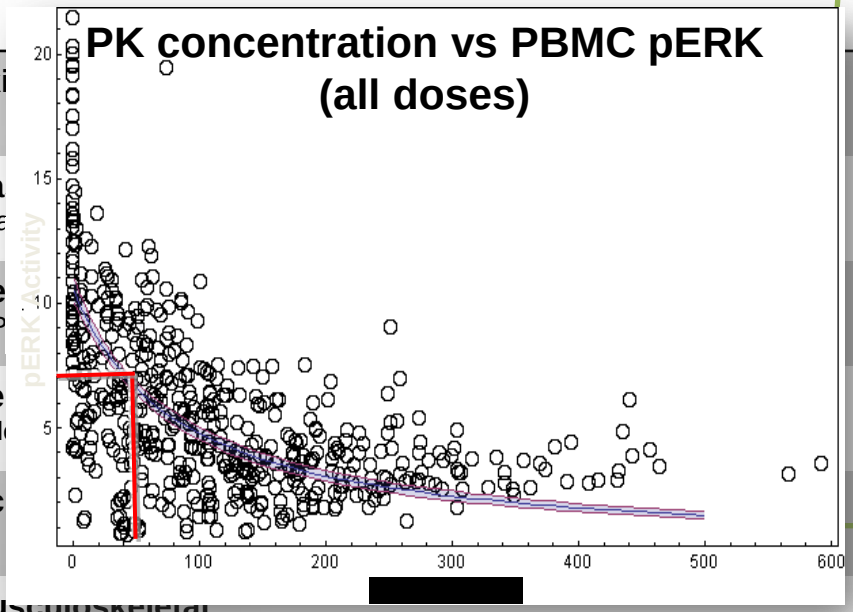


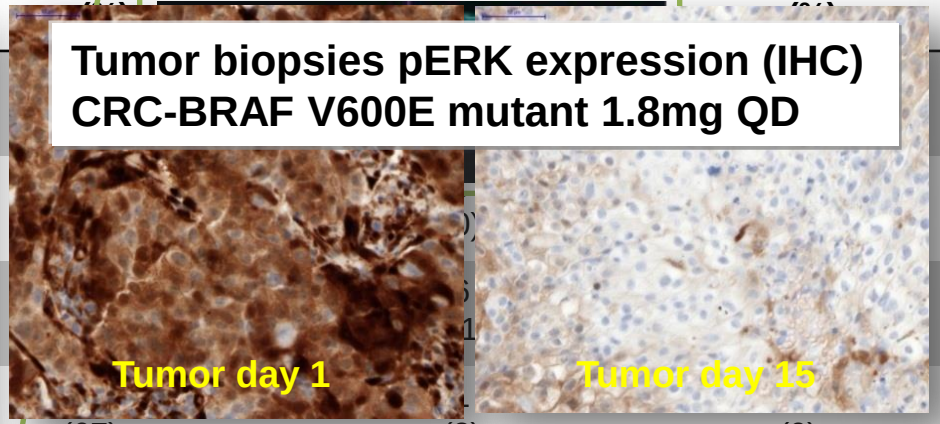
FIH n=52
Cohorts
Once daily (QD) 0.1-2.7 mg
7 days on/7 days off 2.7-5.0 mg
4 days on/3 days off 2.7-4.0 mg

Te

No SCC or keratoacanthoma

Main toxicities	Blurred vision (36%) Macular edema (11%) Photopsia (4%)
Main grade	G1 (46%) G2/3 (15%)

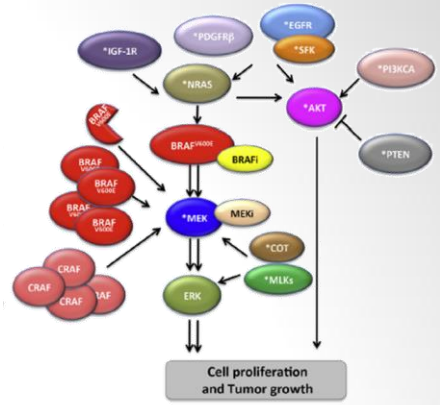




AE Class	All grade		Grade 4
Ski			
Ga (Dia			
Me (CP			
Ge (Ed	(67)	(2)	(0)
Oc	30 (58)	3 (6)	0 (0)
Musculoskeletal (Myopathy, myalgia, joint swelling)	10 (19)	1 (2)	0 (0)

