



**INCONTRO DEI GIC  
NEOPLASIE CUTANEE**



**TORINO • 5 dicembre 2011**  
dalle 13,30 alle 19,00

Coordinatori dell'evento:  
Dott. Oscar Bertotto  
Dott.ssa Monica Viale

Dipartimento "Reti Oncologica  
del Piemonte e delle valli d'Aosta"



# Aspetti farmacologici e bersagli molecolari delle nuove terapie

**Romano Danesi**

Professore ordinario di Farmacologia

Dipartimento di Medicina  
Interna

UOC Farmacologia clinica

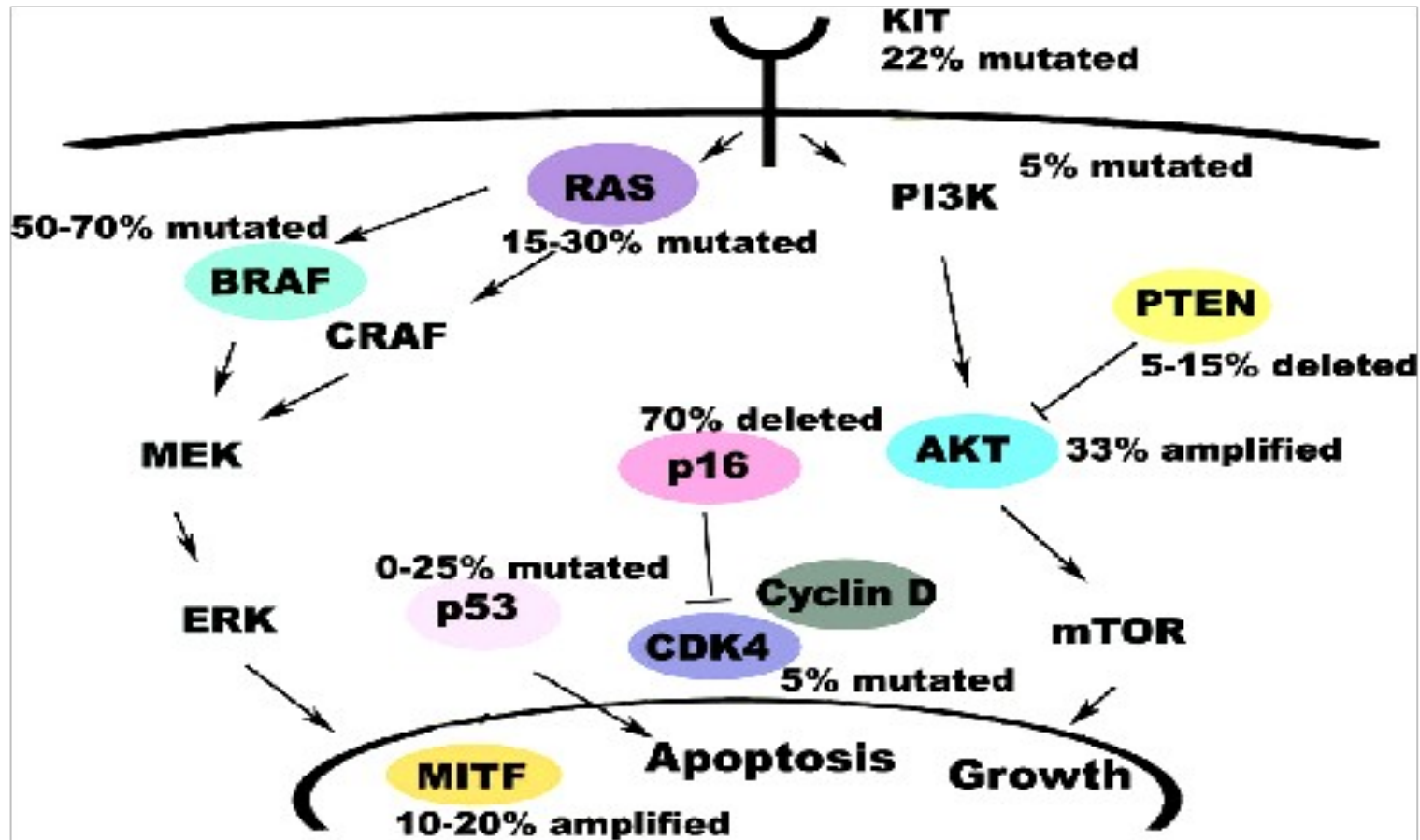
Azienda Ospedaliero-  
Universitaria Pisana



Which is the genetic fingerprint  
of malignant melanoma?



