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Personalized Cancer Medicine

Conceptual, Organizational, Financial Challenges

SHANGHAI
6 July, 2012

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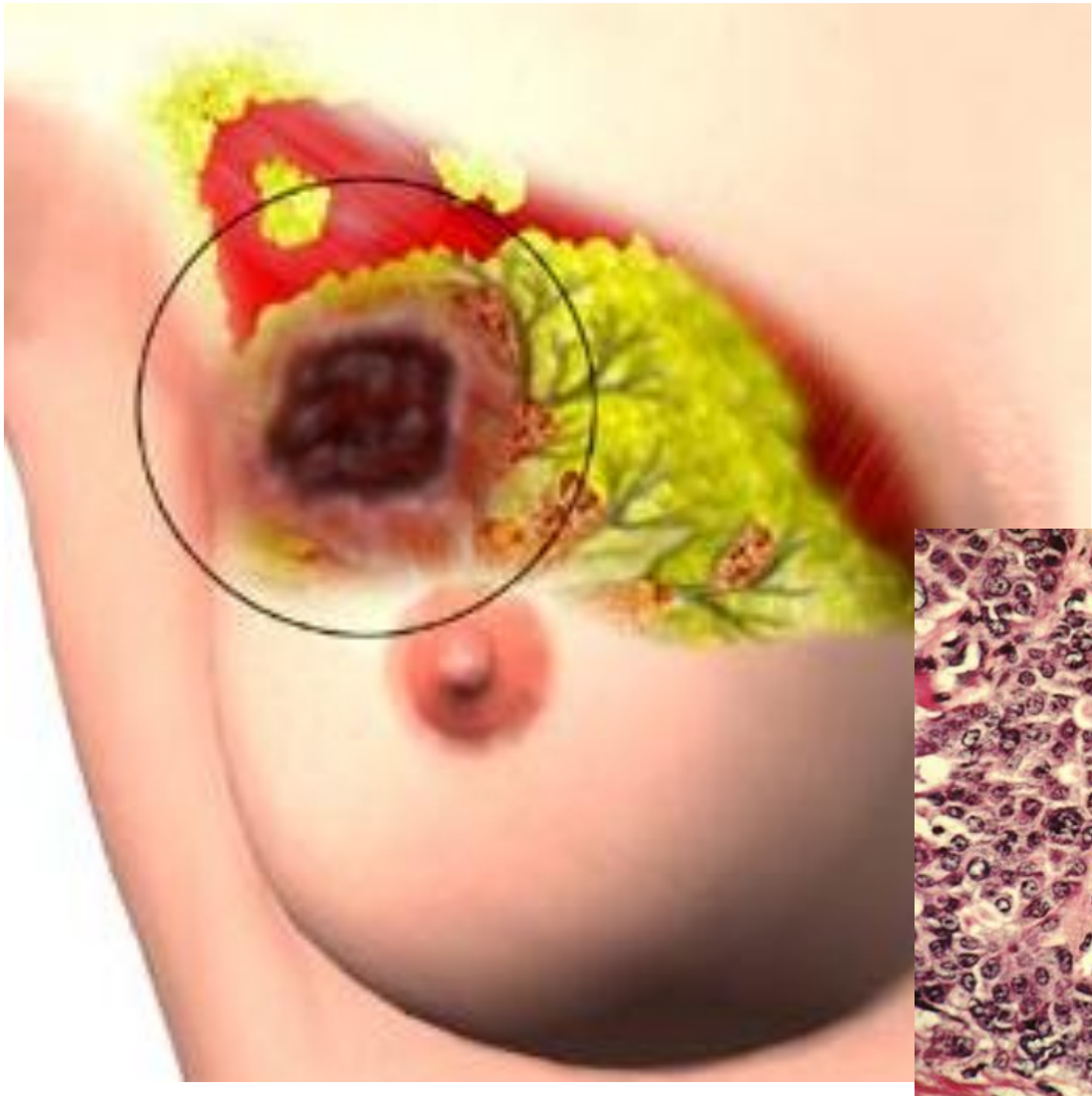
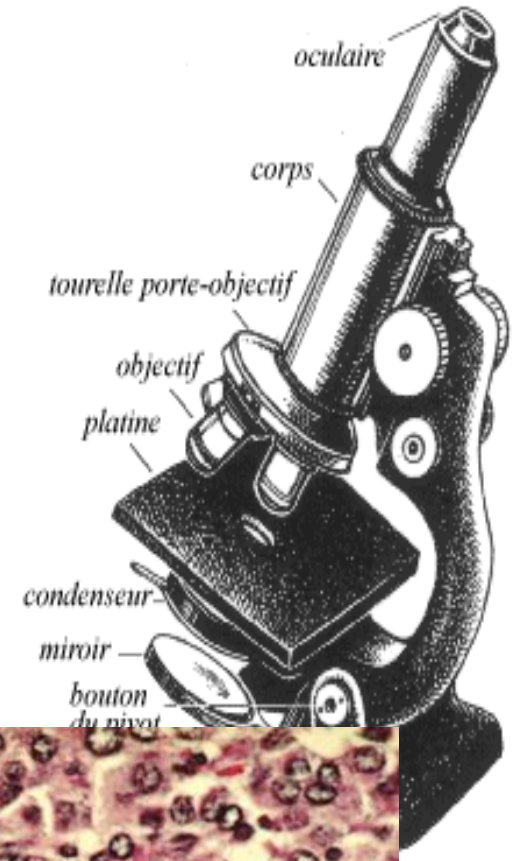
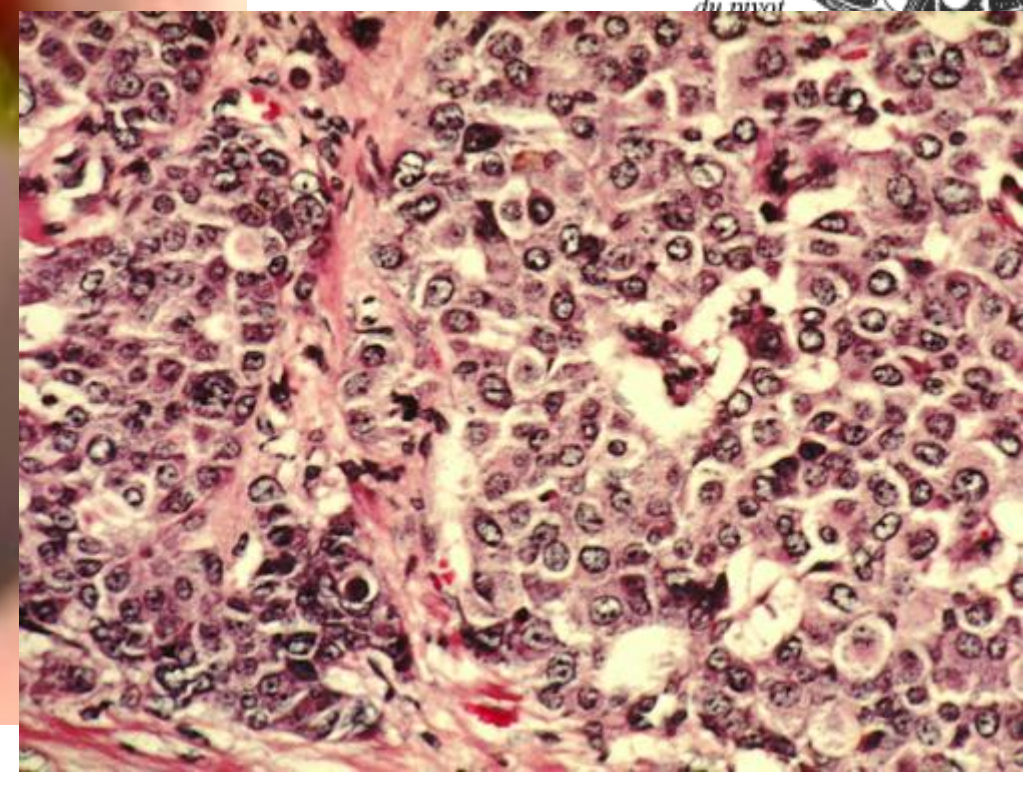
What is breast cancer ? The old perception







