# ERK Inhibition: Is it Feasible?

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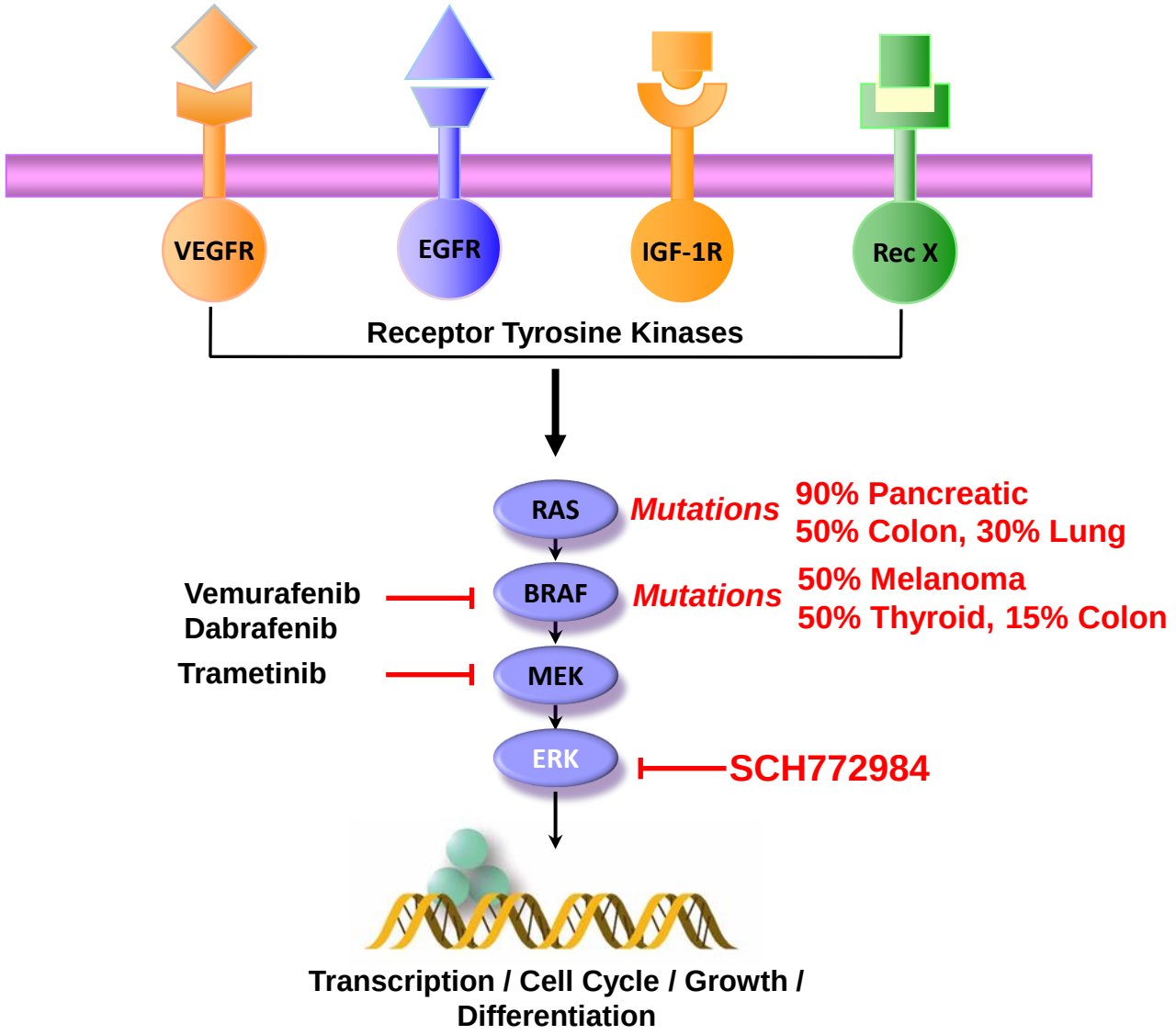
# Disclosure

I have no financial relationships to disclose

# Rational for Targeting RAS-RAF-ERK Pathway

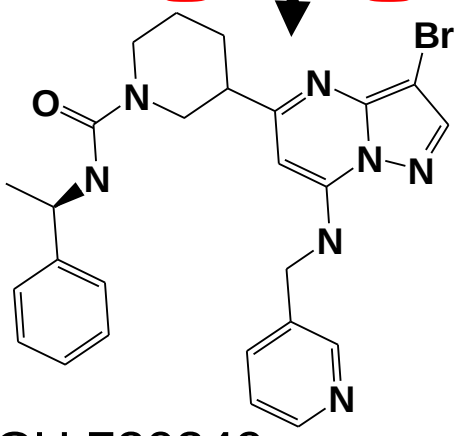



- High frequency of activating RAS or BRAF mutations found in cancer
- Selective BRAF and MAP-ERK kinase (MEK) inhibitors efficacious in melanoma
- Majority of responses are transient
- ERK1/2 kinase inhibitors have antitumor activity in MAPK inhibitor-naïve and inhibitor-resistant cells containing resistant BRAF or RAS mutations

# ERK Screening Strategy

**Initiated assay: 2003**

**Approach: Biochemical Assay (active ERK2)**



SCH 720349

Kinase activity inhibition assay:
active ERK2 + compounds

⊥

ERK2 Kinase activity inhibition

ERK2 $IC_{50}$ = 0.53 µM

**CDK2 $IC_{50}$ = 0.63 µM**

**Approach: Binding Assay (inactive ERK2)**

Inactive ERK2 + compounds

↓

activate ERK2 with MEK

⊥

ERK2 Kinase activity inhibition

**SCH 746514**

**A-ERK2 $IC_{50}$= 2 µM**

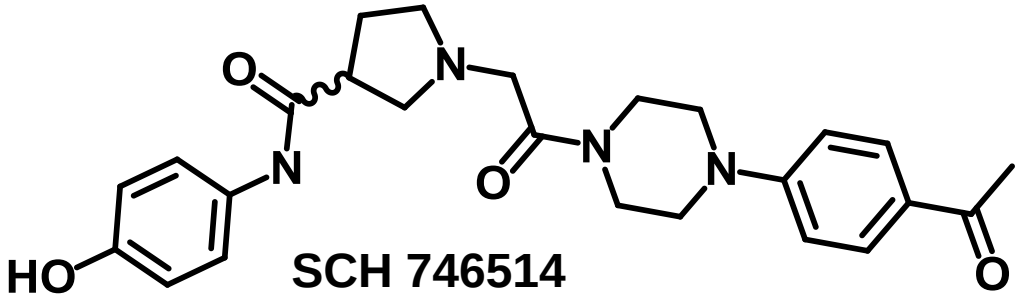
**CDK2 $IC_{50}$ > 10 µM**

**Good kinase selectivity**

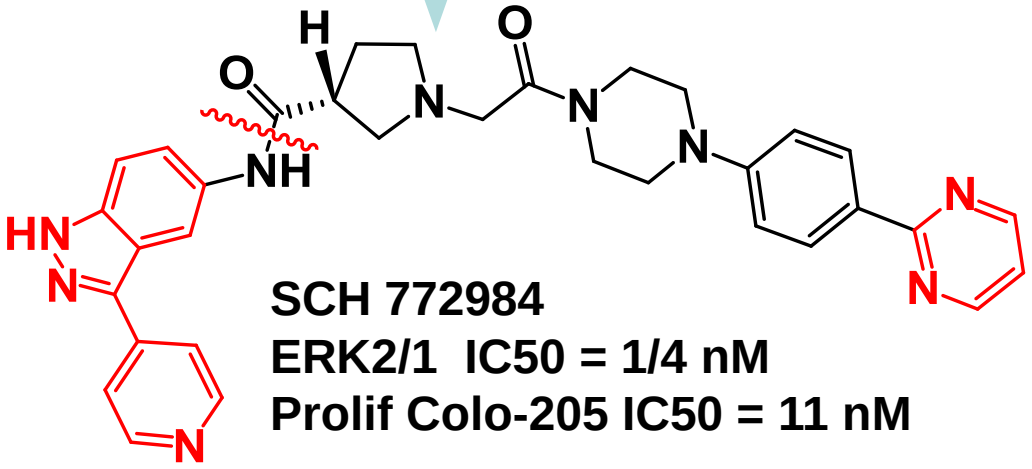
Kinase Selectivity SCH 746514

| Kinase | $IC_{50}$ (uM) |
|---|---|
| ABL | >10 |
| AKT1 | >10 |
| CDK2 | >10 |
| B-RAF | >10 |
| EGFR | >10 |
| EPHB4 | >10 |
| P38 | >10 |
| IGF1R | >10 |
| IRAK4 | >10 |
| JAK2 | >10 |