# Major genetic changes in sporadic cutaneous melanoma





In which way the the genetic fingerprint of malignant melanoma translates into targeted therapeutics?



OPEN ACCESS Freely available online

PLOS one

# A Melanoma Molecular Disease Model

Smruti J. Vidwans<sup>1</sup>, Keith T. Flaherty<sup>2</sup>, David E. Fisher<sup>3</sup>, Jay M. Tenenbaum<sup>1</sup>, Michael D. Travers<sup>1,3</sup>, Jeff Shrager<sup>1,4\*</sup>

March 2011 | Volume 6 | Issue 3 | e18257



# Primary melanoma molecular subtypes

Detailed subtypes	Pathway(s)	Key gene / biomarker(s)	Diagnostic technologies	Potentially relevant therapeutics
1.1	MAPK	BRAF	Targeted sequencing	BRAF inhibitors, MEK inhibitors, Hsp90 inhibitors
1.2		BRAF/PTEN	Targeted sequencing & IHC	(BRAF inhibitors) AND (PI3K inhibitors, AKT inhibitors or mTOR inhibitors)
1.3		BRAF/AKT	Targeted sequencing & copy number	(BRAF inhibitors) AND (AKT inhibitors or mTOR inhibitors)
1.4		BRAF/CDK4	Targeted sequencing & copy number/CGH	BRAF inhibitors AND CDK inhibitors
2.1	c-KIT	c-KIT	Targeted sequencing	Gleevec & other c-KIT inhibitors
3.1	GNAQ GNA11	GNAQ	Targeted sequencing	MEK inhibitors
3.2		GNA11	Targeted sequencing	MEK inhibitors
4.1	NRAS	NRAS	Targeted sequencing	MAPK & PI3K pathway inhibitors; Farnesyl transferase inhibitors
5.1	MITF	MITF	Copy number	HDAC inhibitors



# Secondary melanoma molecular subtypes

Detailed subtypes	Pathway(s)	Key gene / biomarker(s)	Diagnostic technologies	Potentially relevant therapeutics
6.1	AKT/PI3K	PTEN	IHC	PI3K inhibitors, AKT inhibitors or mTOR inhibitors
6.2		AKT	Copy number	AKT inhibitors or mTOR inhibitors
6.3		PI3K	IHC	PI3K inhibitors, AKT inhibitors or mTOR inhibitors
7.1	CDK	ARF/INK4A	Targeted sequencing / CGH	CDK inhibitors
7.2		CDK4	Copy number / CGH	CDK inhibitors
7.3		CCND1 / Cyclin D1	Copy number / CGH	CDK inhibitors
8.1	P53 / BCL	Bcl-2	IHC	TBD
8.2		P53	Targeted sequencing	TBD



[www.thelancet.com/oncology](http://www.thelancet.com/oncology) Vol 12 September 2011

---

# Treatment implications of the emerging molecular classification system for melanoma



*Emanuela Romano, Gary K Schwartz, Paul A Chapman, Jedd D Wolchok, Richard D Carvajal*





# Mutation driven signalling-pathway inhibitors

Target	Drug	Phase-I, -II, -III trial
BRAF		
Non-selective	Sorafenib RAF-265	Phase III negative Phase I ASCO 2011
Selective	Vemurafenib	Phase I Phase II Phase III Phase I-II Phase III ongoing
	GSK2118436	
MEK	AZD6244 PD0325901 GSK1120212	Phase II Phase I Phase I-II 2010 Phase III 2011 activated
NRAS	R115777	Phase II
PI3K	GDC0941 XL 147	Phase I Phase I
Akt	MK-2206 GSK690693	Phase I Phase I
mTOR	Temsirolimus	Phase II
GNAC and GNA 11 (uveal melanoma)	MEK-inhibitors	–
c-KIT	Imatinib Nilotinib	Phase II positive Phase III (ongoing)