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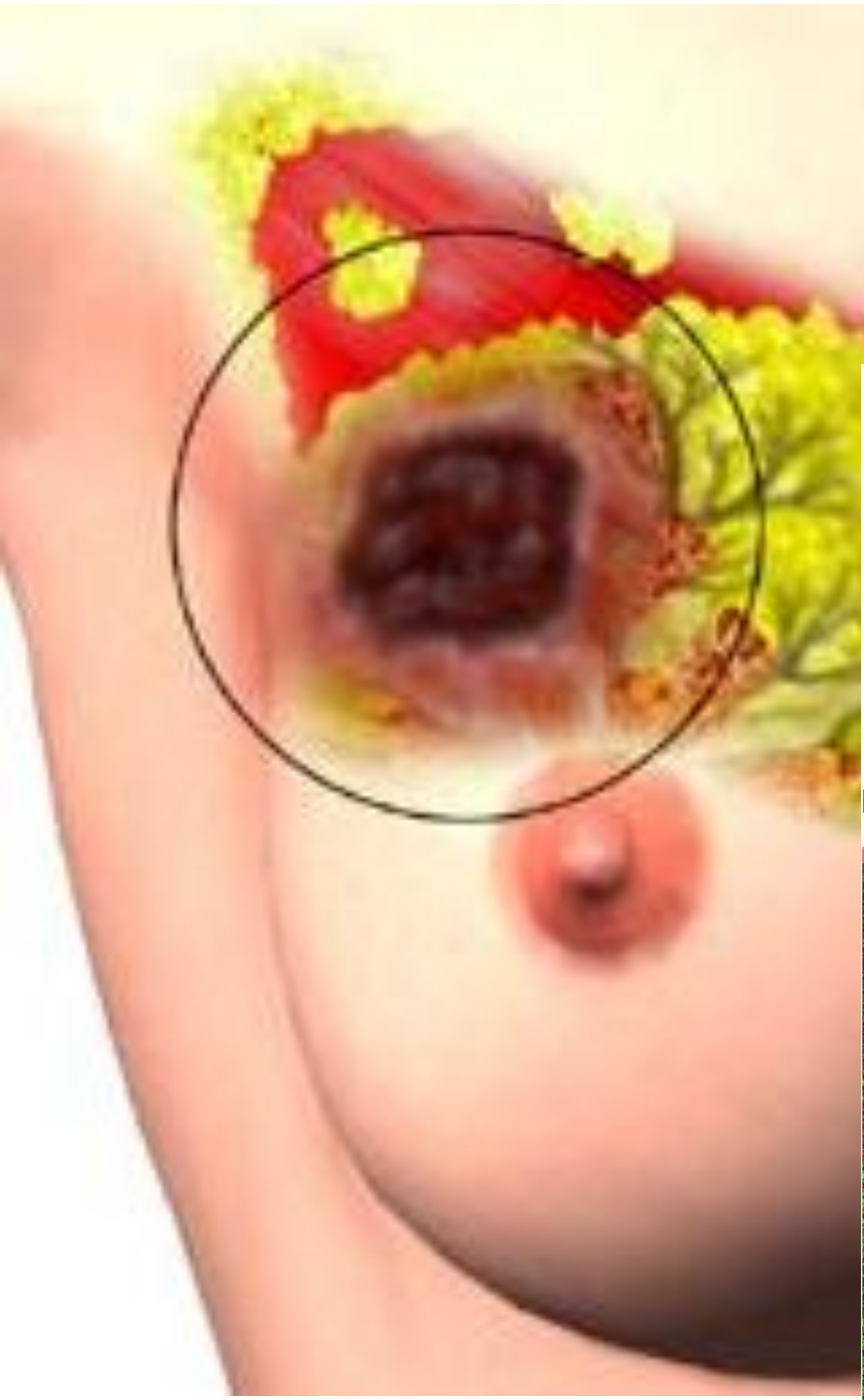
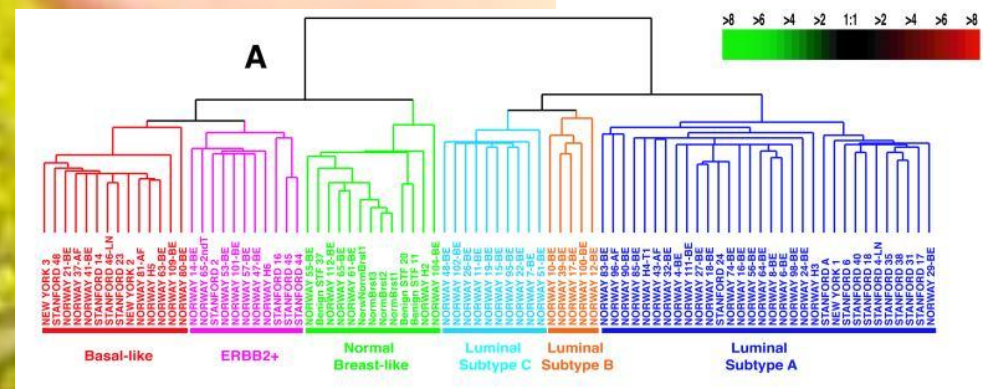
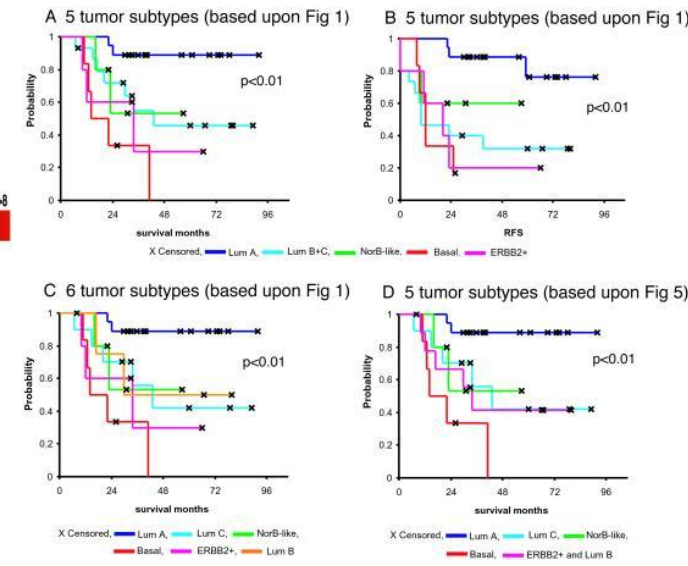
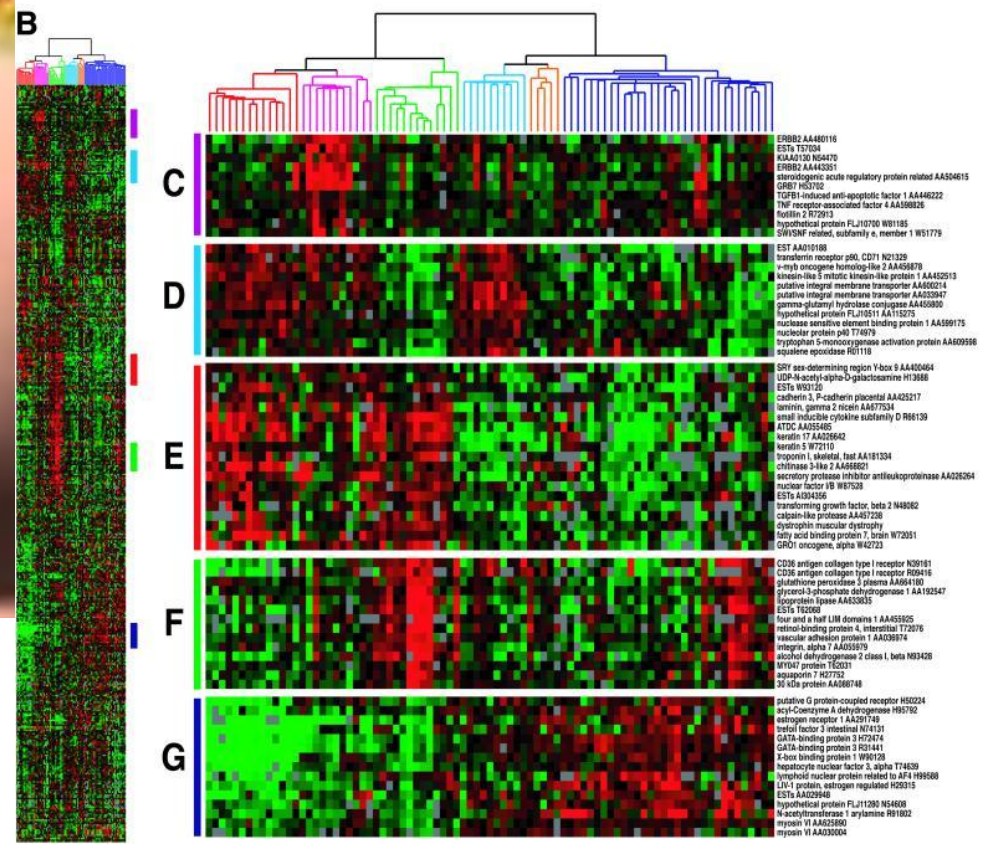
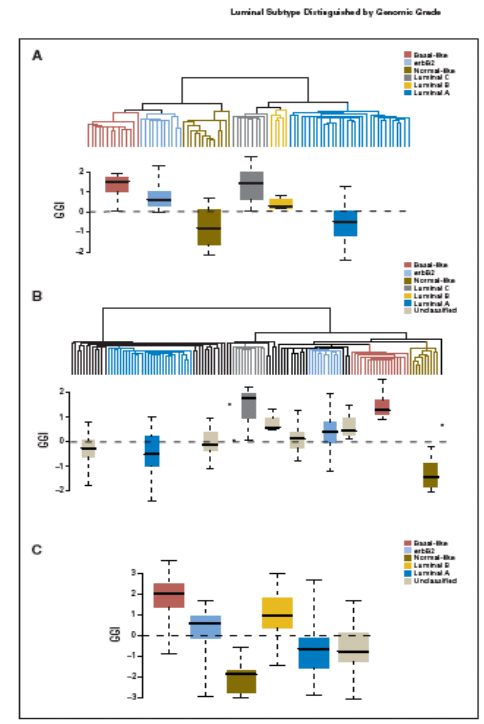
The New Family of Diseases Perception / Molecular Portraits