# Development of ERK Inhibitors



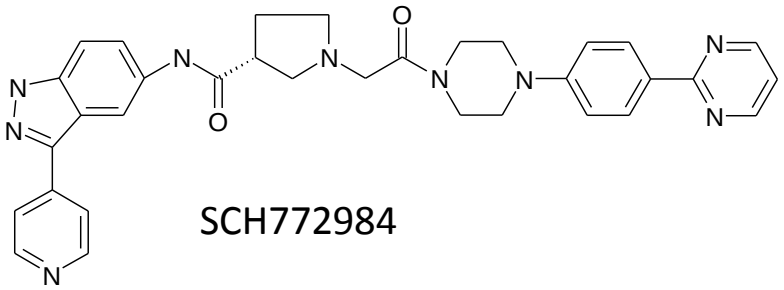

**SCH 746514**
**ERK2 $IC_{50}$= 2 uM**
**Issue: Potency**




**SCH 772984**
**ERK2/1 IC50 = 1/4 nM**
**Prolif Colo-205 IC50 = 11 nM**

# SCH772984 (ERKi) Profile

- Potent ERK inhibitor (enzyme and cell)
- Good kinase selectivity profile
- ATP competitive



SCH772984

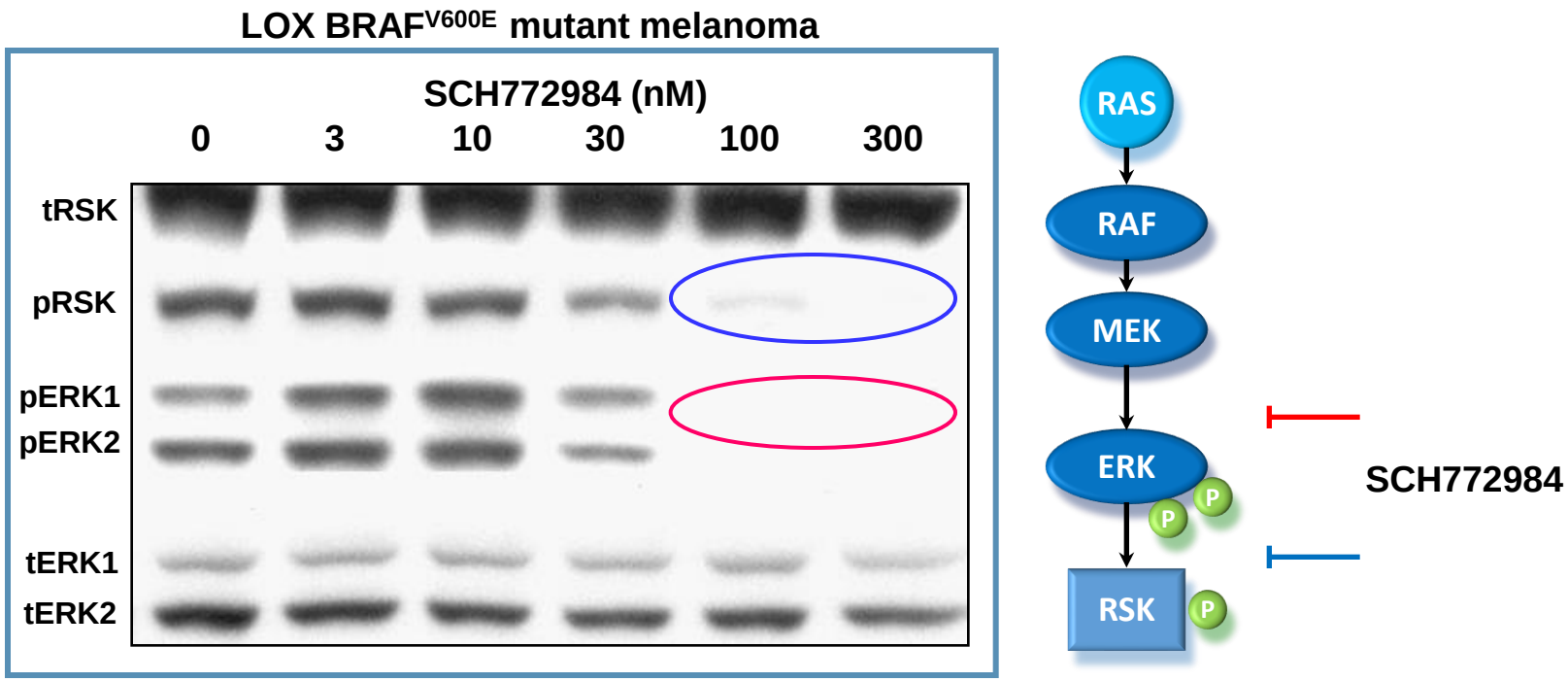
| Binding | ERK2 | MEK1 |
|---|---|---|
| Compound | $K_D$ (nM) | $K_D$ (nM) |
| GSK1120212 | No binding | 7± 2.7 |
| SCH772984 | 0.48± 0.14 | No binding |

Kinome Selectivity

| Kinase | $IC_{50}$ (µM) |
|---|---|
| ERK1 | 0.001 |
| ERK2 | 0.004 |
| CDK2 | > 10 |
| MEK1 | **> 10** |
| CRAF | **> 10** |
| p38b | >10 |
| EGFR | >10 |
| GSK3b | >10 |
| RSK2 | >10 |
| CAMK4 | >10 |
| MST2 | >10 |
| PKCa | >10 |
| ROCK2 | >10 |