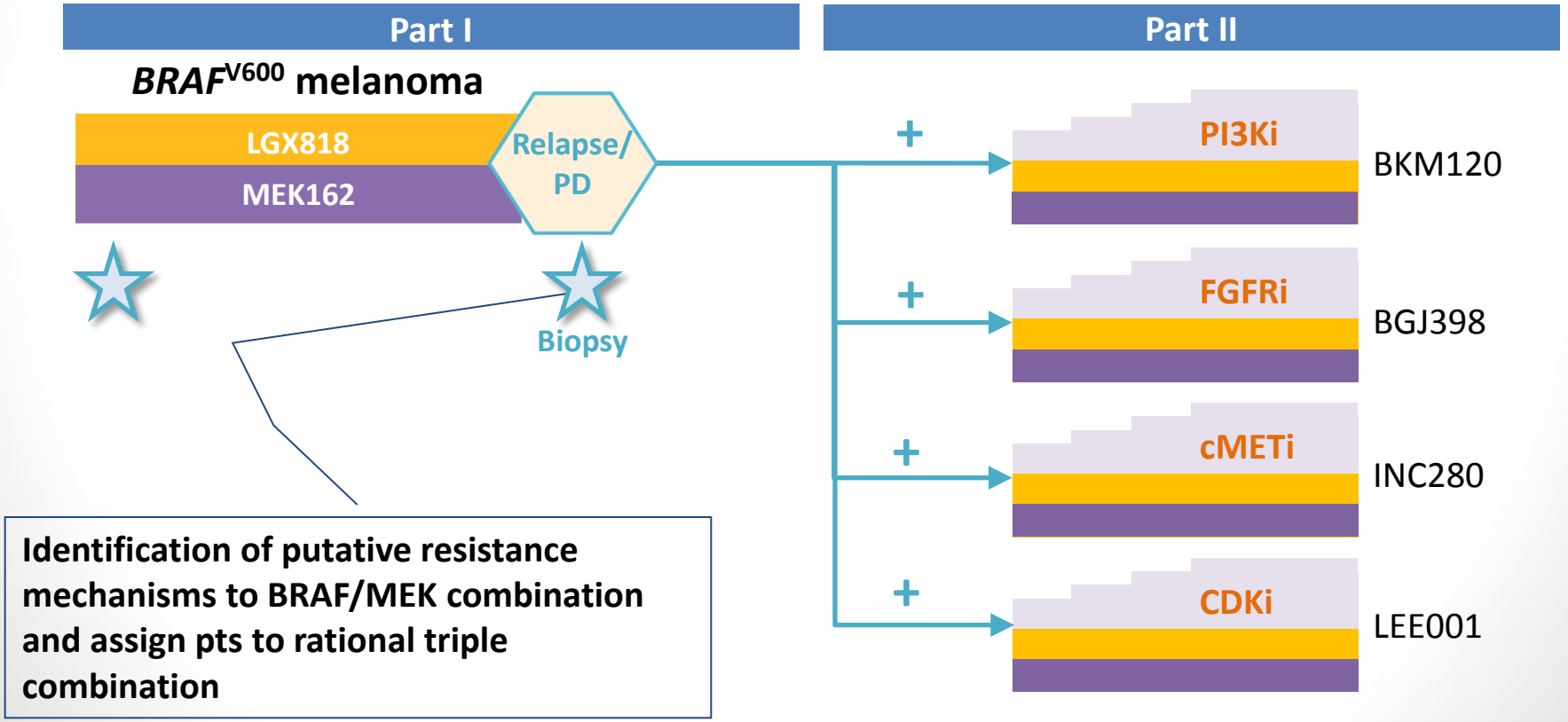
Martinez M. Clin Cancer Res 2012

Other combos



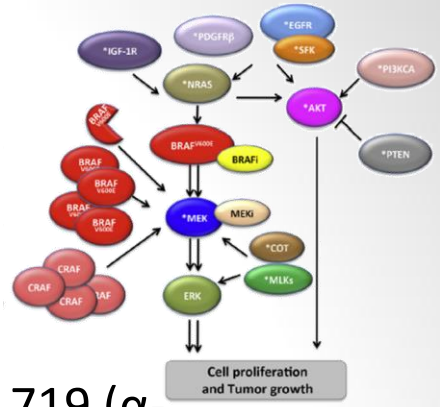
- PI3K/AKT/MTORi + MEKi
- PI3K/AKT/MTORi + BRAFi
- EGFRi (and other surface receptors)+ MEKi
- EGFRi (and other surface receptors)+ BRAFi
- Immunotherapy (anti CTLA4, antiPD1/PDL1) + BRAFi
- Immunotherapy (anti CTLA4, antiPD1/PDL1) + MEKi
- HSP90i + BRAFi
- METi + BRAFi
- CDKi + BRAFi
- VEGFRi + BRAFi
- FGFRi + BRAFi

Logic 2: A phase II, multi-center, open-label study of sequential LGX818/MEK162 combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma



Clinicaltrials.gov: NCT02159066

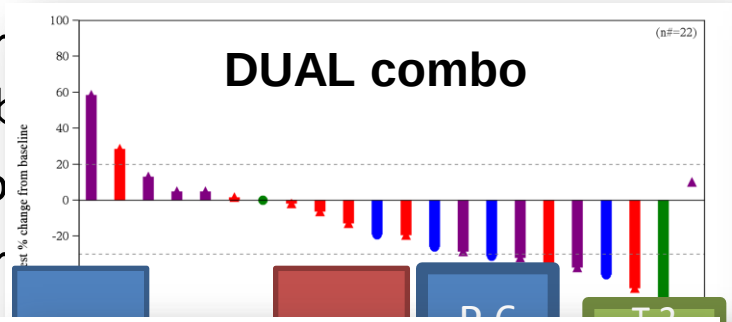
Triple combinations…

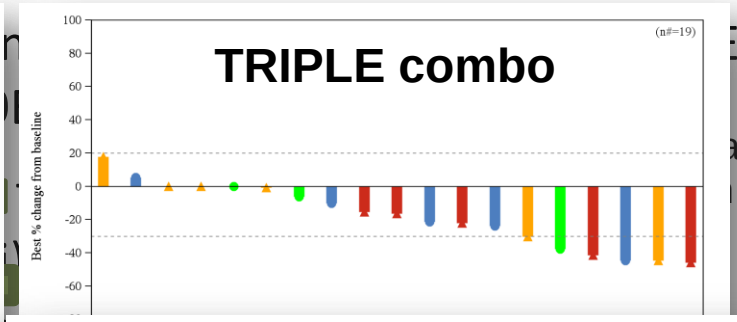


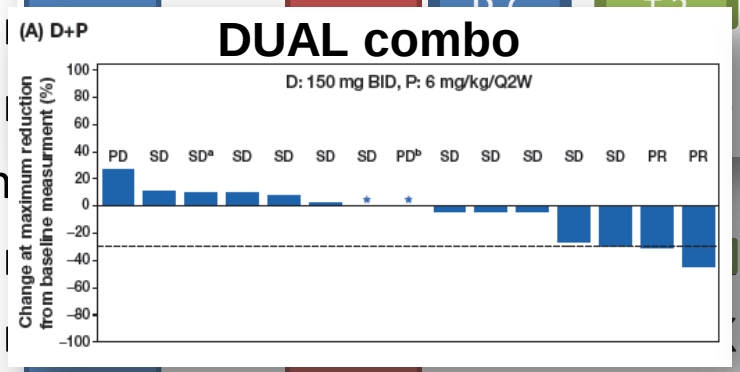
- Encorafenib (BRAFi) + cetuximab (Anti-EGFR Antibody) +/- BYL719 (α-specific PI3K inhibitor) in Patients with BRAF V600E Mutated Colorectal Cancer