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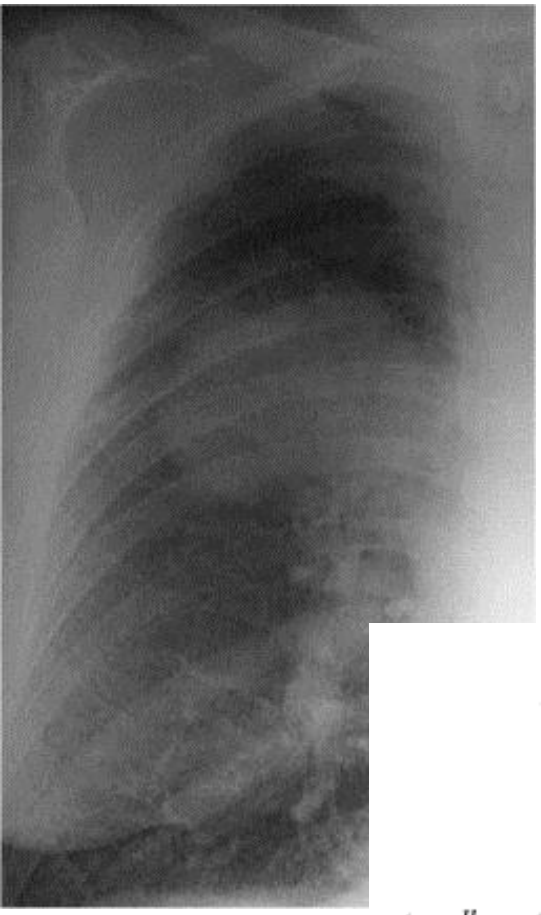
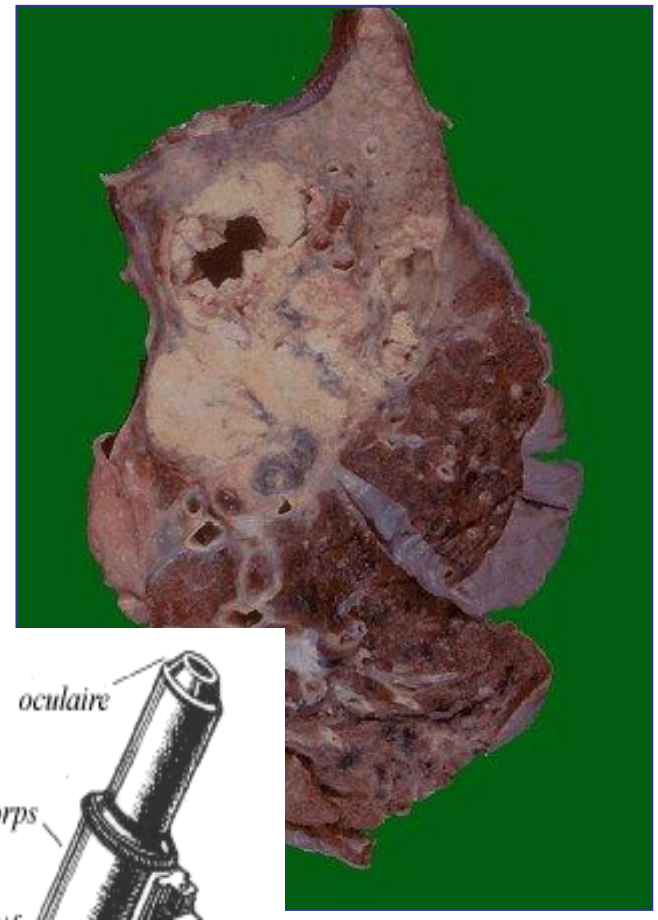
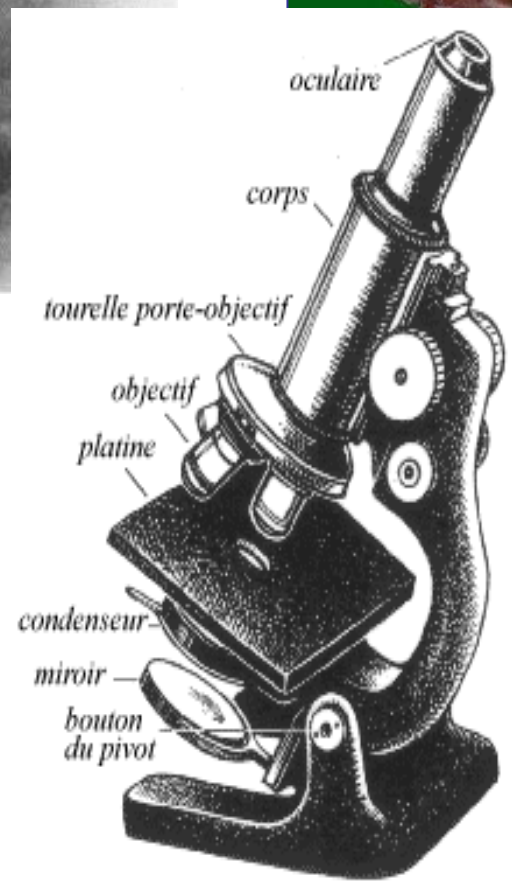
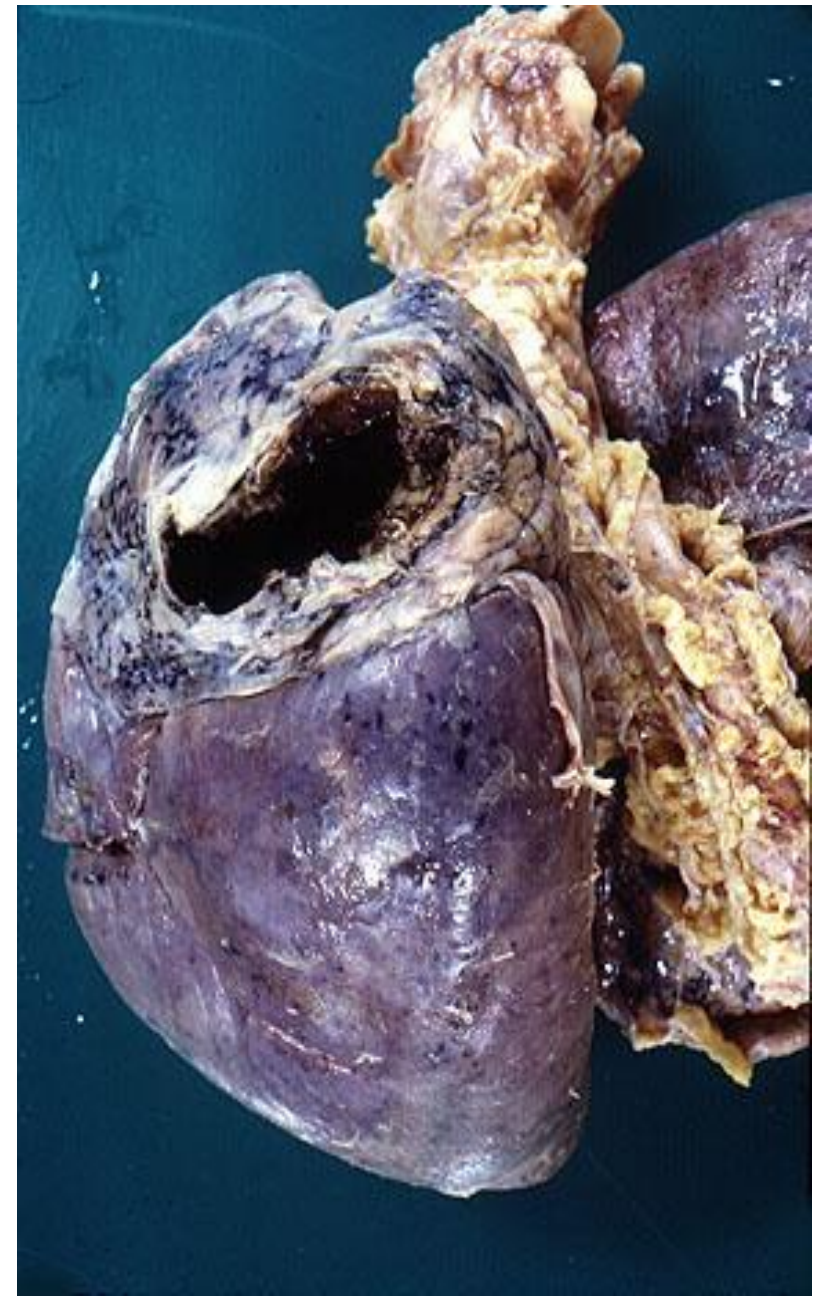
What is lung cancer ? The old perception