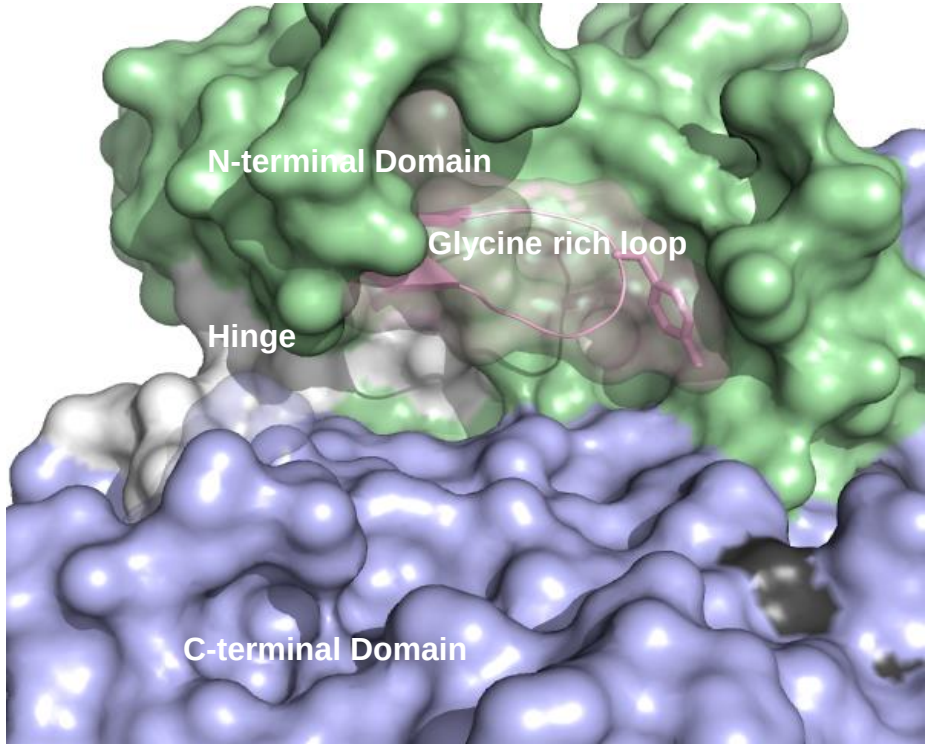
Selective against 320 kinases

# SCH772984: Novel Dual Mechanism of Inhibition

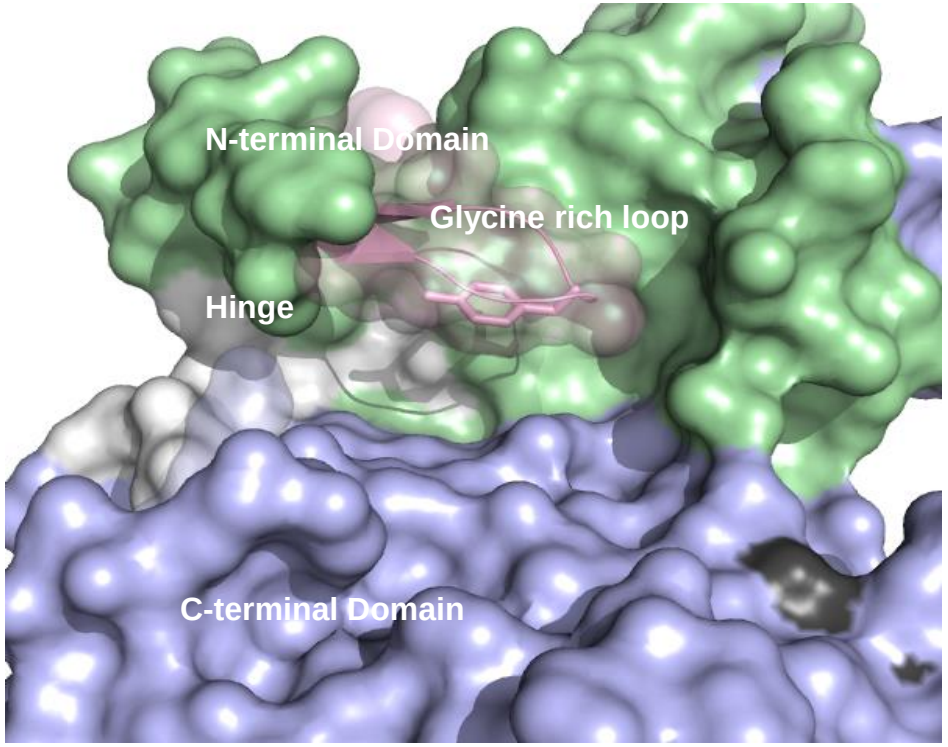



- MEK phosphorylation residues T202/Y204 & T185/187 of ERK
- SCH772984 does not bind or inhibit MEK

# SCH772984 Binding to ERK2 Induces Conformation Change

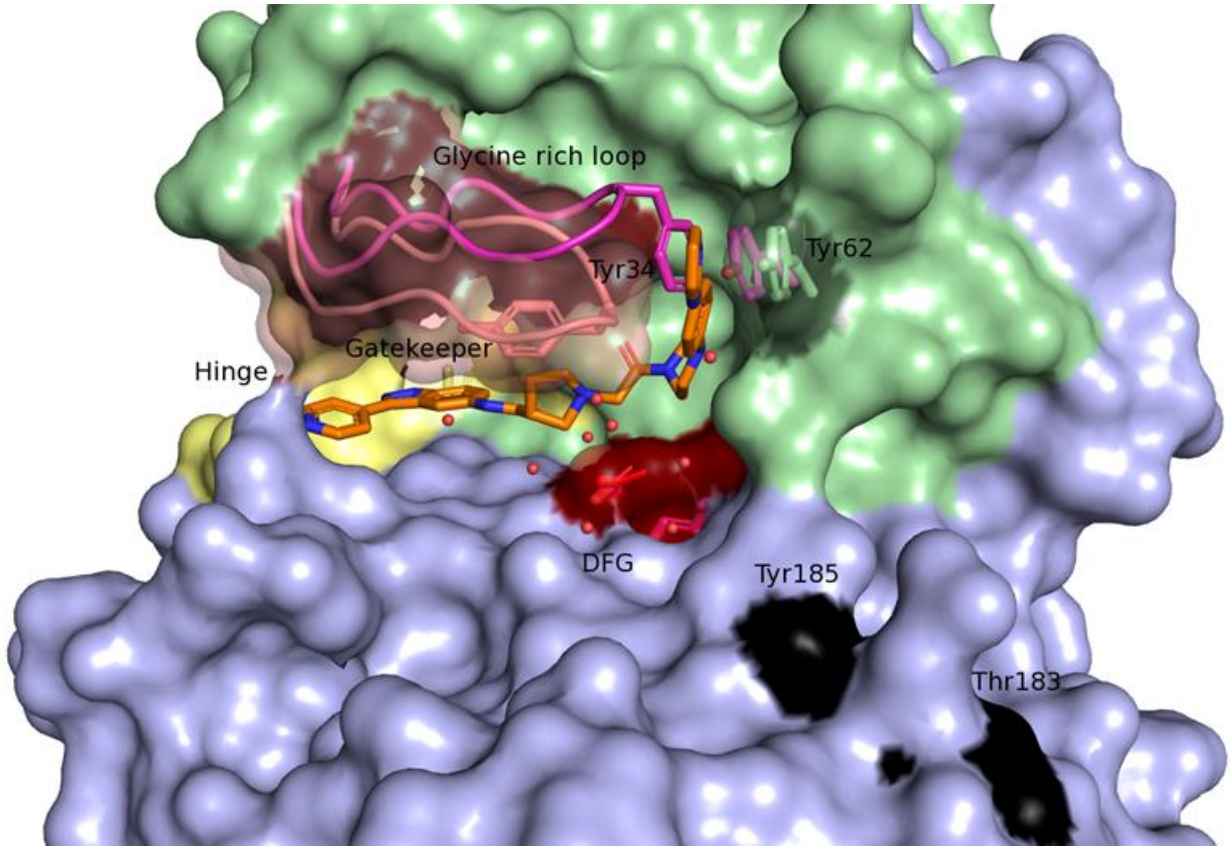



Unbound ERK2




ERK2 bound to ERK inhibitor

# SCH772984 Binding to ERK2 Induces Conformation Change: Dual Mechanism of Inhibition



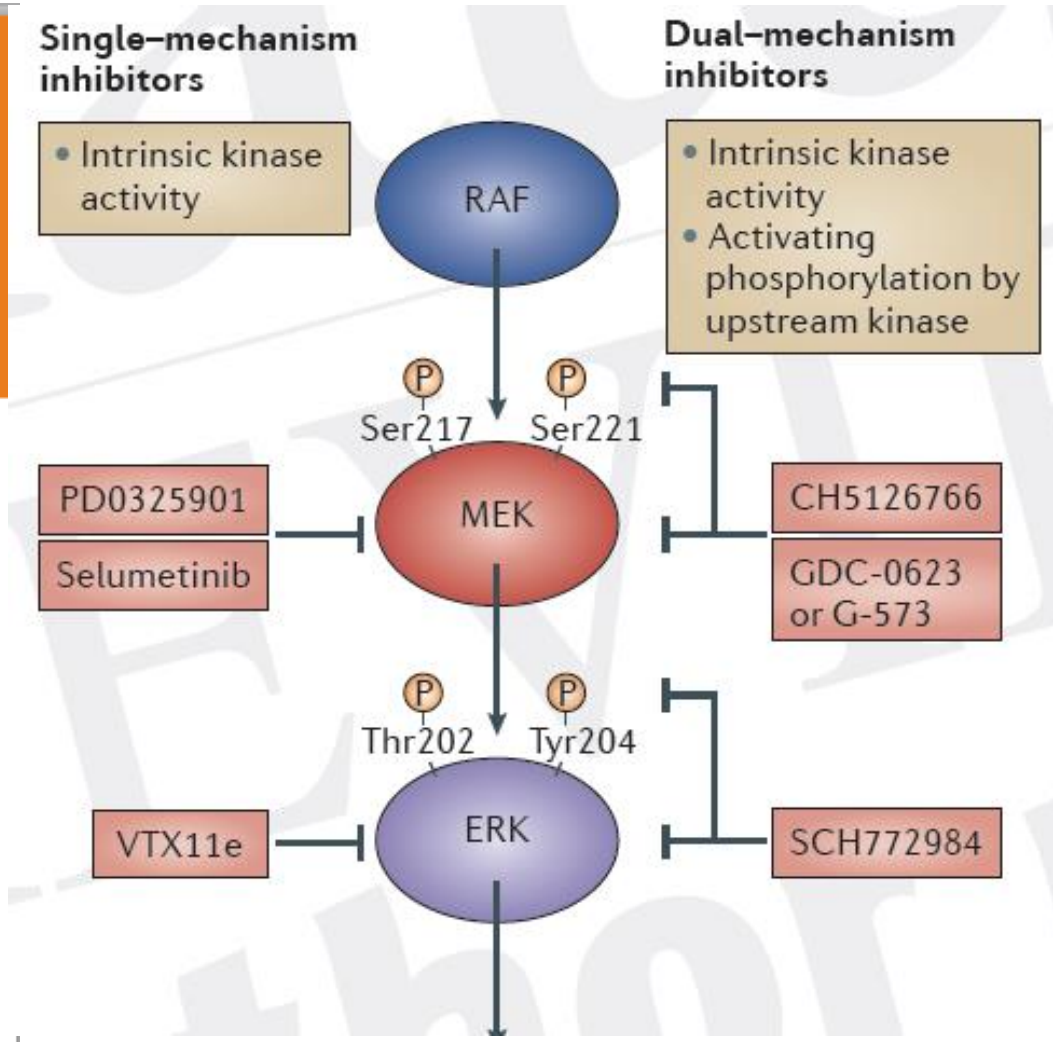

**ERK2 / SC772984 complex**

- Binds active site of ERK & inhibits kinase activity
- Distorts conformation / hinders MEK ability to phosphorylate ERK
- pERK can be used as biomarker for target engagement