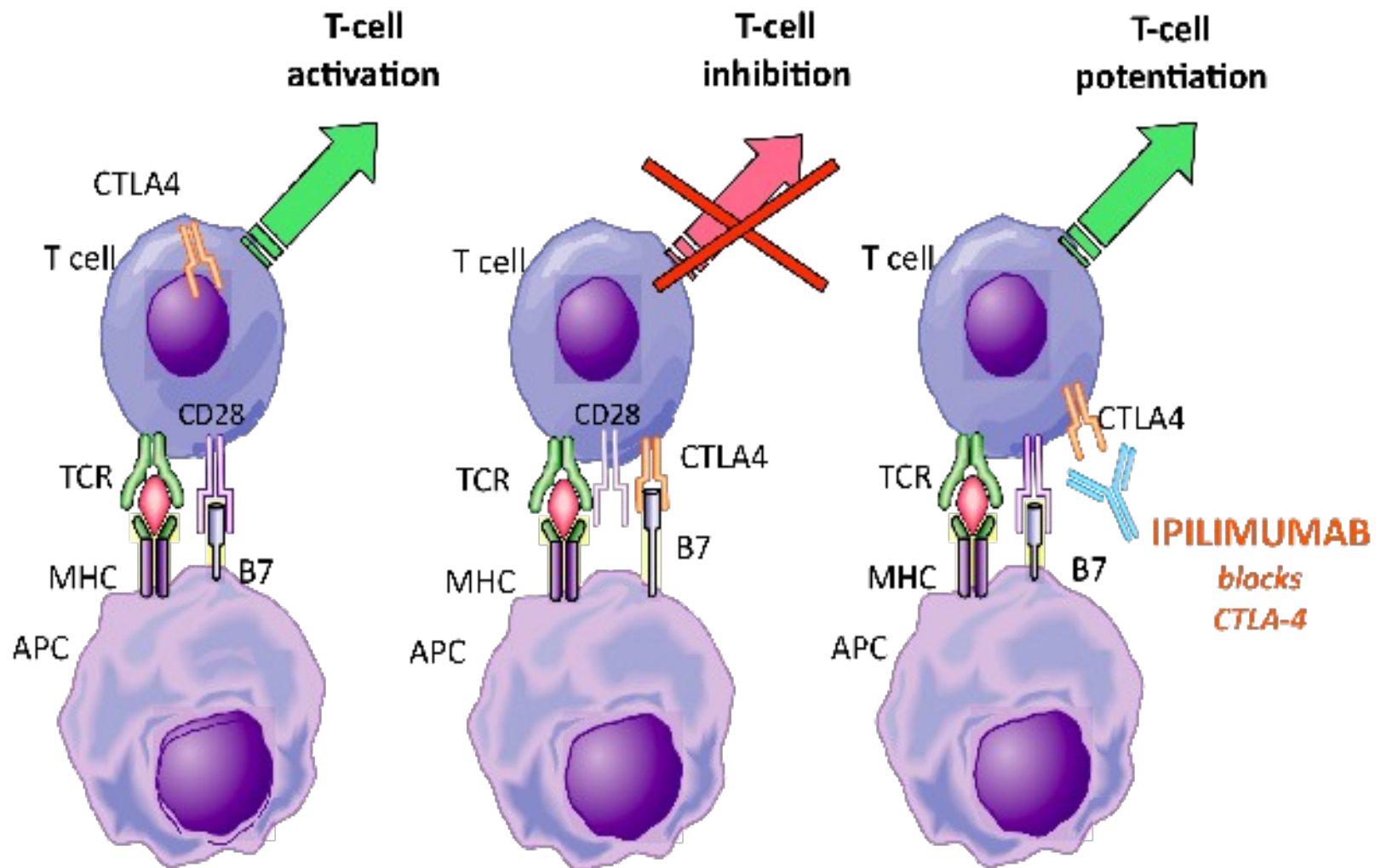
# Ipilimumab and the treatment of cancer

- **CTLA-4<sup>1</sup>:**
  - Downregulates T-cell activation
- **Ipilimumab:**
  - Fully human monoclonal antibody
  - Blocks CTLA-4 receptor
  - Potentiates T cell activation

<sup>1</sup>: Korman, Peggs and Allison: Adv. In Immunol 2006, 90; 297-339



# Ipilimumab: mechanism of action





# Biomarkers and clinical response to ipilimumab

The following biomarkers have been shown to positively correlate with clinical benefit/OS:

1. absolute lymphocyte count  $>1000/\mu\text{L}$  after 2 ipilimumab treatments;
2. **high expression** of the inducible costimulator (ICOS) molecule on T cells, which is required for optimal anti-tumor response by anti-CTLA-4;
3. **low expression** of FOXP3 (forkhead box P3) and IDO (indoleamine 2,3-dioxygenase) at baseline and an increase from baseline of tumor infiltrating lymphocytes in tumor biopsies.