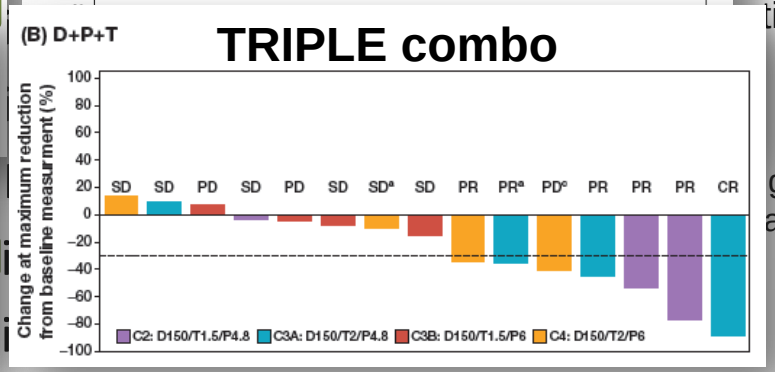
C

D 150



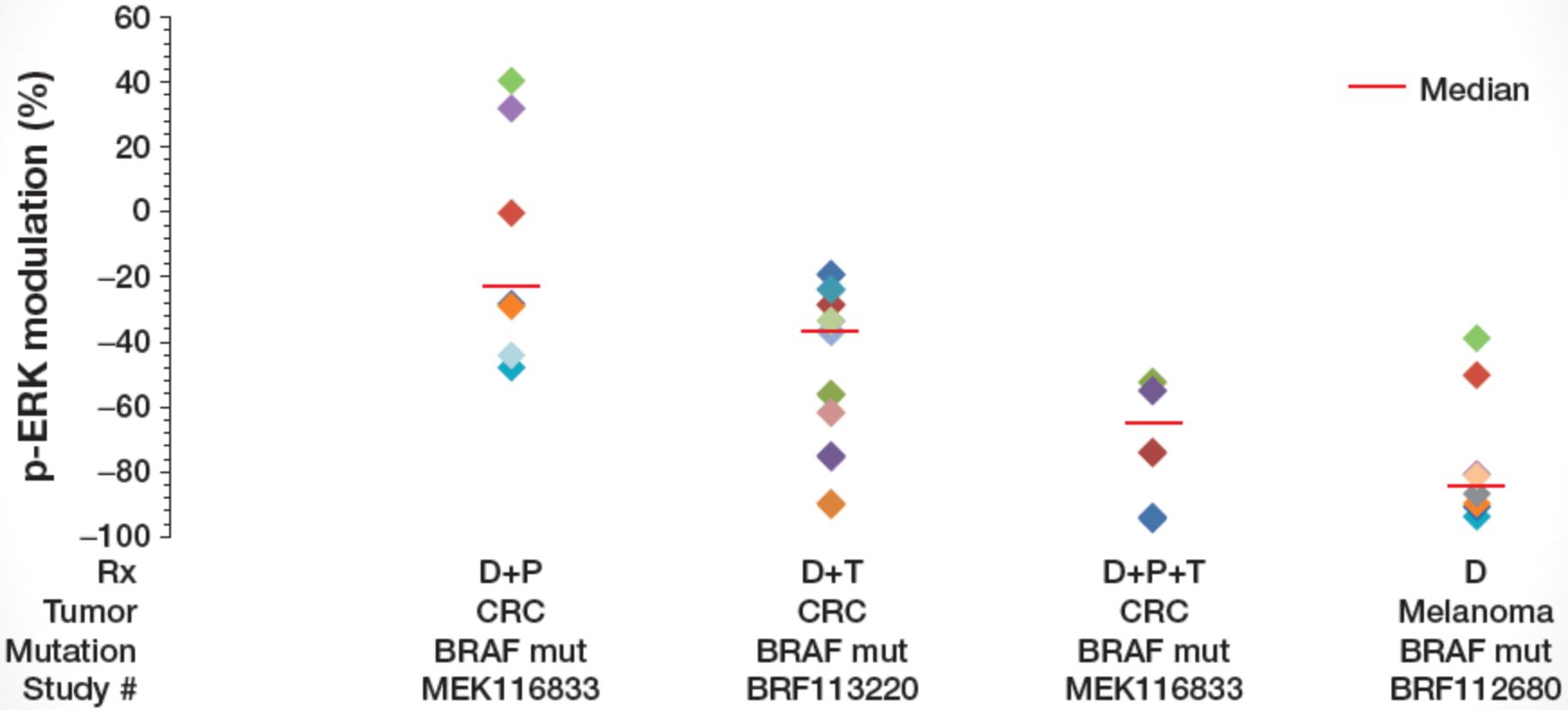






van Geel Robin M, 2014: Bendell J, ASCO 2014

Cross-Study Comparison of Phospho-ERK Modulation Between DUAL (D+P, D+T) vs TRIPLE (D+P+T) Therapy in CRC and Monotherapy (D) Therapy in Melanoma