# Targeting RAS–ERK signalling in cancer: promises and challenges

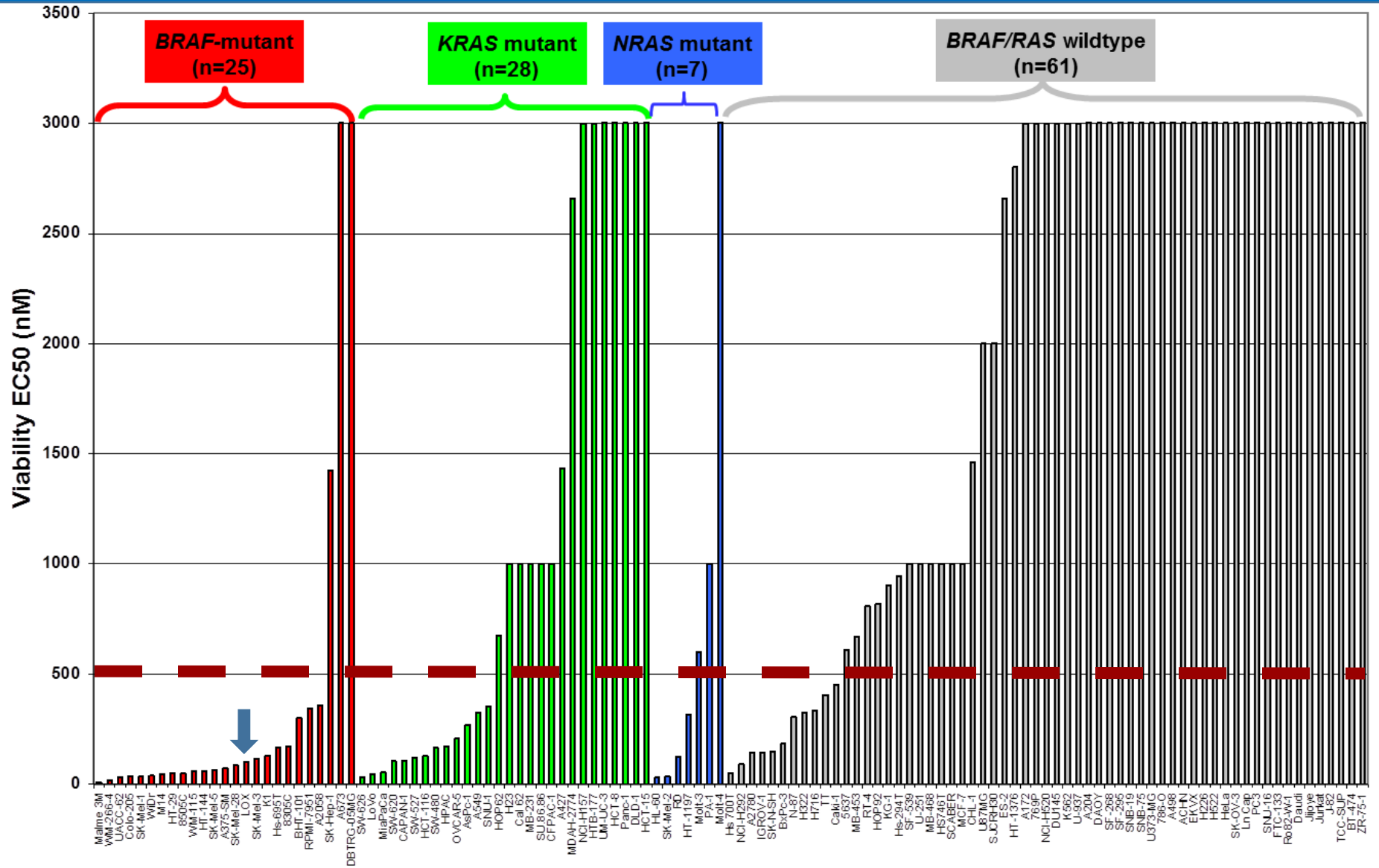
*Ahmed A. Samatar and Poulikos I. Poulikakos*

Abstract | The RAS–RAF–MEK–ERK signalling pathway is hyperactivated in a high percentage of tumours, most frequently owing to activating mutations of the *KRAS*, *NRAS* and *BRAF* genes. Recently, the use of compounds targeting components of ERK signalling, such as RAF or MEK inhibitors, has led to substantial improvement in clinical outcome in

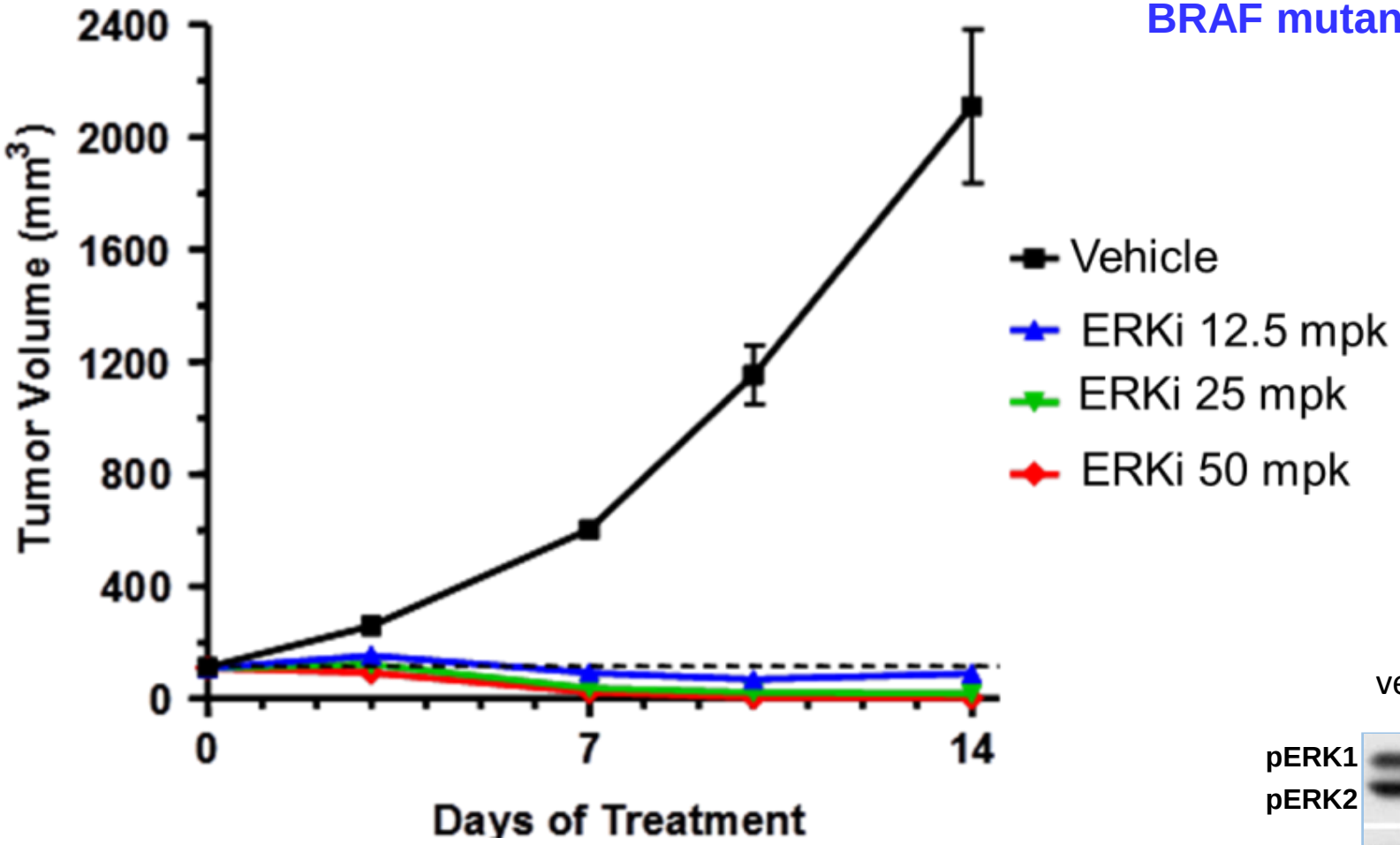



Nat Rev Drug Discov. 2014 Dec;13(12):928-42.