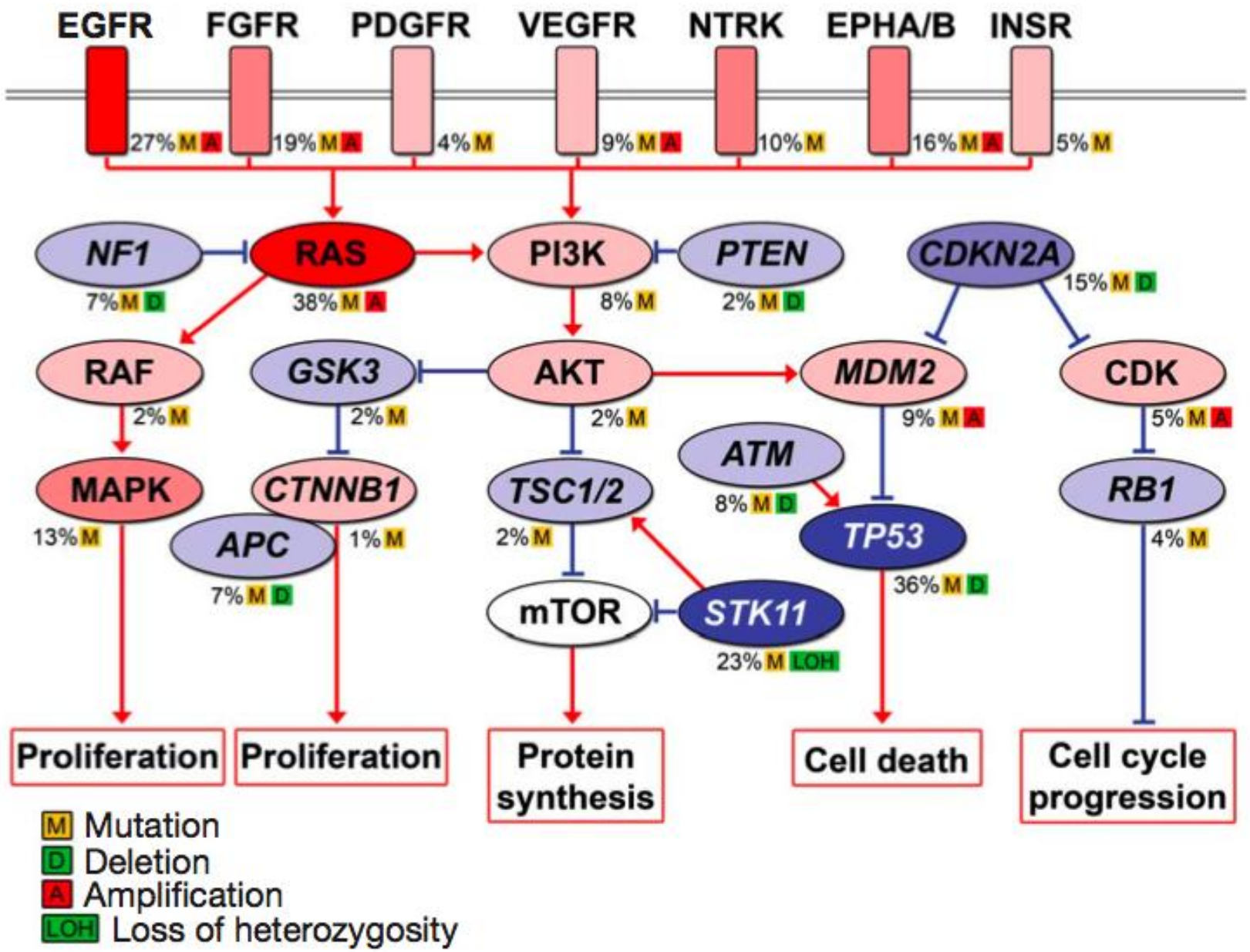








Significantly mutated pathways in adenocarcinoma of the lung



Ding et al. Nature 455, 1069, 2008

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Drug Development 2011

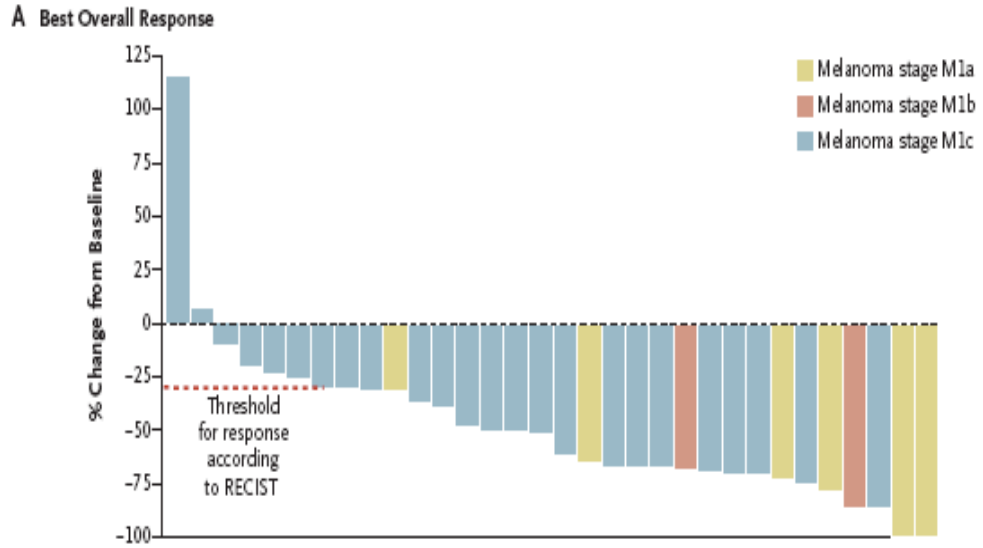
- In Phase I-II "forever"
- Characterize tumors that will allow for very high specific activity
- Early Detection Resistance
- Early development of combinations
  (intrapathway AND interpathway)
- Fewer and Smaller Phase III trials

Specific genetic traits can predict for the success of targeted agents

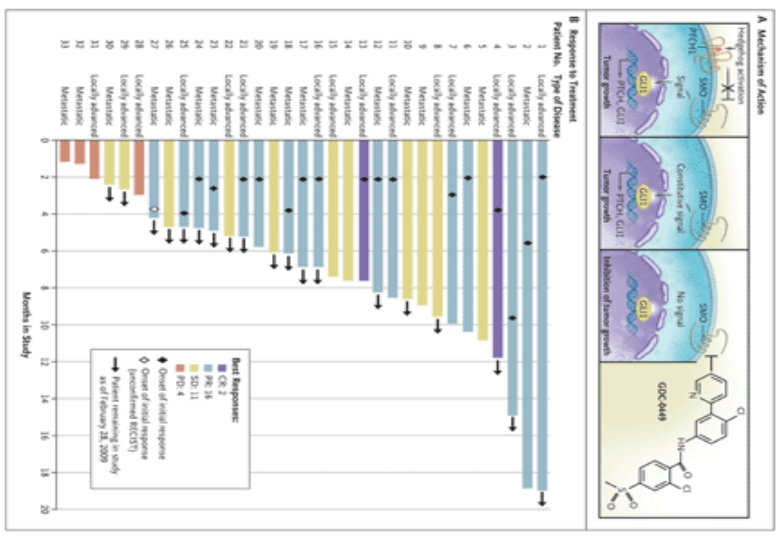
PHASE 1 DATA

TELL IT ALL !

B-RAF inhibitor in melanoma (V600E BRAF mutation) *NEJM 2010*



Hedgehog inhibitor in BCC (PTCH mutation) *NEJM 2010*



ALK inhibitor in NSCLC (ALK translocation) *NEJM 2010*

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THE MELANOMA PARADIGM

MUTATION DRIVEN DRUG DEVELOPMENT

INNOVATIVE IMMUNOMODULATION

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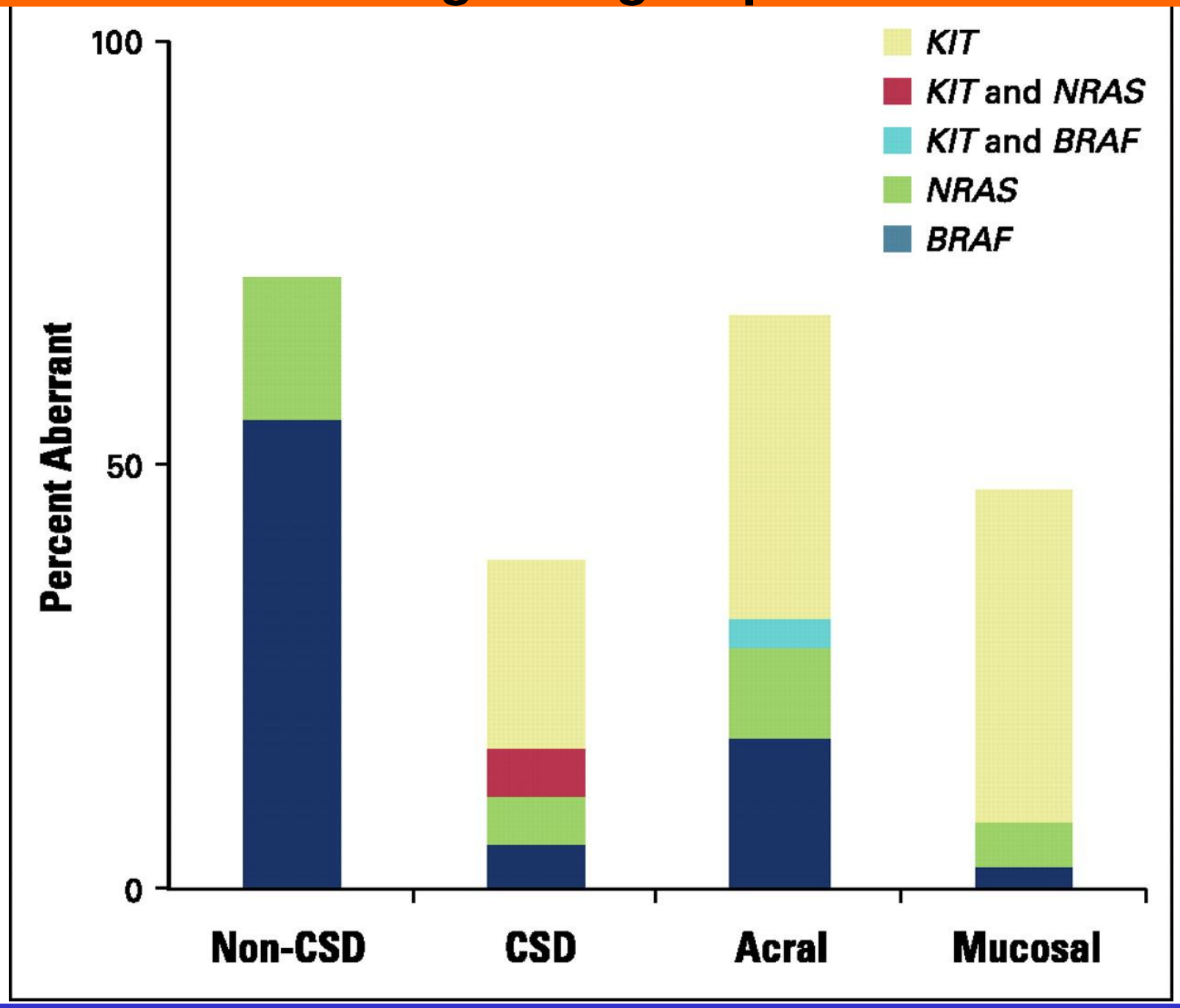
Frequency distribution of genetic alterations in BRAF, NRAS, and KIT among four groups of melanoma



Curtin, J. A. et al. J Clin Oncol; 24:4340-4346 2006

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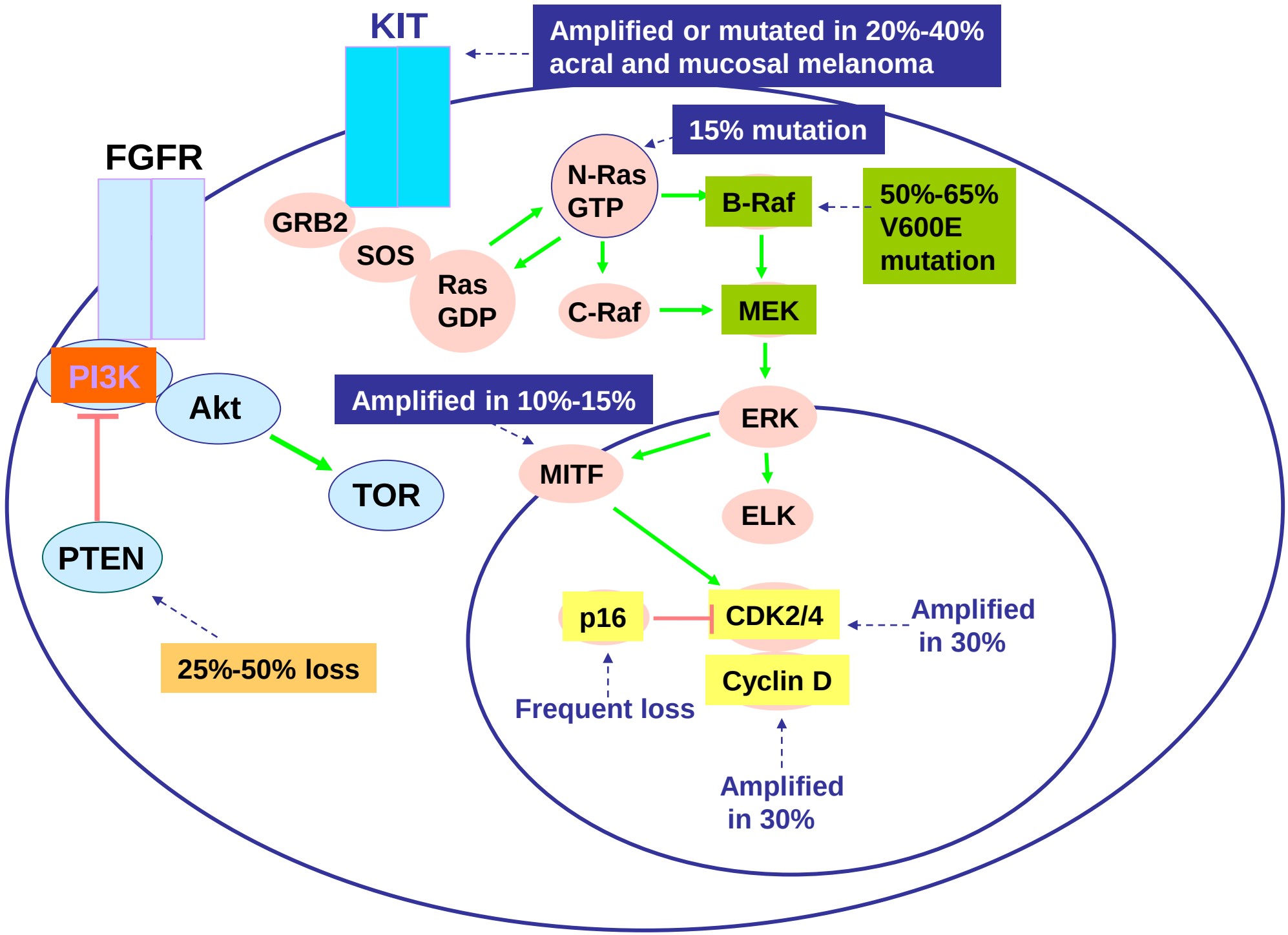
Molecular Alterations in Melanoma