# Unanticipated adverse events of BRAF inhibitors and induction of proliferation of normal cells



## NEWS & VIEWS

NATURE|Vol 464|18 March 2010

---

### DRUG DISCOVERY

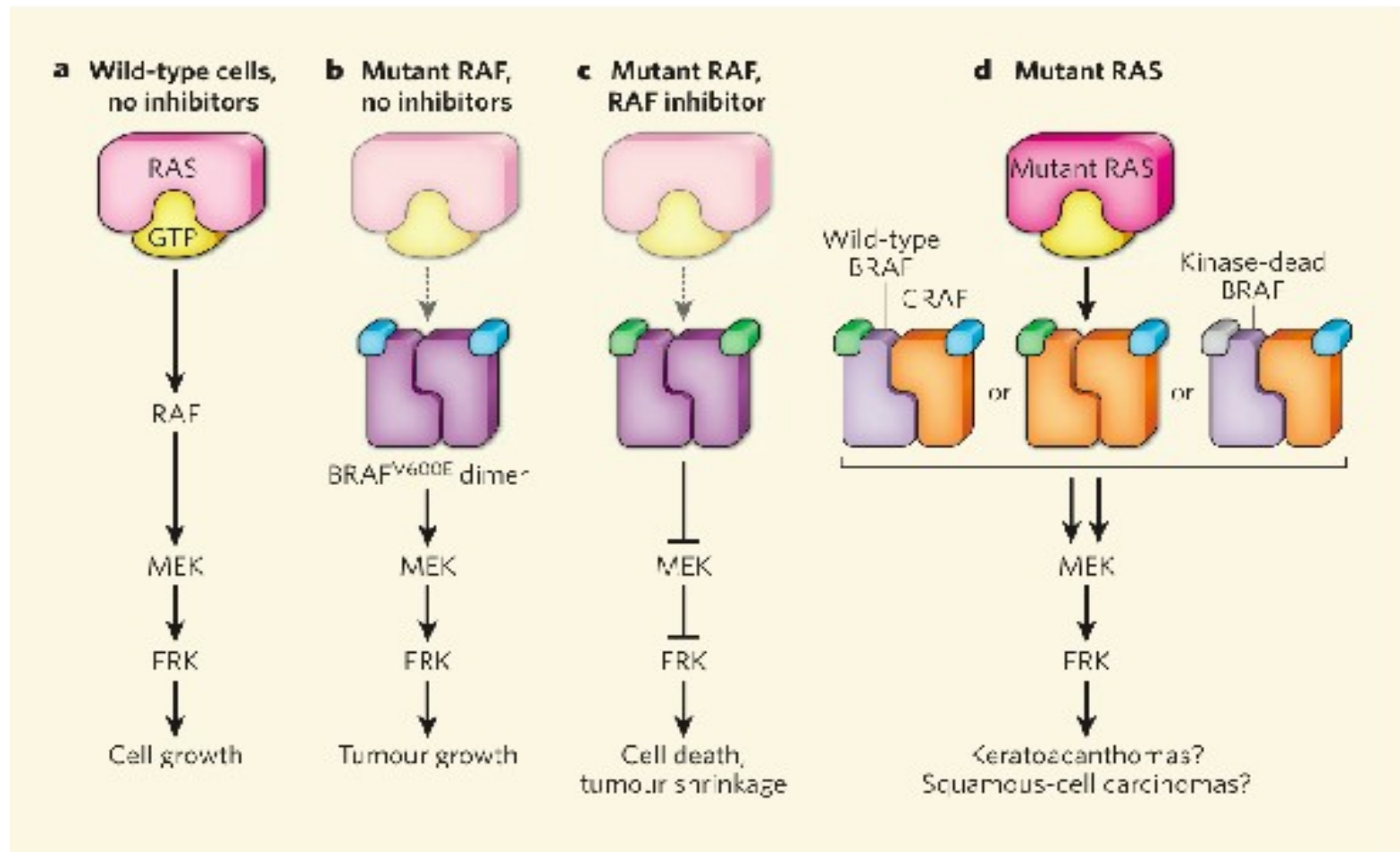
# Inhibitors that activate

Karen Cichowski and Pasi A. Jänne

**Inhibitors of RAF enzymes can suppress or activate the same signalling pathway. The details of how this happens provide a cautionary note for those targeting the pathway for anticancer drug discovery.**