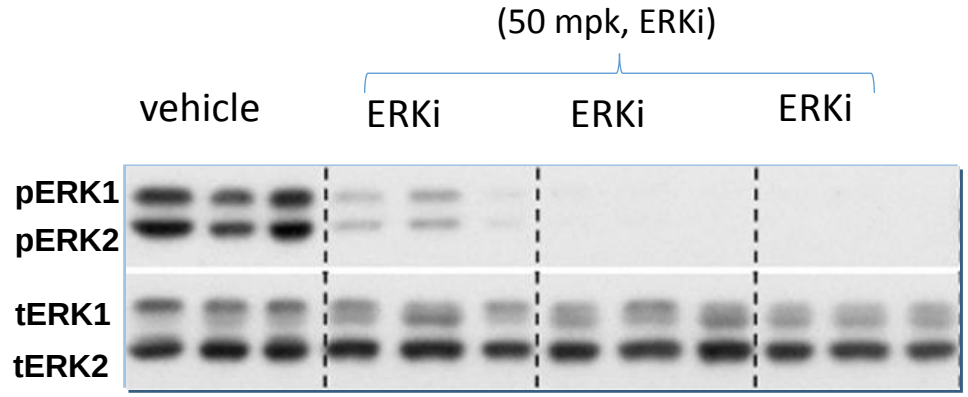
# Tumors with RAF / RAS Mutations are Sensitive to ERKi



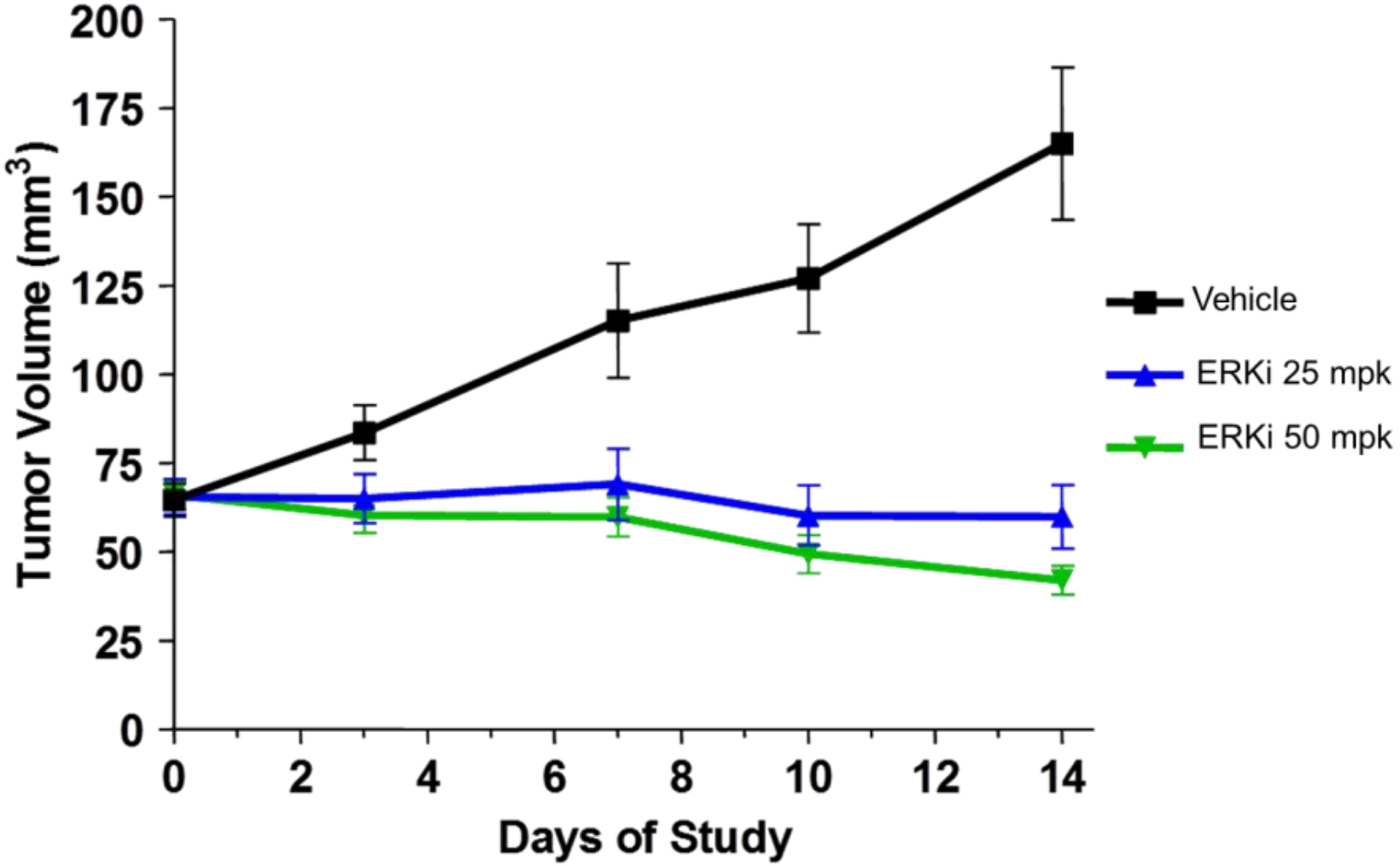
# ERKi Induces Tumor Regressions in Melanoma Tumor Xenograft Model