Adapted from Sosman, *Curr. Oncol. Rep*. 11, 405 (2009)

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B-RAF INHIBITOR

PLX4032/RG7402

vemurafenib

Keith Flaherty et al
NEJM 2010

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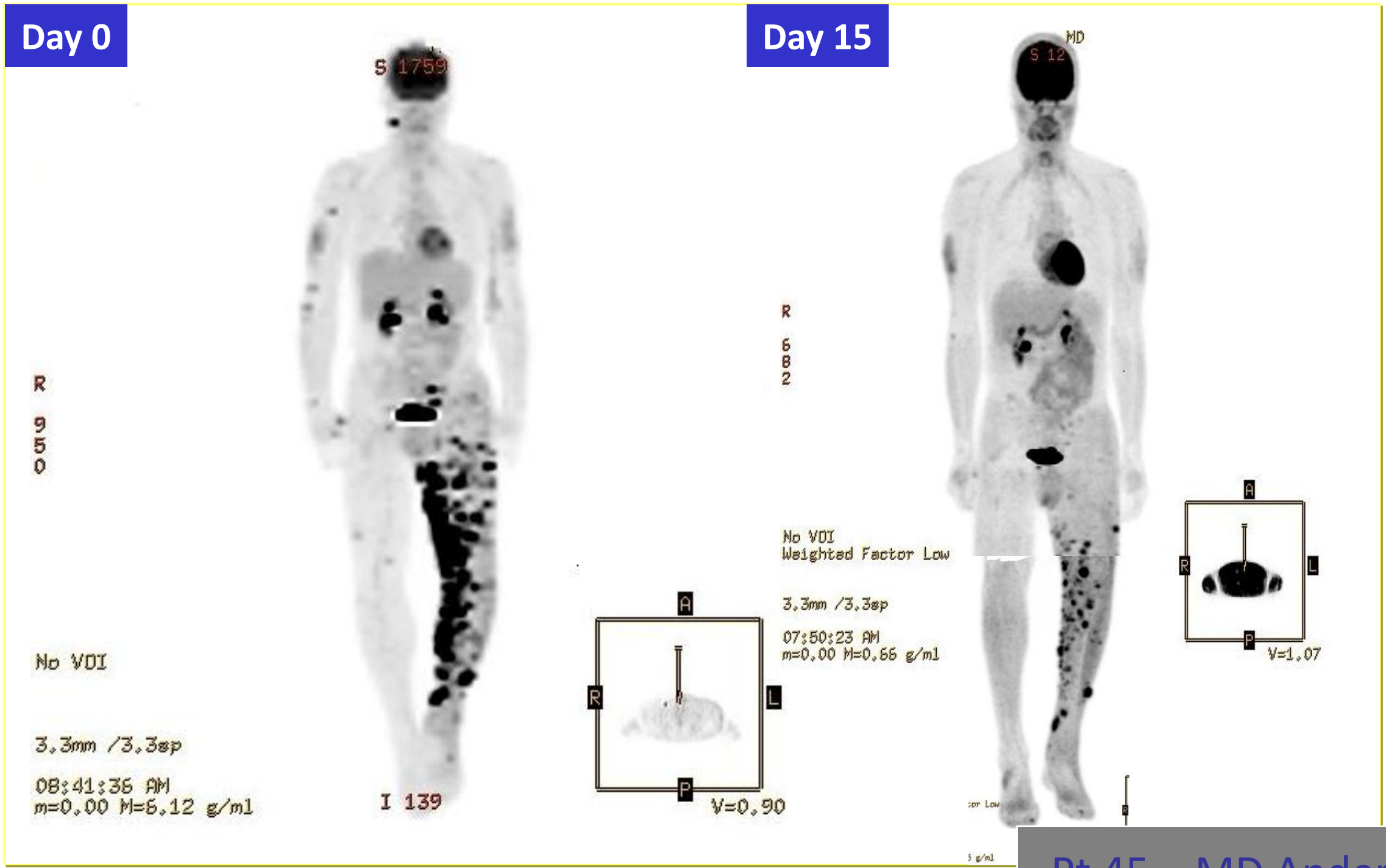
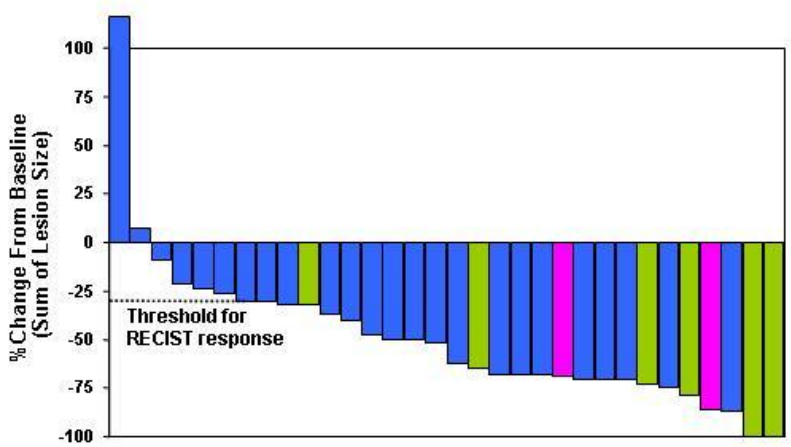
$BRAF^{V600E}$ melanoma patient PET scan at baseline and day +15 after PLX4032 treatment at 320 mg BID

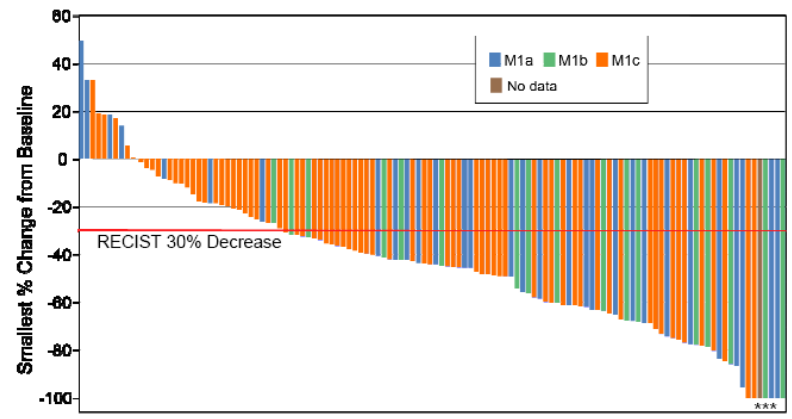


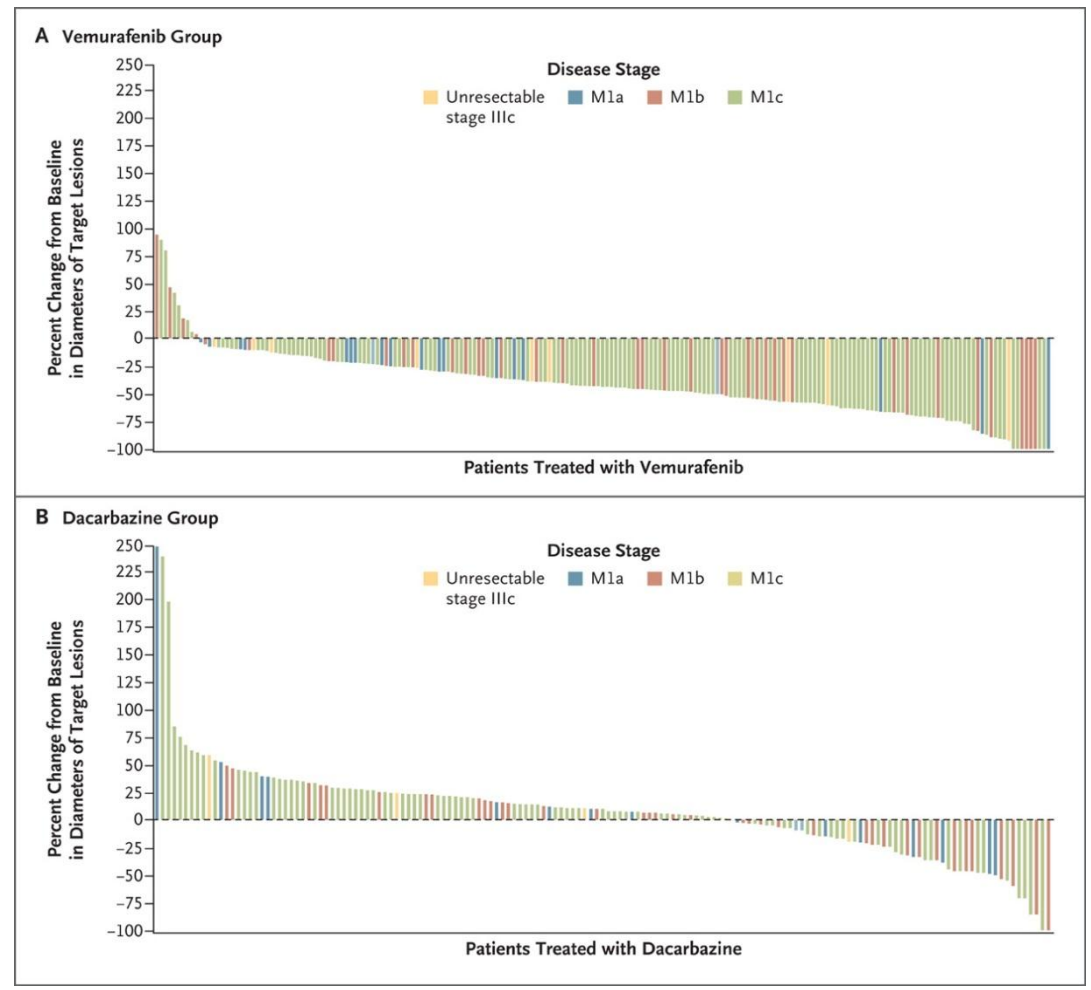
Pt 45 – MD Anderson

BRIM 1, BRIM 2 and BRIM 3



Tumor Regression (Target Lesions) Occurred in Majority of Patients (IRC)