# The effects of RAF inhibitors in mutant and wild-type cells





# LETTERS

## **RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth**

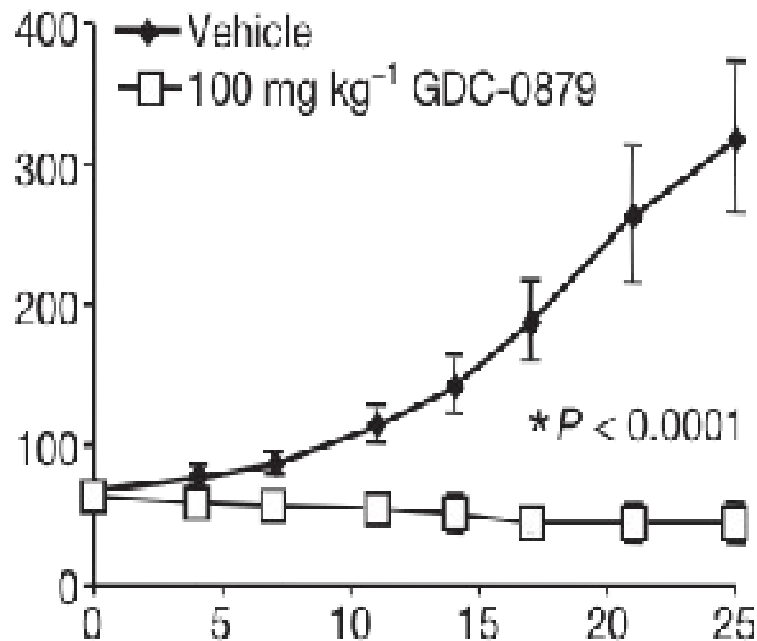
Georgia Hatzivassiliou<sup>1</sup>, Kyung Song<sup>1</sup>, Ivana Yen<sup>1</sup>, Barbara J. Brandhuber<sup>2</sup>, Daniel J. Anderson<sup>1</sup>, Ryan Alvarado<sup>1</sup>, Mary J. C. Ludlam<sup>1</sup>, David Stokoe<sup>1</sup>, Susan L. Gloor<sup>2</sup>, Guy Vigers<sup>2</sup>, Tony Morales<sup>2</sup>, Ignacio Aliagas<sup>1</sup>, Bonnie Liu<sup>1</sup>, Steve Sideris<sup>1</sup>, Klaus P. Hoeflich<sup>1</sup>, Bijay S. Jaiswal<sup>1</sup>, Somasekar Seshagiri<sup>1</sup>, Hartmut Koeppen<sup>1</sup>, Marcia Belvin<sup>1</sup>, Lori S. Friedman<sup>1</sup> & Shiva Malek<sup>1</sup>



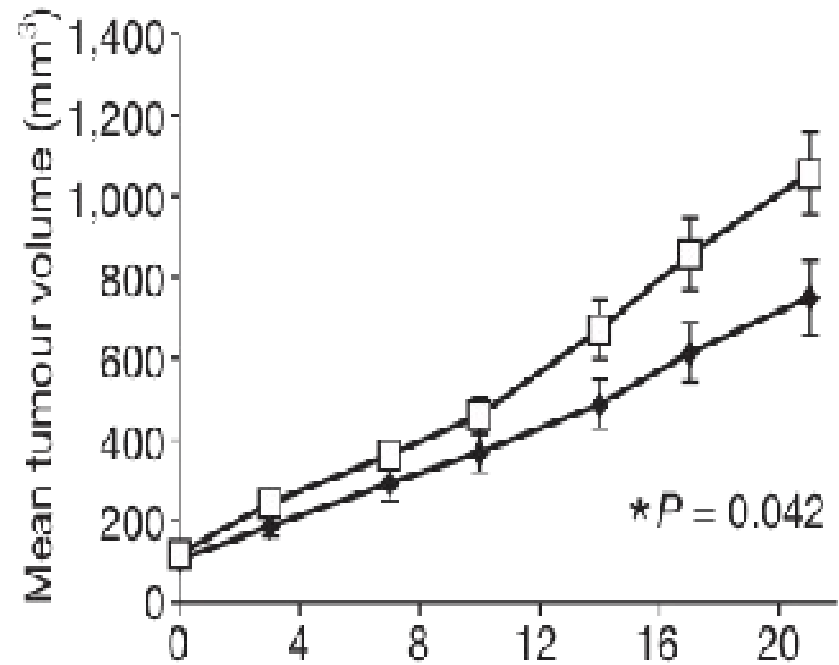


# RAF inhibitors selectively inhibits growth and proliferation of BRAF(V600E) lines

MEXF514 (BRAF(V600E)) tumour xenograft



LXFA983 (KRAS-MT) tumour xenograft



Days of treatment



Which are the resistance mechanisms to BRAF inhibitors?