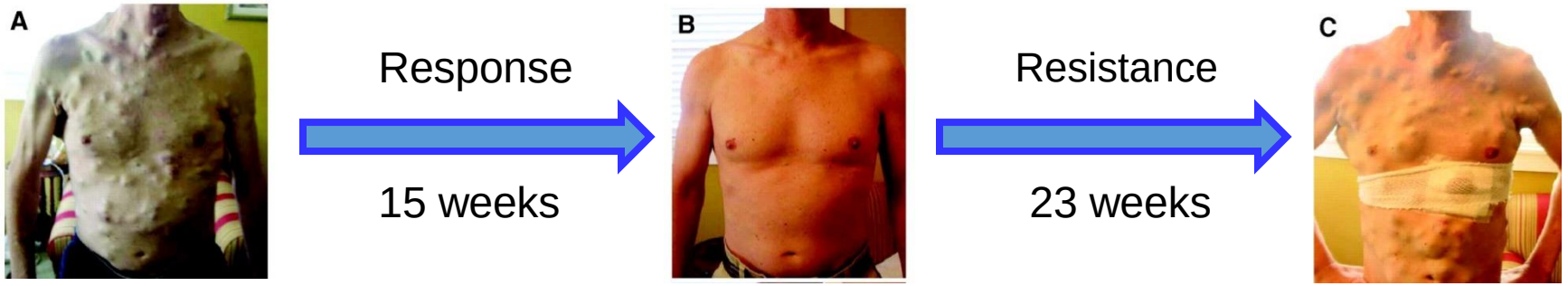

**BRAF mutant model**



# ERKi Induces Tumor Regressions in Pancreatic KRAS Mutant Tumor Xenograft Model

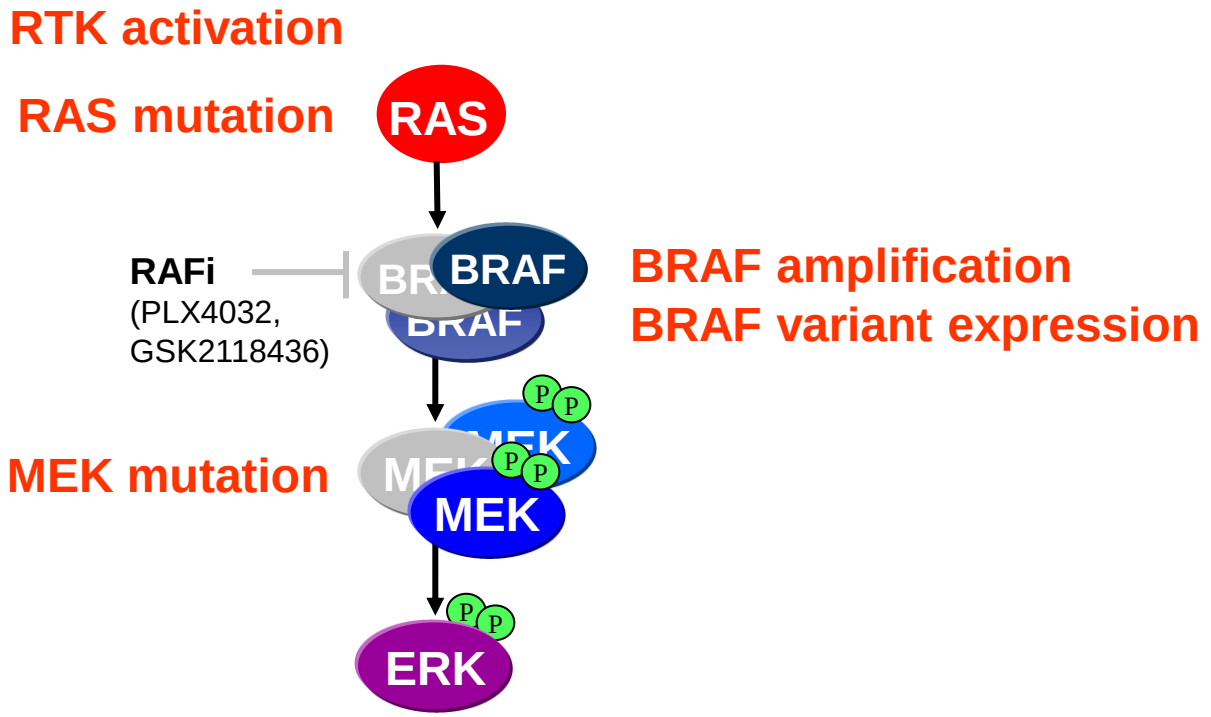


# Mechanisms of resistance to BRAF inhibitors




*Wagle et al., JCO 2011*

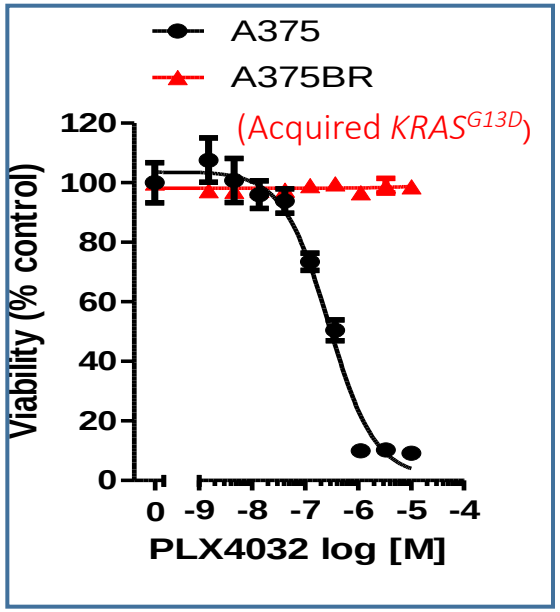
## Resistance Mechanisms to RAFi



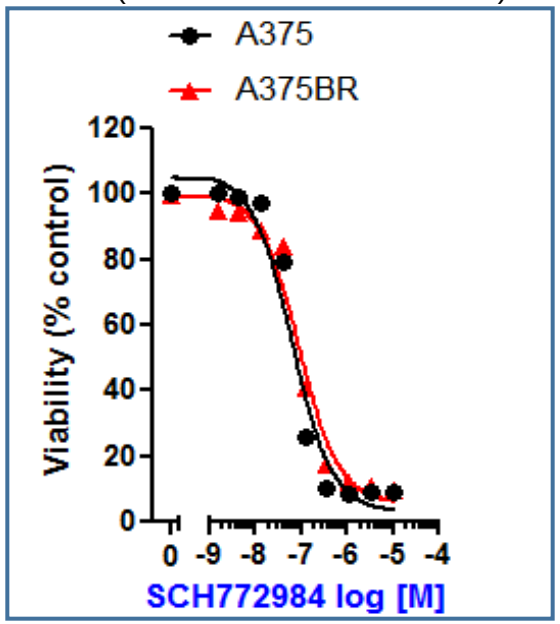

- Can ERK inhibitor overcome resistance conferred by RAF inhibitors?

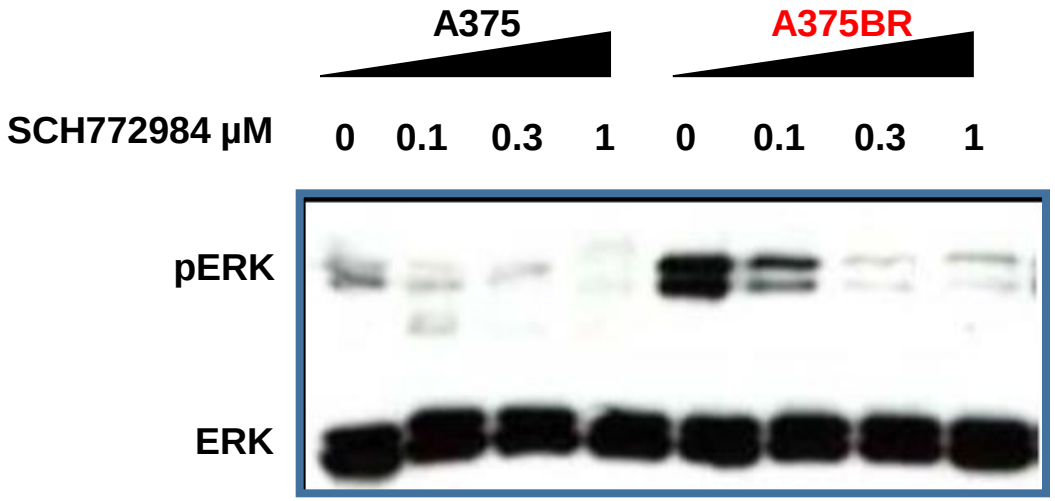
# ERKi Overcomes Resistance to BRAF Inhibitors (Vemurafenib)

A375 (BRAF$^{V600E}$mutant melanoma)



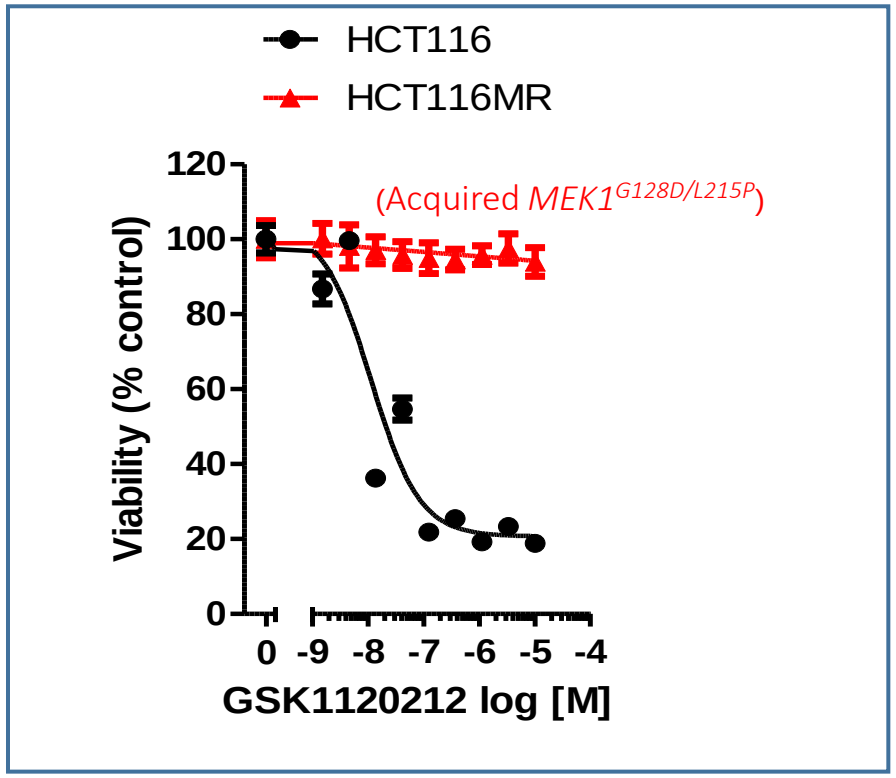

A375 (BRAF$^{V600E}$mutant melanoma)