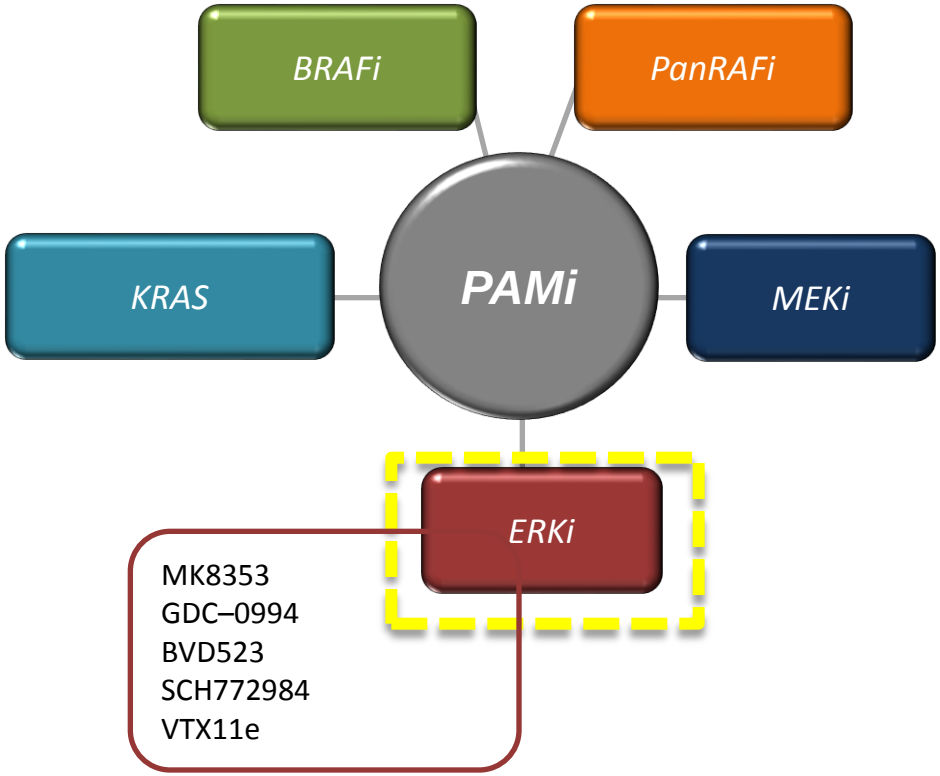
Comparison of p-ERK modulation using dabrafenib based combination therapies in BRAFm CRC and BRAFm melanoma. Treatment in BRAFm CRC was dabrafenib (150 mg BID) , trametinib (1.5-2 mg QD) and/or panitumumab (4.5-6 mg every two weeks). Treatment in BRAFm melanoma was dabrafenib (70 -200 mg BID). Average +/- SD for median pERK decrease in CRC was D+P (n= 7): -11 % (± 35.7%), -28; D+T (n=9): 47 % (± 24 %) , -36.7%; D+P+T (n=2): -84 (± 14%), -84%. Average +/- SD for pERK decrease in melanoma was D (n=8): 76 % (± 20 %), -84%.