VOLUME 29 • NUMBER 22 • AUGUST 1 2011

JOURNAL OF CLINICAL ONCOLOGY

BIOLOGY OF NEOPLASIA

## Dissecting Therapeutic Resistance to RAF Inhibition in Melanoma by Tumor Genomic Profiling

*Nikhil Wagle, Caroline Emery, Michael F. Berger, Matthew J. Davis, Allison Sawyer, Panisa Pochanard, Sarah M. Kehoe, Cory M. Johannessen, Laura E. MacConaill, William C. Hahn, Matthew Meyerson, and Levi A. Garraway*

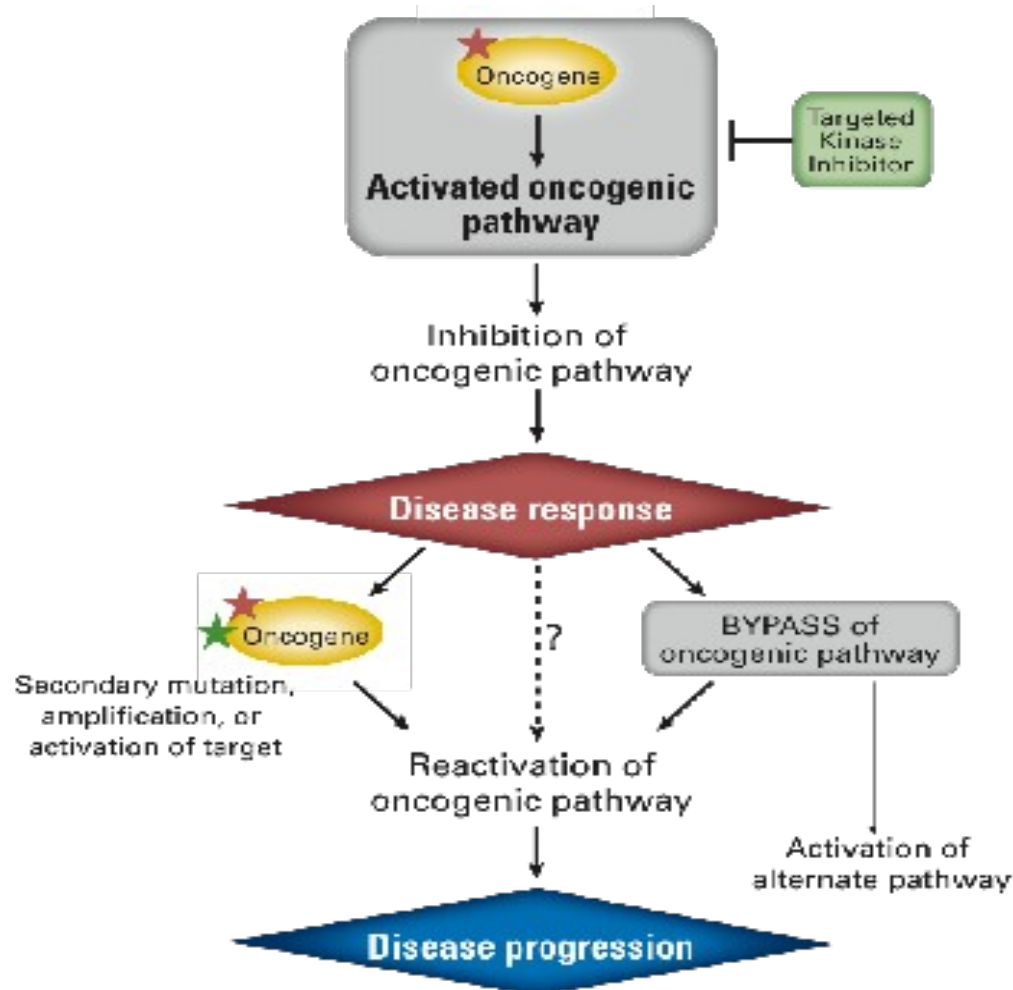


# Melanoma before PLX4032, after 15 weeks of therapy with PLX4032, and after relapse, after 23 weeks of therapy





# Kinase oncogene dependence and principles of drug resistance





# Resistance to TKI by secondary mutation or bypass

Targeted Agent	Target Gene	Acquired Resistance via Secondary Mutation, Amplification, or Activation of Target	Acquired Resistance via Bypass