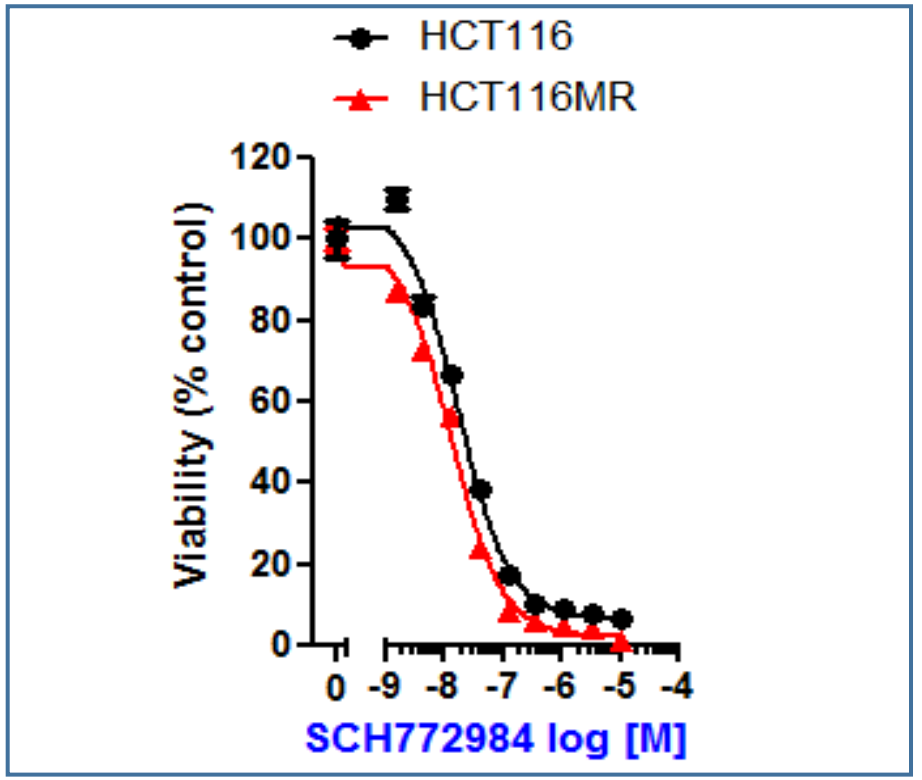



# ERKi Overcomes Resistance to MEK Inhibitor (Trametinib)

KRAS$^{G13D}$ mutant colon cancer




KRAS$^{G13D}$ mutant colon cancer



# MEKi + BRAFi Delay Resistance to BRAF Inhibition

ORIGINAL ARTICLE

## Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty, M.D., Jeffery R. Infante, M.D., Adil Daud, M.D., Rene Gonzalez, M.D., Richard F. Kefford, M.D., Ph.D., Jeffrey Sosman, M.D., Omid Hamid, M.D., Lynn Schuchter, M.D., Jonathan Cebon, M.D., Ph.D., Nageatte Ibrahim, M.D., Ragini Kudchadkar, M.D., Howard A. Burris III, M.D., Gerald Falchook, M.D., Alain Algazi, M.D., Karl Lewis, M.D., Georgina V. Long, M.D., Ph.D., Igor Puzanov, M.D., M.S.C.I., Peter Lebowitz, M.D., Ph.D., Ajay Singh, M.D., Shonda Little, M.P.H., Peng Sun, Ph.D., Alicia Allred, Ph.D., Daniele Ouellet, Ph.D., Kevin B. Kim, M.D., Kiran Patel, M.D., M.B.A., and Jeffrey Weber, M.D., Ph.D.

ABSTRACT

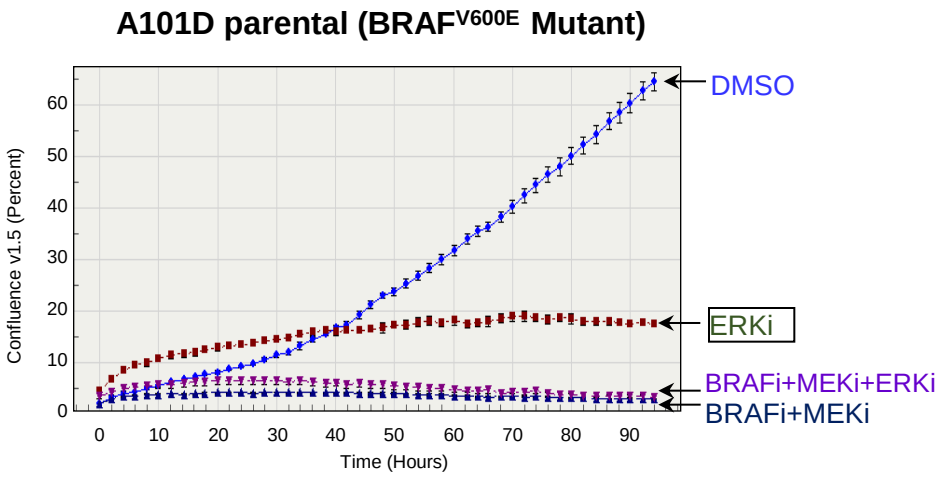
**BACKGROUND**

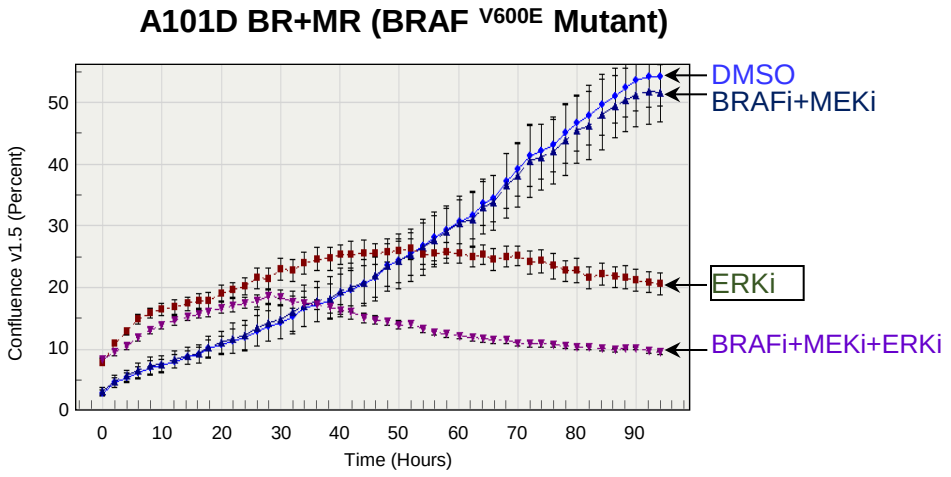
Resistance to therapy with BRAF kinase inhibitors is associated with reactivation of the mitogen-activated protein kinase (MAPK) pathway. To address this problem, we conducted a phase 1 and 2 trial of combined treatment with dabrafenib, a selective BRAF inhibitor, and trametinib, a selective MAPK kinase (MEK) inhibitor.

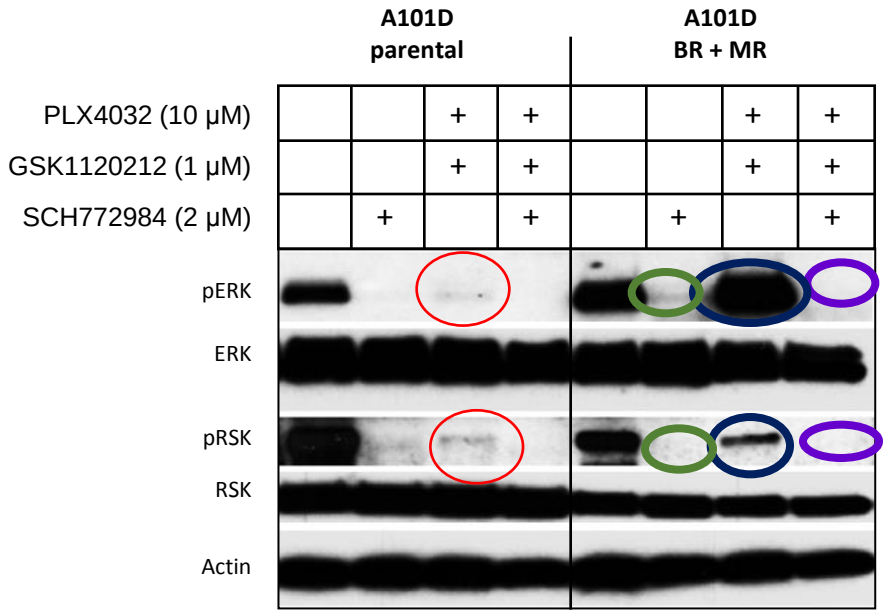
**METHODS**

In this open-label study involving 247 patients with metastatic melanoma and BRAF V600 mutations, we evaluated the pharmacokinetic activity and safety of oral dabrafenib (75 or 150 mg twice daily) and trametinib (1, 1.5, or 2 mg daily) in 85