Bendell J, ASCO 2014

New Kids on the block…

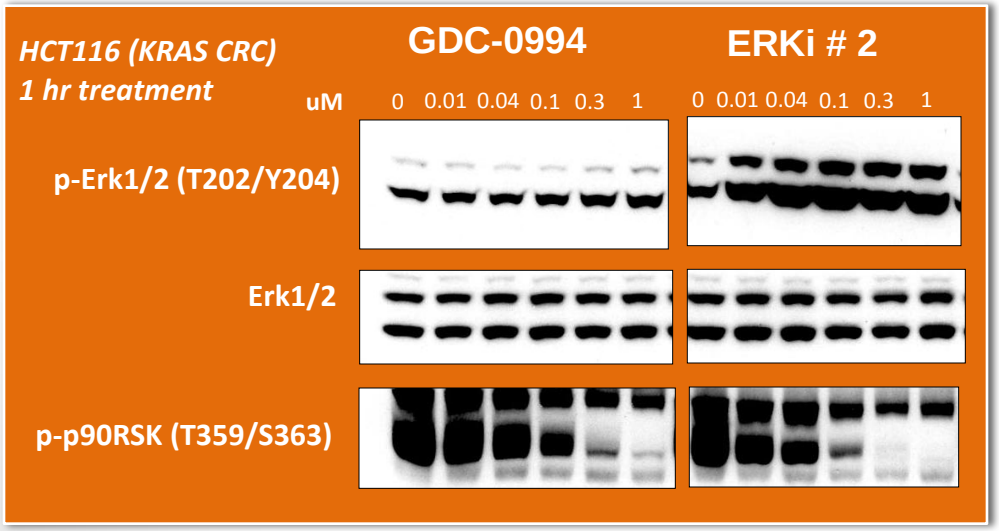
…ERKi

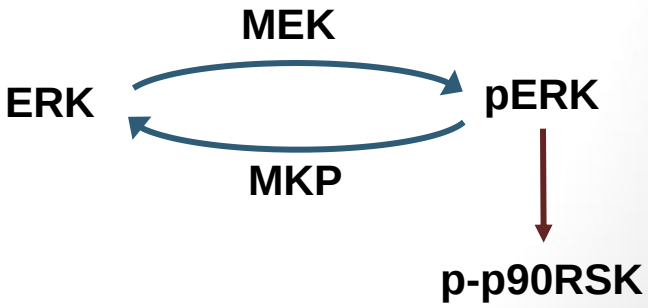
…targeting KRAS

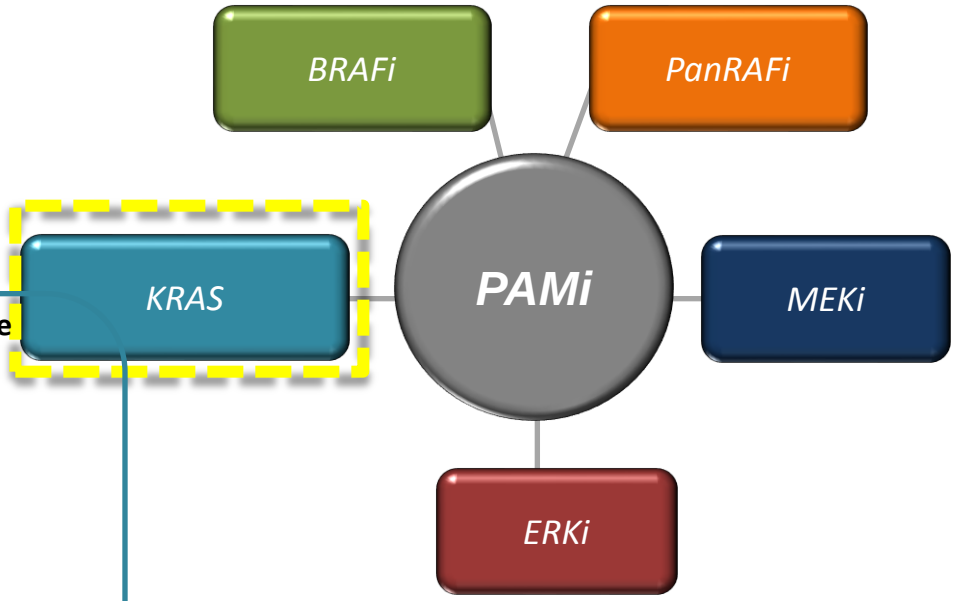

BRAFi
PanRAFi
KRAS
PAMi
MEKi
ERKi
MK8353
GDC–0994
BVD523
SCH772984
VTX11e

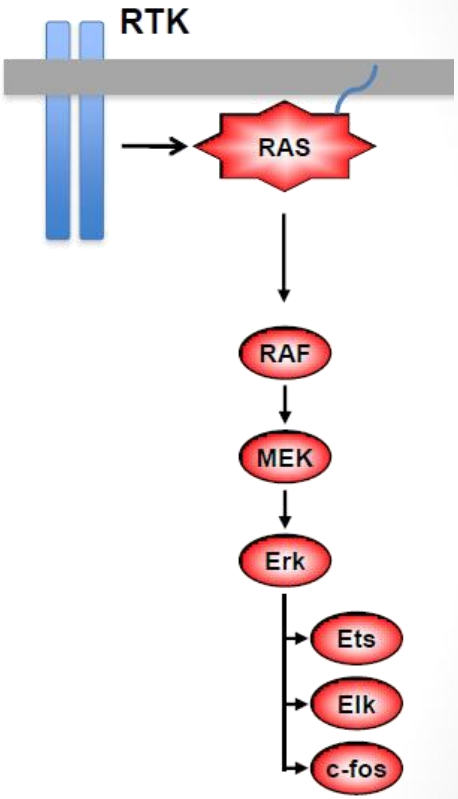
ERKi

- *In vitro* profiles of ERK inhibitors can differ
  - Effects on phospho-ERK levels vary between different ERK inhibitor series:
    - Most chemical series show rapid and sustained increase in phospho-ERK
    - GDC-0994 has little acute effect on phospho-ERK *in vitro*
    - In contrast SCH772984 is reported to decrease phospho-ERK *(Cancer Disc. 2013; 3:742)*
  - Inhibition of phospho-p90RSK correlates well with biochemical potency
- Biochemical activities(kinetic differences in phosphorylation and dephosphorylation of ERK) of diverse ERK inhibitors suggest a range of conformational effects









Inhibitors of membrane association
Minerval
FTIs
GGTIs
Deltarasin

Mutation Specific
Direct KRAS inhibitor G12C

Targeting RAS at RNA level
Anti-sense oligonucleotids
siRNA

Direct KRAS targeting

siRNA

PNAS

Mutant KRAS is a druggable target for pancreatic cancer

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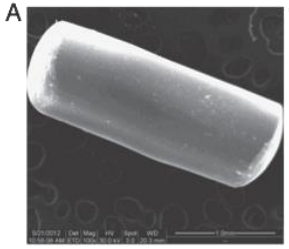
[a]Silenseed LTD, and [d]Goldyne Savad Institute of Gene Therapy, Hadassah Hebrew University Medical Center, Jerusalem 91120, Israel; [b]Oncology Institute, Chaim Sheba Medical Center, Tel HaShomer, Sackler School of Medicine, Tel Aviv University, Tel Aviv 91120, Israel; [c]Institute of Drug Research, School of Pharmacy, Faculty of Medicine, Center for Nanoscience and Nanotechnology and Alex Grass Center for Drug Design and Synthesis, Hebrew University, Jerusalem 91120, Israel; [f]Department of Surgery, [g]Sharett Institute of Oncology, [h]Gastroenterology Institute, and [i]Department of Obstetrics and Gynecology, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel; [e]Department of Gastroenterology, Chaim Sheba Medical Center, Tel HaShomer, Tel Aviv 91120, Israel; and [j]Digestive Diseases Institute, Shaare Zedek Medical Center, Jerusalem 91120, Israel

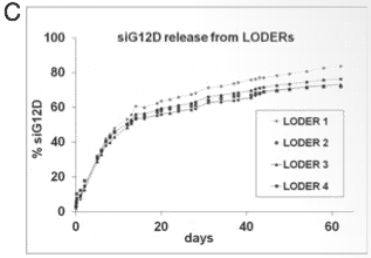
Edited by Michael Sela, Weizmann Institute of Science, Rehovot, Israel, and approved October 28, 2013 (received for review August 1, 2013)