" PHASE I TELLS IT ALL "

Flaherty, Sosman and Chapman NEJM 2010, 2011, 2012

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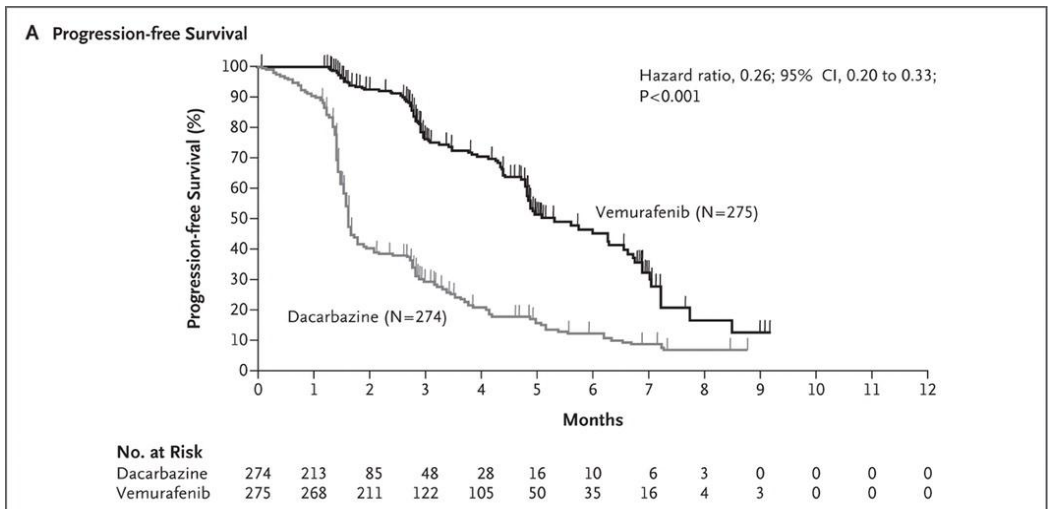
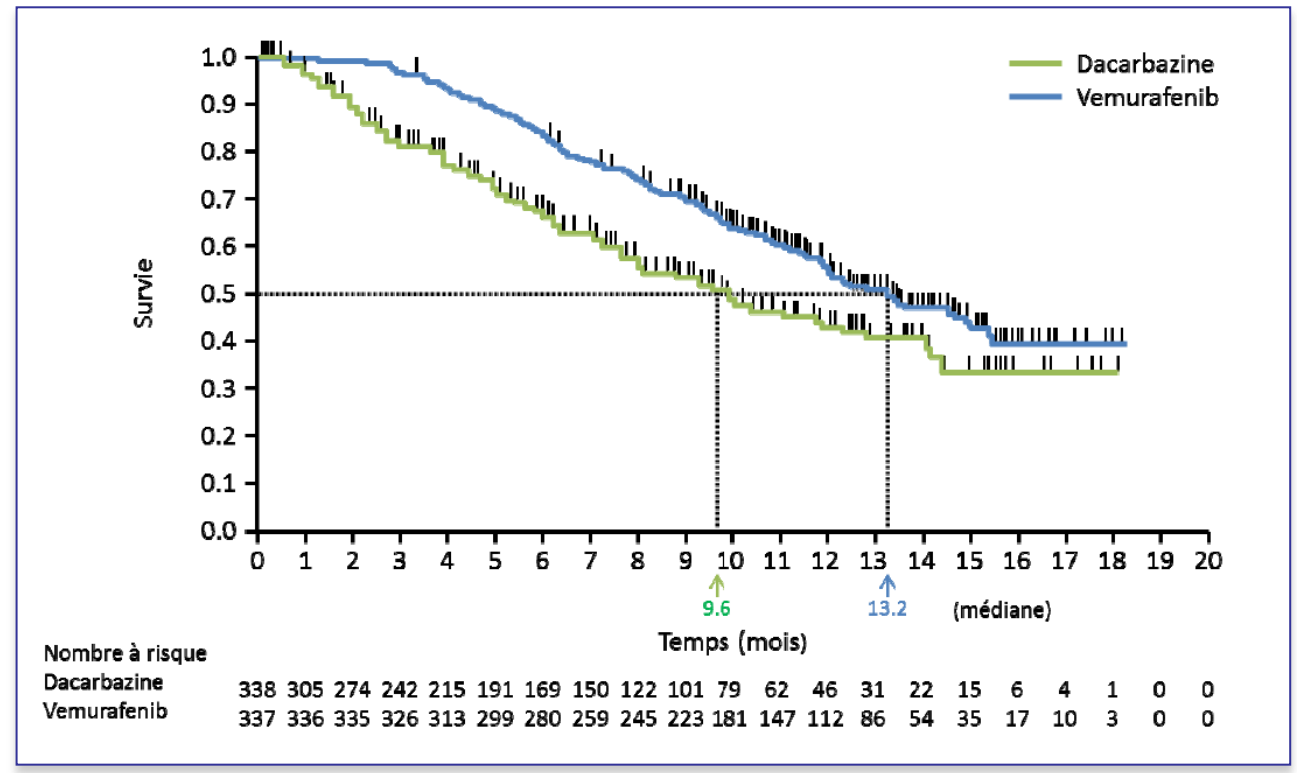
BRIM 3