Imatinib	ABL	T315	IGF1R amplification AXL overexpression <sup>†</sup>
		Y253F/H	
		E255K/V	
		ABL amplification	
		T670	
		V654A	
		D816V/G/H/V	
	KIT	D820A/E/G/Y	
		Y323D	
	PDGFR-α	KIT amplification	
		I674	



# Resistance to TKI by secondary mutation or bypass

Targeted Agent	Target: Gene	Acquired Resistance via Secondary Mutation, Amplification, or Activation of Target		Acquired Resistance via Downstream Mutation
		Acquired Resistance via Secondary Mutation, Amplification, or Activation of Target	Acquired Resistance via Bypass	
AEZ-106044	MEK1	MEK1 P124I BRAF amplification*		
PLX4032	BRAF	NRAS Q61K	COT overexpression* PDGFRβ overexpression† CRAF overexpression*‡ AXL overexpression*† HHV2 overexpression†‡	VILK1 G121S



# LETTER

doi:10.1038/nature09626

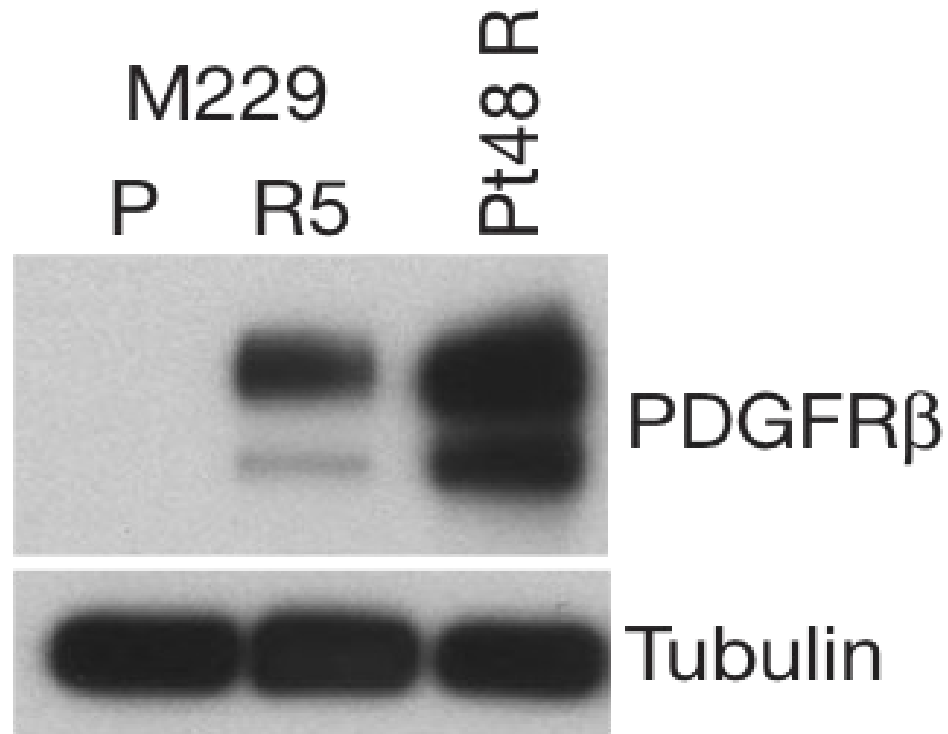
## **Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation**