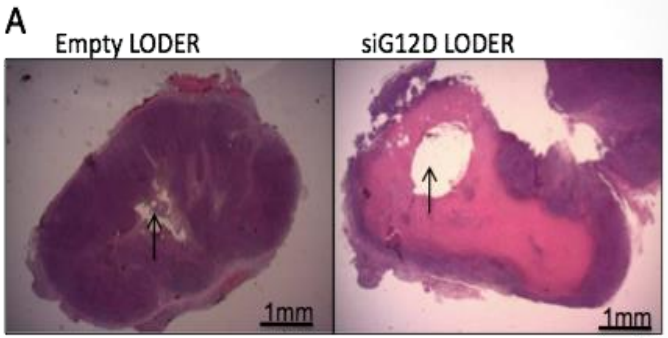
Pancreatic ductal adenocarcinoma (PDA) represents an unmet therapeutic challenge. PDA is addicted to the activity of the mutated KRAS oncogene which is considered so far an undruggable therapeutic target. We propose an approach to target KRAS effectively in patients using RNA interference. To meet this challenge, we have developed a local prolonged siRNA delivery system (Local Drug EluteR, LODER) shedding siRNA against the mutated KRAS (siG12D LODER). The siG12D LODER was assessed for its structural, release, and delivery properties in vitro and in vivo. The effect of the siG12D LODER on tumor growth was assessed in s.c. and

periods of time, reduction of side effects, and cost reduction (13). A prominent method of controlling the release rate of a drug in a pharmaceutical dosage is to embed the active agent within a polymeric matrix (14, 15). The polymer must be biocompatible, and in the case of parenteral administration, preferably biodegradable, to avoid the need to remove empty remnants.

In the present study, we exploited the slow-release characteristics of the biodegradable polymer matrix, which we named local drug eluter (LODER) for the treatment of solid tumors.







A phase I trial of a local delivery of siRNA against k-ras in combination with chemotherapy for locally advanced pancreatic adenocarcinoma.

Khvalevsky EZ, PNAS 2013

Allosteric inhibitors

LETTER

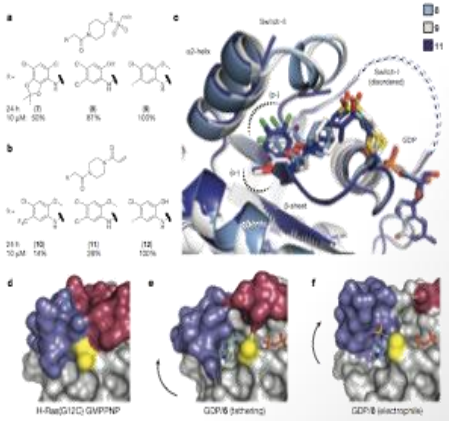
doi:10.1038/nature12796

K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions

Jonathan M. Ostrem[1]*, Ulf Peters[1]*, Martin L. Sos[2], James A. Wells[2] & Kevan M. Shokat[1]

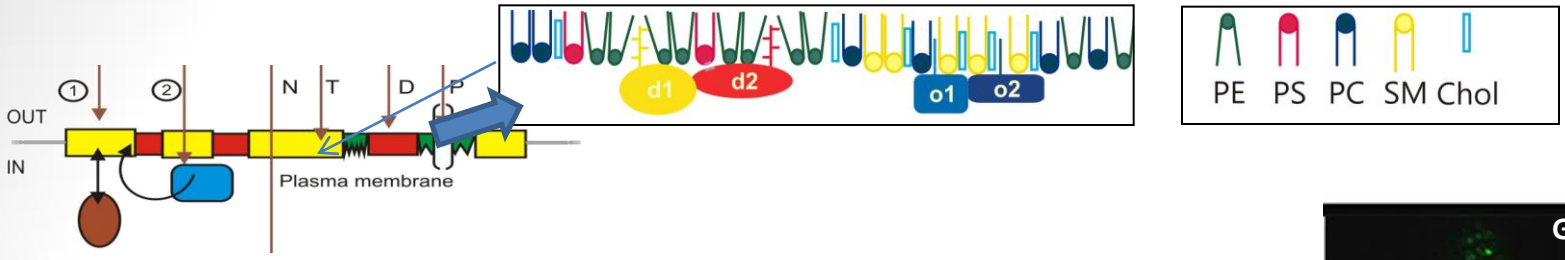
Somatic mutations in the small GTPase K-Ras are the most common activating lesions found in human cancer, and are generally associated with poor response to standard therapies[1–3]. Efforts to target this oncogene directly have faced difficulties owing to its picomolar affinity for GTP/GDP[4] and the absence of known allosteric regulatory sites. Oncogenic mutations result in functional activation of Ras family proteins by impairing GTP hydrolysis[5,6]. With diminished regulation by GTPase activity, the nucleotide state of Ras becomes more dependent on relative nucleotide affinity and concentration. This gives GTP an advantage over GDP[7] and increases the proportion of active GTP-bound Ras. Here we report the development of small molecules that irreversibly bind to a common oncogenic mutant, K-Ras(G12C). These compounds rely on the mutant

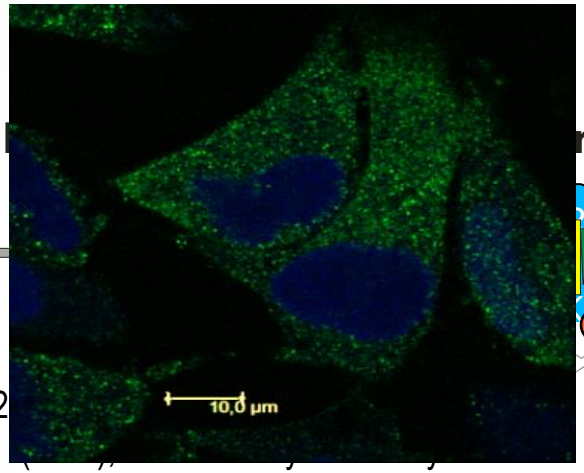
mutant over wild-type K-Ras. Notably, the mutant Cys 12 sits in close proximity to both the nucleotide pocket and the switch regions involved in effector interactions (Fig. 1a). To identify a chemical starting point, we used a disulphide-fragment-based screening approach called tethering[8]. We screened a library of 480 tethering compounds against K-Ras(G12C) in the GDP state using intact protein mass spectrometry[9,10] (see Methods and Extended Data Table 1). Fragments 6H05 (94 ± 1% (mean ± s.d.)) and 2E07 (94.6 ± 0.3%) gave the greatest degree of modification (Fig. 1b, c). Reaction with wild-type K-Ras, which contains three native cysteine residues, was not detected. Conversely, both compounds modify the oncogenic G12C mutant of the highly homologous protein H-Ras[11,12] (Fig. 1b). Binding was not diminished by 1 mM GDP in the presence of EDTA, suggesting that the compounds bind in an allosteric site not