PFS 1.6-5.5 mts
Gain: 3.9 mts
HR 0.26

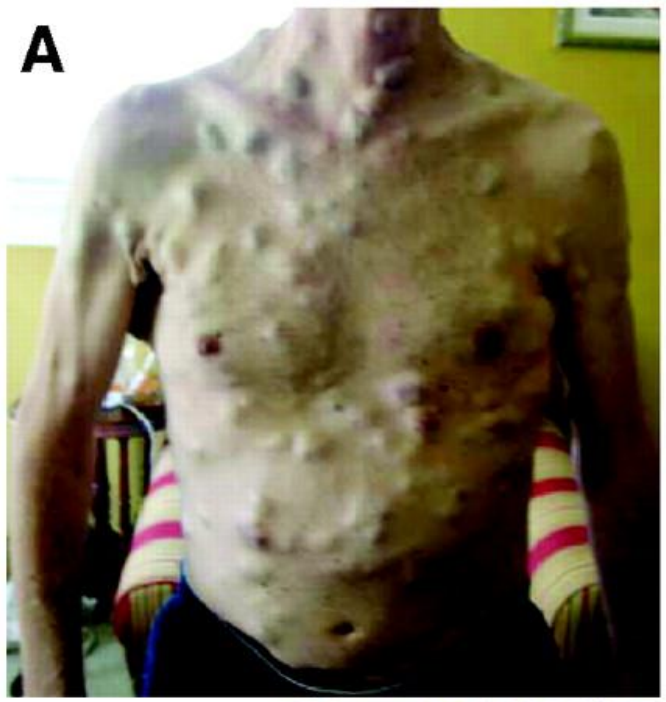
OS 9.6-13.2 mts
Gain 3.6 mts*
HR 0.62

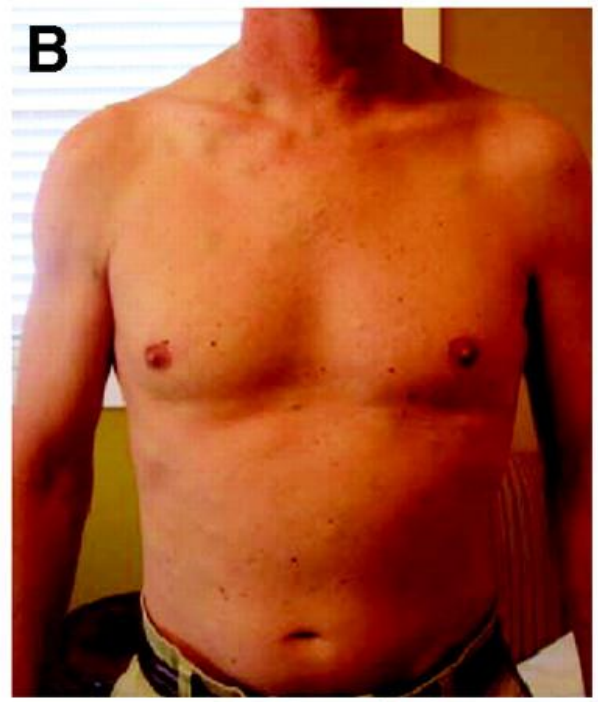


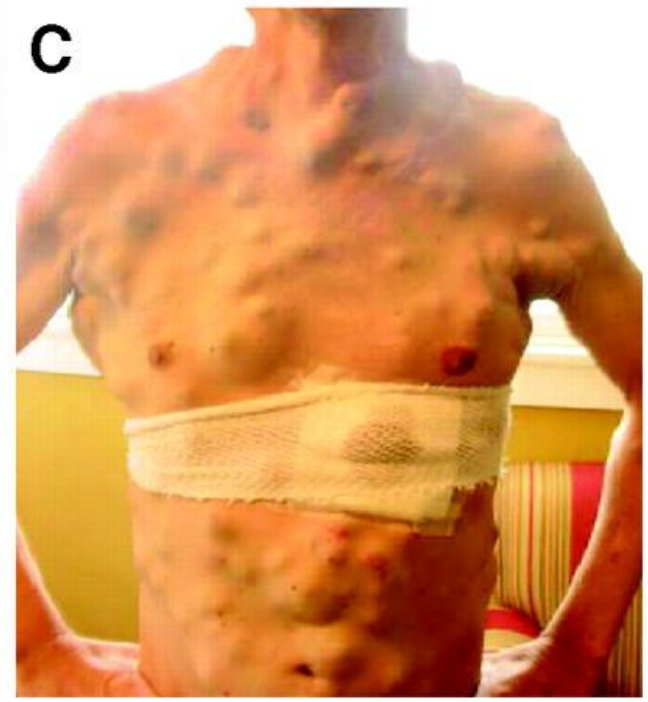


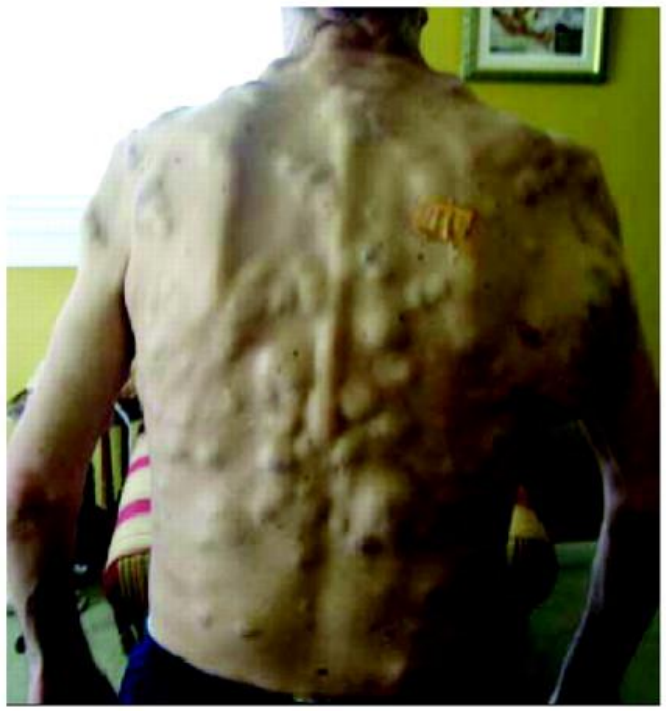
al. N Engl J Med 2011
pdate October 2011

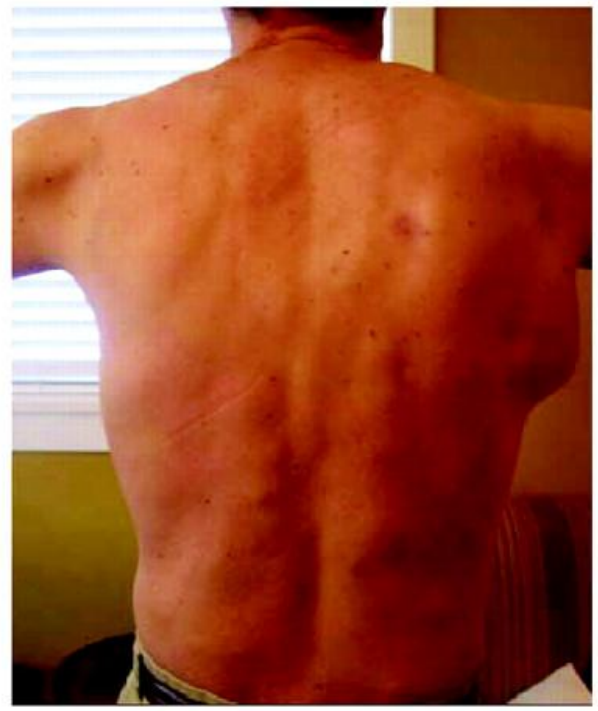
SUCCESS AND FAILURE











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Multiple Mechanisms of Prexisting or Acquired Resistance to BRAFinhibitors Identified

LETTER

doi:10.1038/nature09626

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

Ramin Nazarian[1,2]*, Hubing Shi[1,2]*, Qi Wang[1,2], Xiangju Kong[1,2], Richard C. Koya[2,3], Hane Lee[2,4], Zugen Chen[2,4], Mi-Kyung Lee[1,2], Narsis Attar[2,5], Hooman Sazegar[2,5], Thinle Chodon[2,5], Stanley F. Nelson[2,4,6], Grant McArthur[7], Jeffrey A. Sosman[8], Antoni Ribas[2,3,5] & Roger S. Lo[1,2]

LETTER

doi:10.1038/nature09627

COT drives resistance to RAF inhibition through MAP kinase pathway reactivation

Cory M. Johannessen[1,2]*, Jesse S. Boehm[1]*, So Young Kim[1,2,3]†, Sapana R. Thomas[1,2], Leslie Wardwell[2], Laura A. Johnson[1,2], Caroline M. Emery[2], Nicolas Stransky[1], Alexandria P. Cogdill[4], Jordi Barretina[1,2,5], Giordano Caponigro[6], Haley Hieronymus[1,7,8], Ryan R. Murray[3,9,10], Kourosh Salehi-Ashtiani[3,9,10], David E. Hill[3,9,10], Marc Vidal[3,9,10], Jean J. Zhao[9,11], Xiaoping Yang[2], Ozan Alkan[1], Sungjoon Kim[12], Jennifer L. Harris[12], Christopher J. Wilson[6], Vic E. Myer[6], Peter M. Finan[6], David E. Root[1], Thomas M. Roberts[9], Todd Golub[1,5,8], Keith T. Flaherty[4], Reinhard Dummer[13], Barbara L. Weber[6], William R. Sellers[6], Robert Schlegel[6], Jennifer A. Wargo[4], William C. Hahn[1,2,3,5] & Levi A. Garraway[1,2,5]

Cancer Cell
Article

Cell PRESS

Acquired Resistance to BRAF Inhibitors Mediated by a RAF Kinase Switch in Melanoma Can Be Overcome by Cotargeting MEK and IGF-1R/PI3K

Jessie Villanueva,[1] Adina Vultur,[1] John T. Lee,[1] Rajasekharan Somasundaram,[1] Mizuho Fukunaga-Kalabis,[1] Angela K. Cipolla,[1] Bradley Wubbenhorst,[2] Xiaowei Xu,[3] Phyllis A. Gimotty,[4] Damien Kee,[5] Ademi E. Santiago-Walker,[1] Richard Letrero,[2] Kurt D'Andrea,[2] Anitha Pushparajan,[3] James E. Hayden,[1] Kimberly Dahlman Brown,[6] Sylvie Laquerre,[7] Grant A. McArthur,[5] Jeffrey A. Sosman,[6] Katherine L. Nathanson,[2] and Meenhard Herlyn[1,*]

JOURNAL OF CLINICAL ONCOLOGY | BIOLOGY OF NEOPLASIA

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

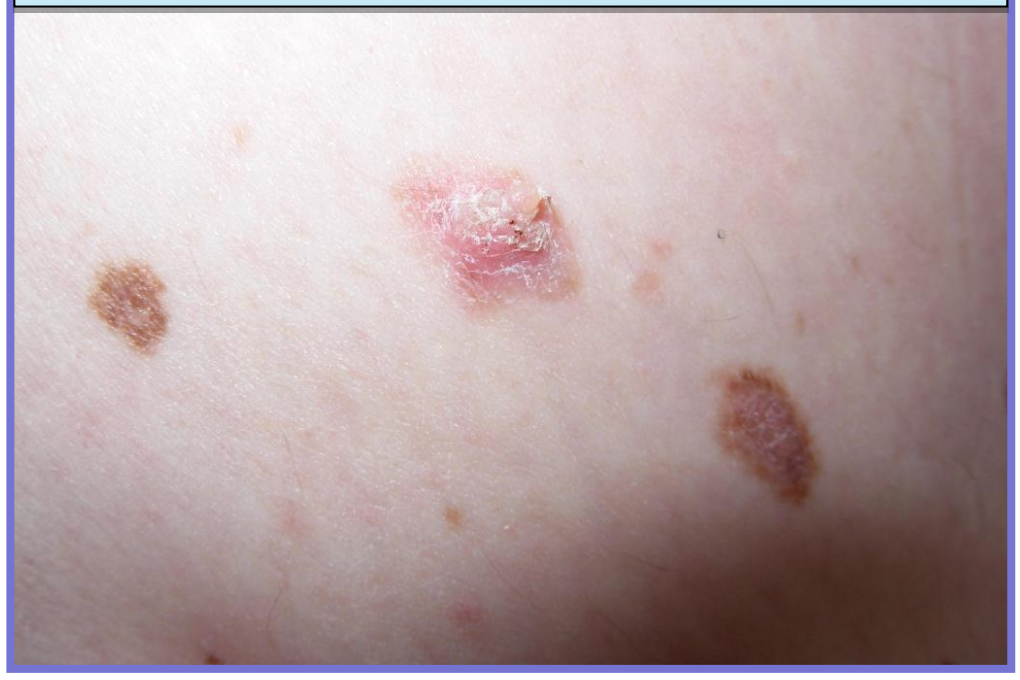
Nikhil Wagle, Caroline Emery, Michael F. Berger, Matthew J. Davis, Allison Sawyer, Pankaj Pochanard, Sarah M. Kehoe, Cory M. Johannessen, Laura E. MacConaill, William C. Hahn, Matthew Meyerson, and Levi A. Garraway

- PDGFRβ overexpression: 4/11 biopsies from relapsed patients[1]
- NRAS mutations (Q61K orR): 2/15 samples[1]
- Elevated COT expression which reactivated ERK signaling: 2/3 samples[2]
- Increased levels of IGF-1R and pAKT: activated PI3K pathway signaling (1/5)[3]
- Acquired a MEK mutation at C121S which reactivates the ERK signaling (1/1)[4]