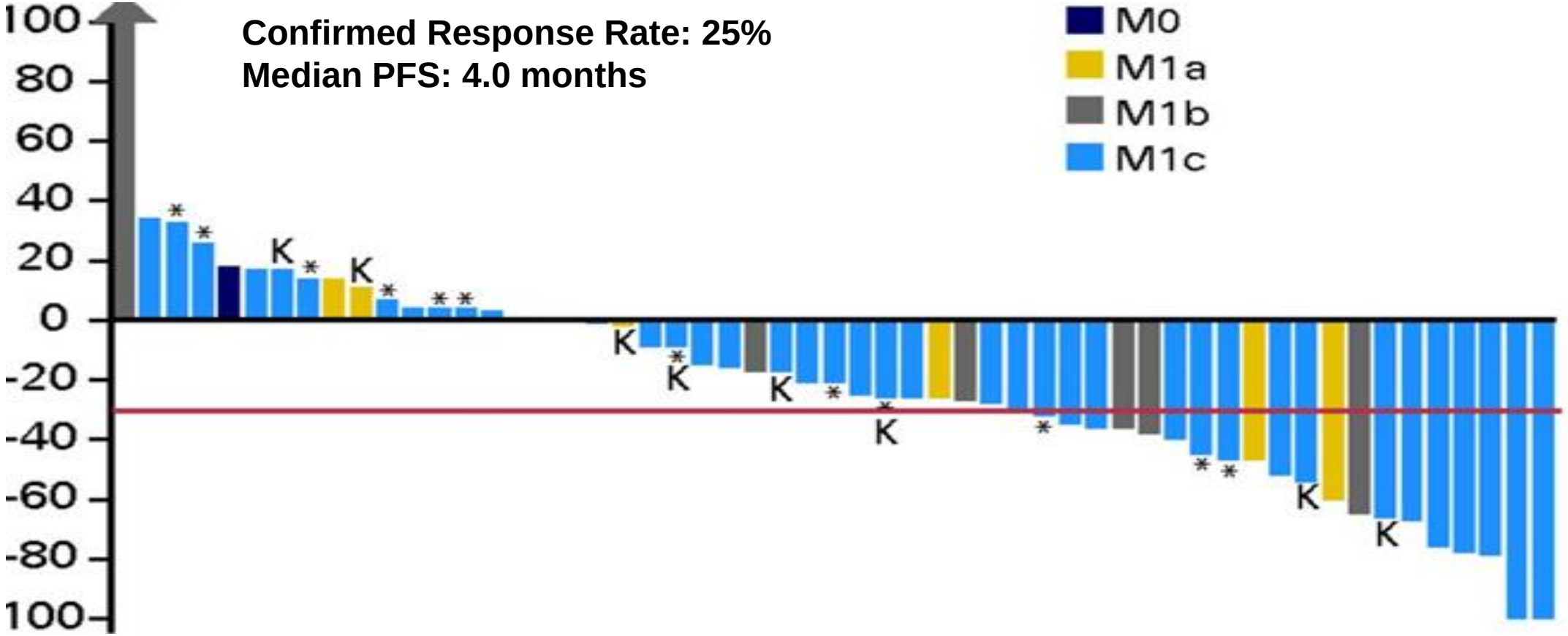
# ERKi Overcomes Resistance to the Combination of BRAFi and MEK Inhibitors in BRAF Mutant Melanoma



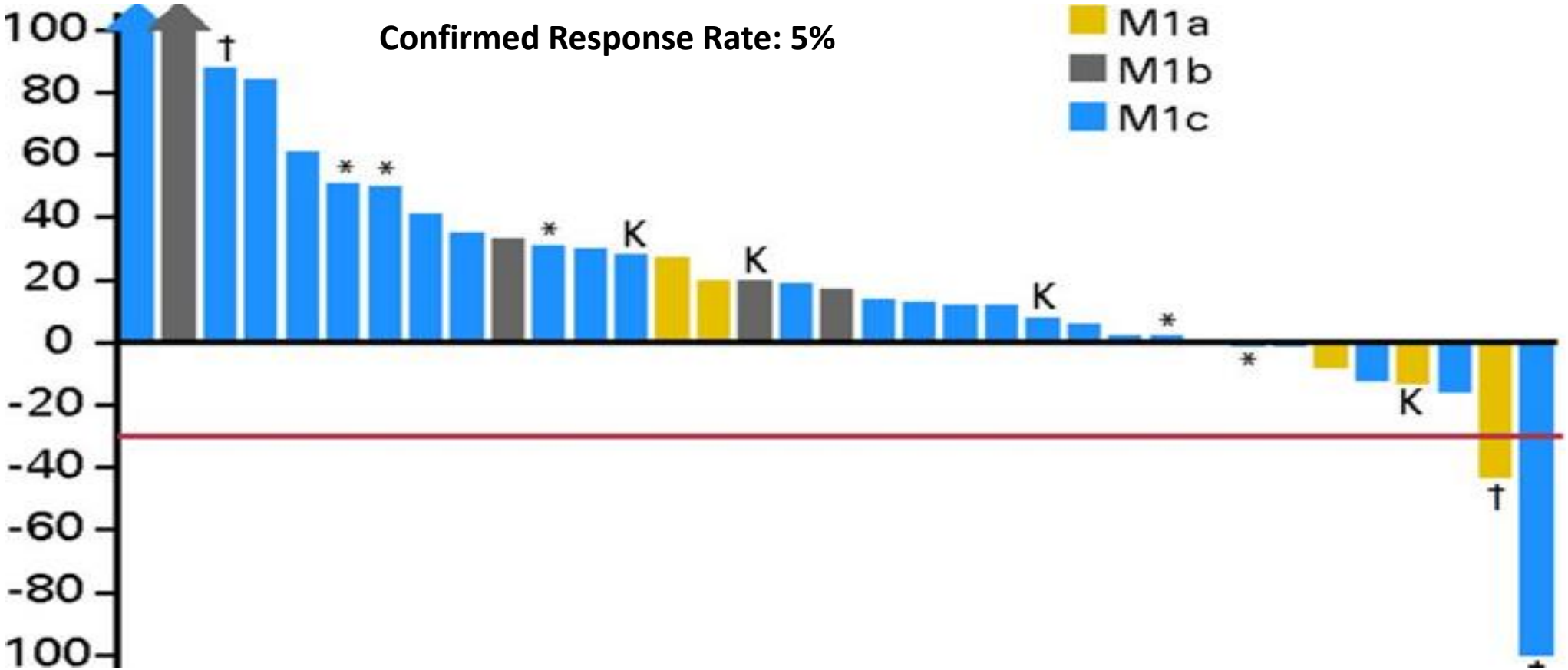



# Trametinib (MEKi) activity in BRAF inhibitor naïve patients




Kim, Kefford, Pavlick *et al*. J Clin Oncol. 2013

# Trametinib (MEKi) not Effective in Patients Who Had Prior BRAFi Therapy



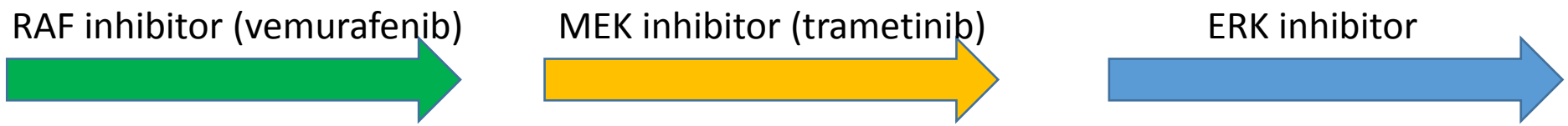

Kim, Kefford, Pavlick *et al*. J Clin Oncol. 2013

# Clinical Utility for ERK Inhibitors

- Target RAF / MEK inhibitors refractory tumors

- Develop ERK inhibitor in combination
  - ERKi + RAFi
  - ERKi + MEKi
  - ERKi + PI3Ki
  - ERKi + BRAFi + MEKi

- Sequential treatment with MAPK pathway inhibitors to prevent / delay resistance:




  - ERK Inhibitors may address a large unmet medical needs: NSCL , Pancreatic cancers, NRAS mutant melonam

# ERK Inhibition: Is it Feasible?

# YES (preclinical)

# Summary

- SCH772984 is a first-in-class novel, potent & selective ERK inhibitor that demonstrates:
  - Potency & selectivity
  - a unique dual mechanism of action
  - *in vivo* anti-tumor activity in BRAF/RAS mutant tumors
  - activity in resistance settings with ERK reactivation

- ERKi and BRAFi combination results in enhanced anti-tumor activity

- ERK inhibitors in clinical trials: MK8353, BVD-0994 & GDC-0994

# Thank you for your attention !