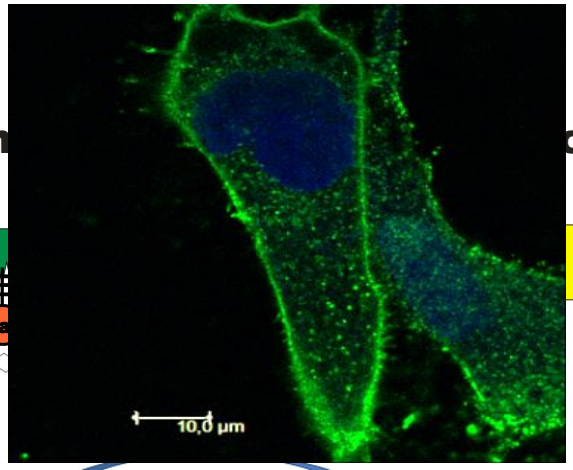


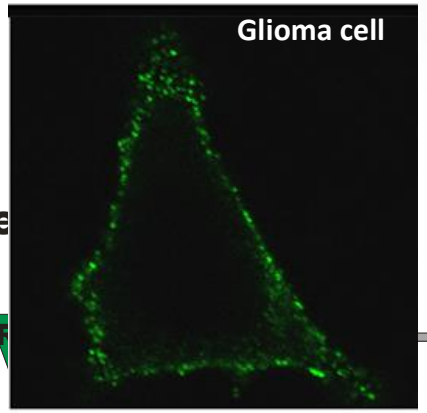
Ostem JM, Nature, 2014

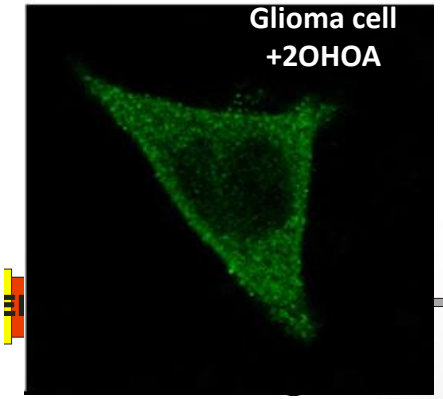
Inhibitors of membrane association of KRAS