16 DECEMBER 2010 | VOL. 468 | NATURE | 973



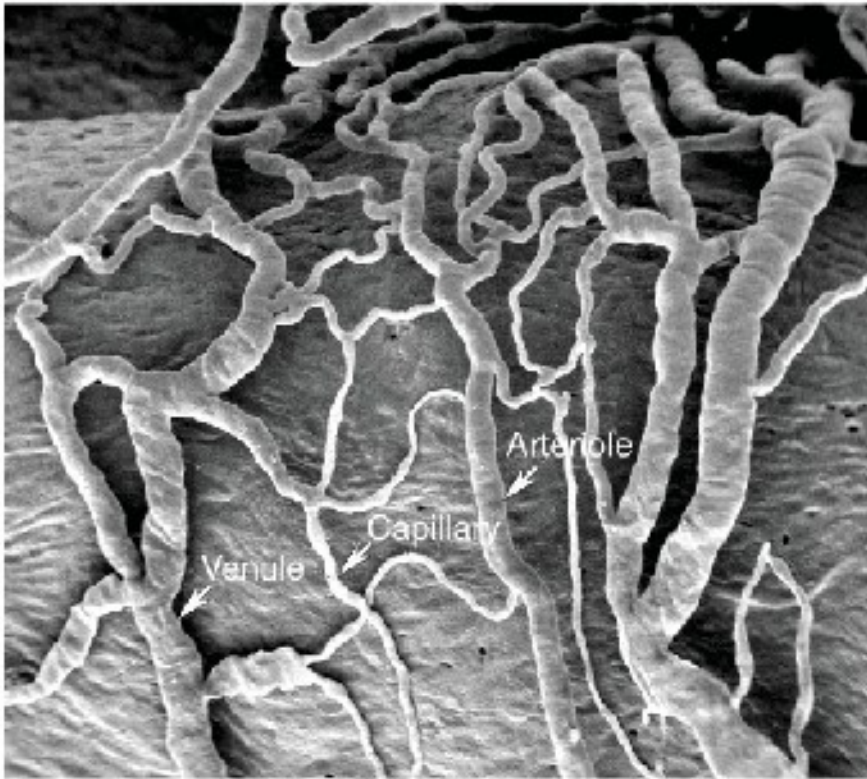


# PDGFR $\beta$ upregulation is correlated with vemurafenib acquired resistance

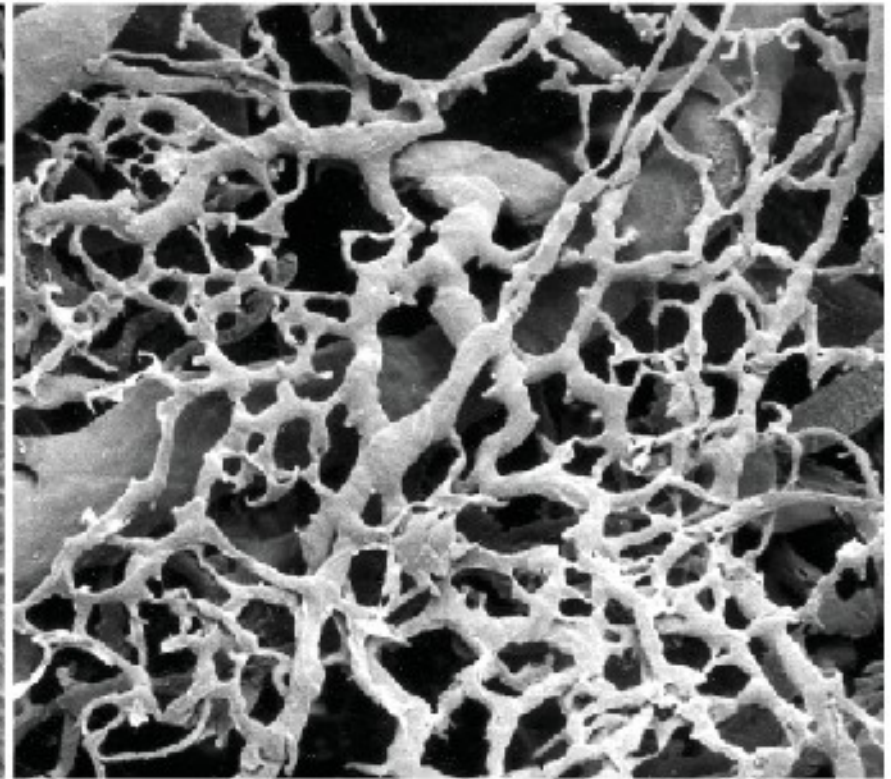




# Images of angiogenesis



**Normal vasculature**



**Tumor angiogenesis**



# Conclusions

How to prevent or delay drug resistance in melanoma?



# Overview of single agent, in pathway or cross pathway combinations of targeted and/or immunotherapy