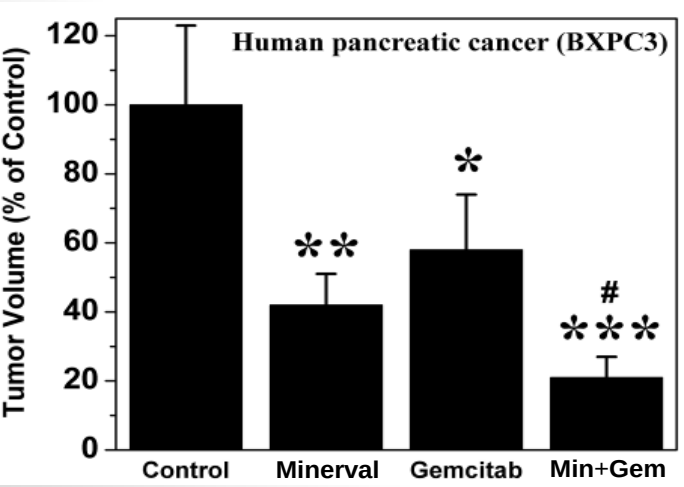


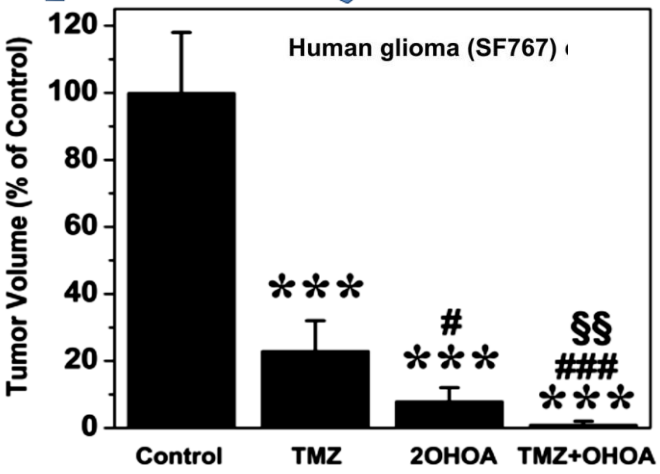






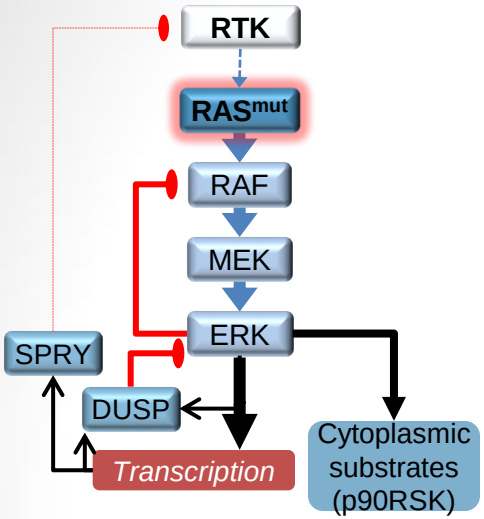
Ras localization



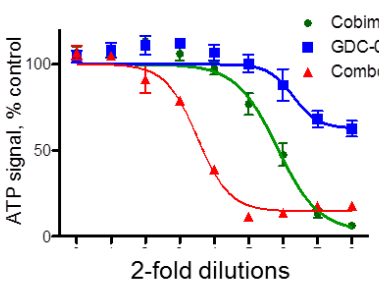


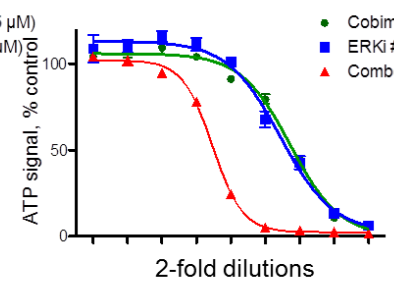
Smart downstream inhibition: MEKi+ERKi combo

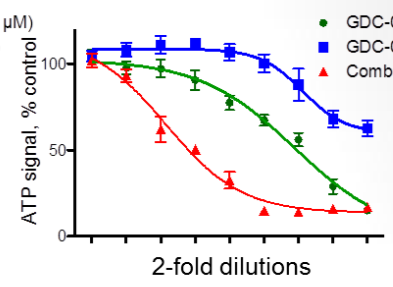
RAS-mutant

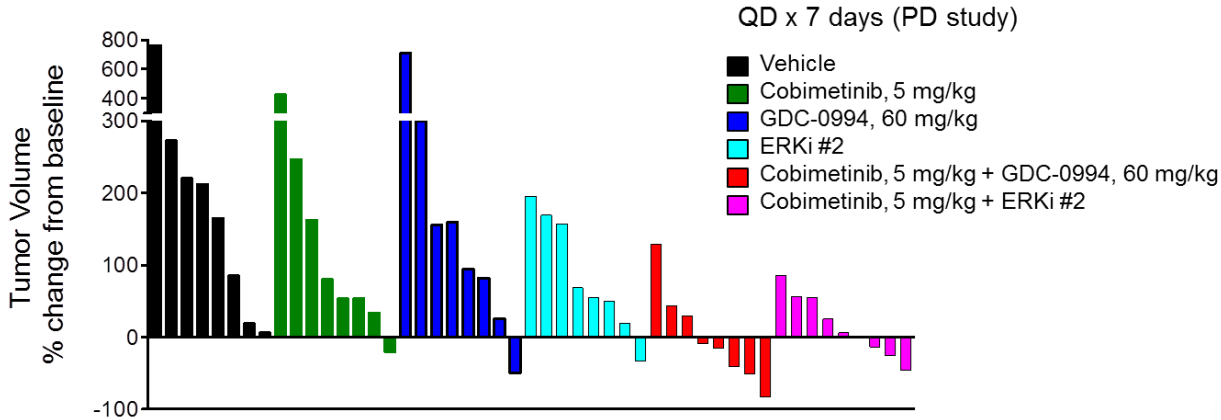


H2122, KRAS NSCLC

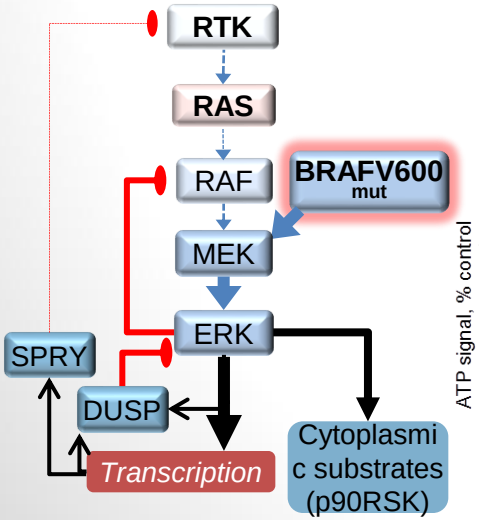




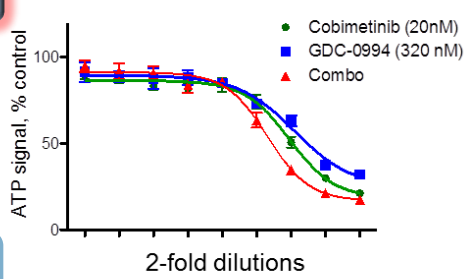


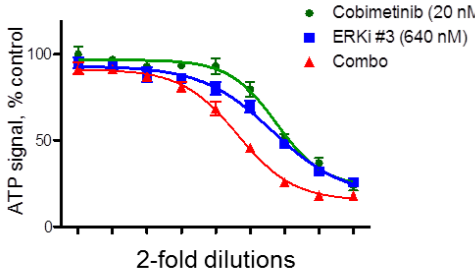


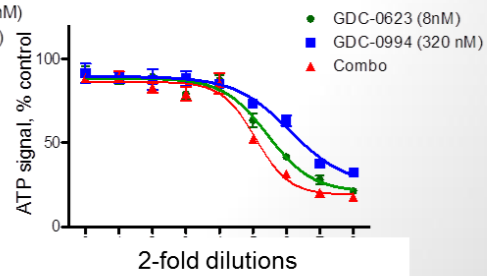
BRAF-mutant



A375, BRAF melanoma







Moffat, J et al. AACR 2014

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Maria Martinez (H del Mar)

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Sheng-Bin Peng (Eli Lilly)

Thank you for your attention

VHIO
VALL D'HEBRON
Institute of Oncology