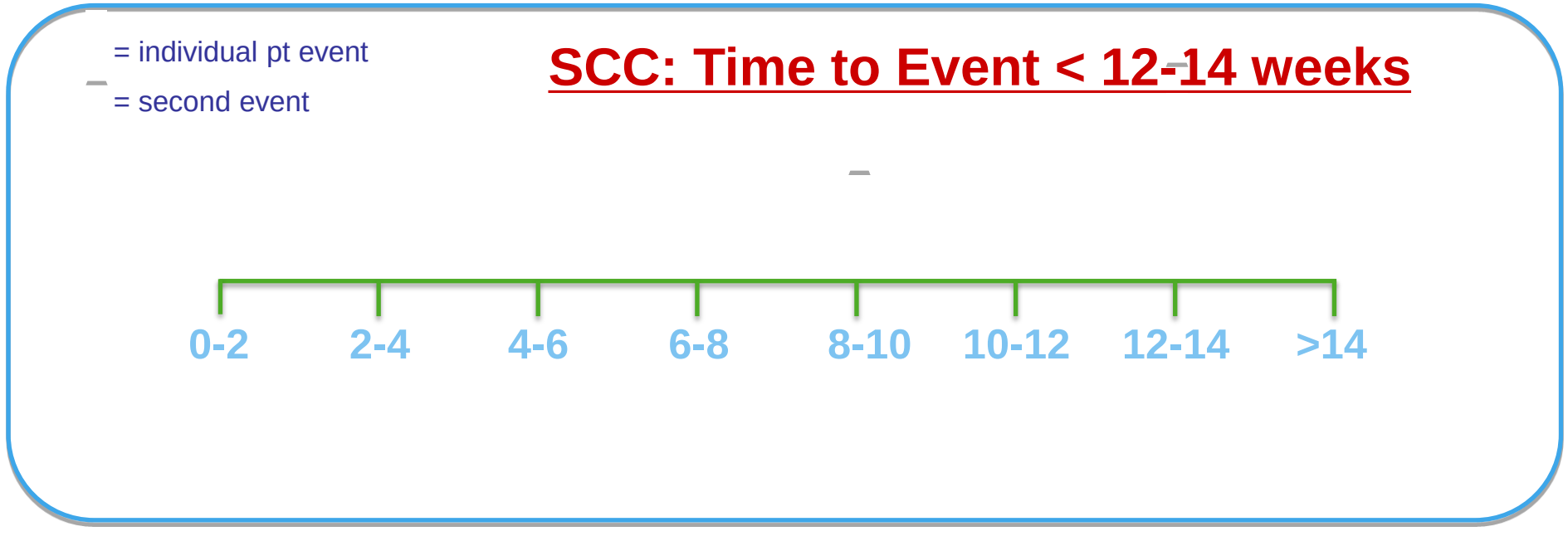
1. Nazarian R et al. Nature 2010; 2. Johannessen CM et al. Nature 2010;
3. Villanueva J et al. Cancer Cell 2010; 4. Wagle N et al. J. Clin. Oncol. 2011;

Squamous Cell Carcinoma (Skin)

Thigh: Week 6



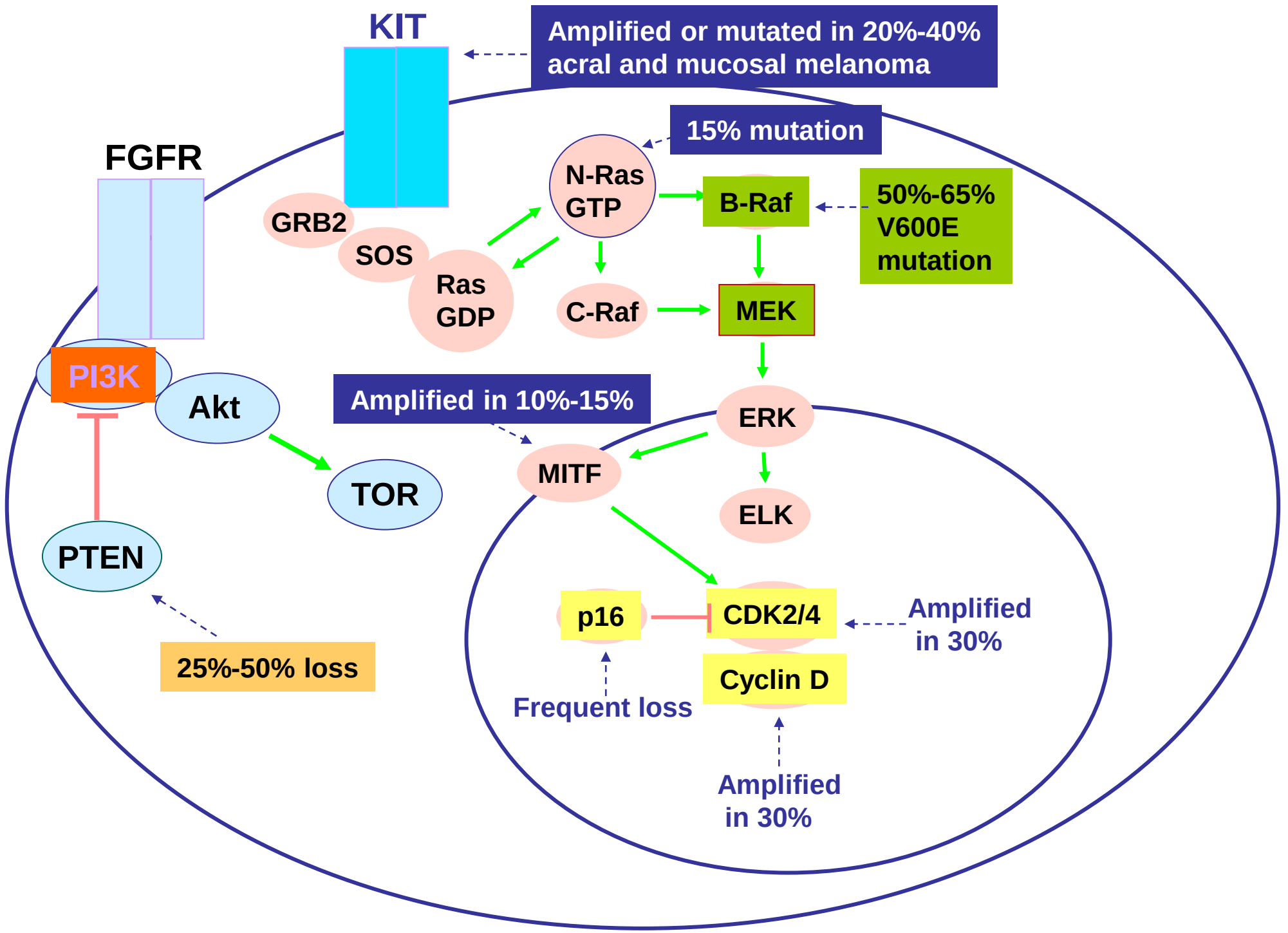
- **Histopathology: Low-grade squamous cell carcinoma**
- **In 20-25% of patients**
- **Induced in first 4 months (?)**



Kefford et al, Sydney 2010

Molecular Alterations in Melanoma

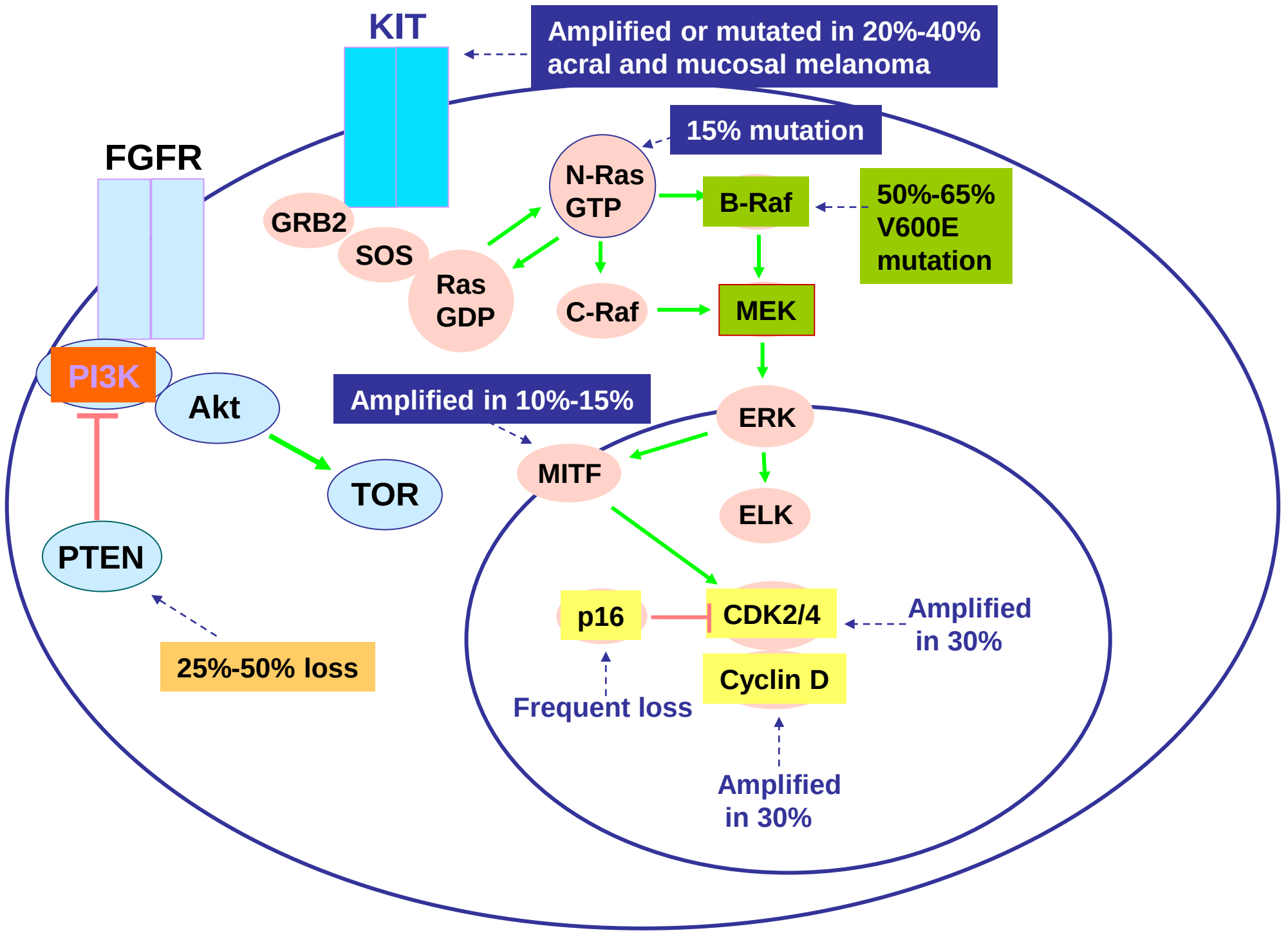
MEK Inhibitors (ASCO 2012)



Adapted from Sosman, *Curr. Oncol. Rep*. 11, 405 (2009)

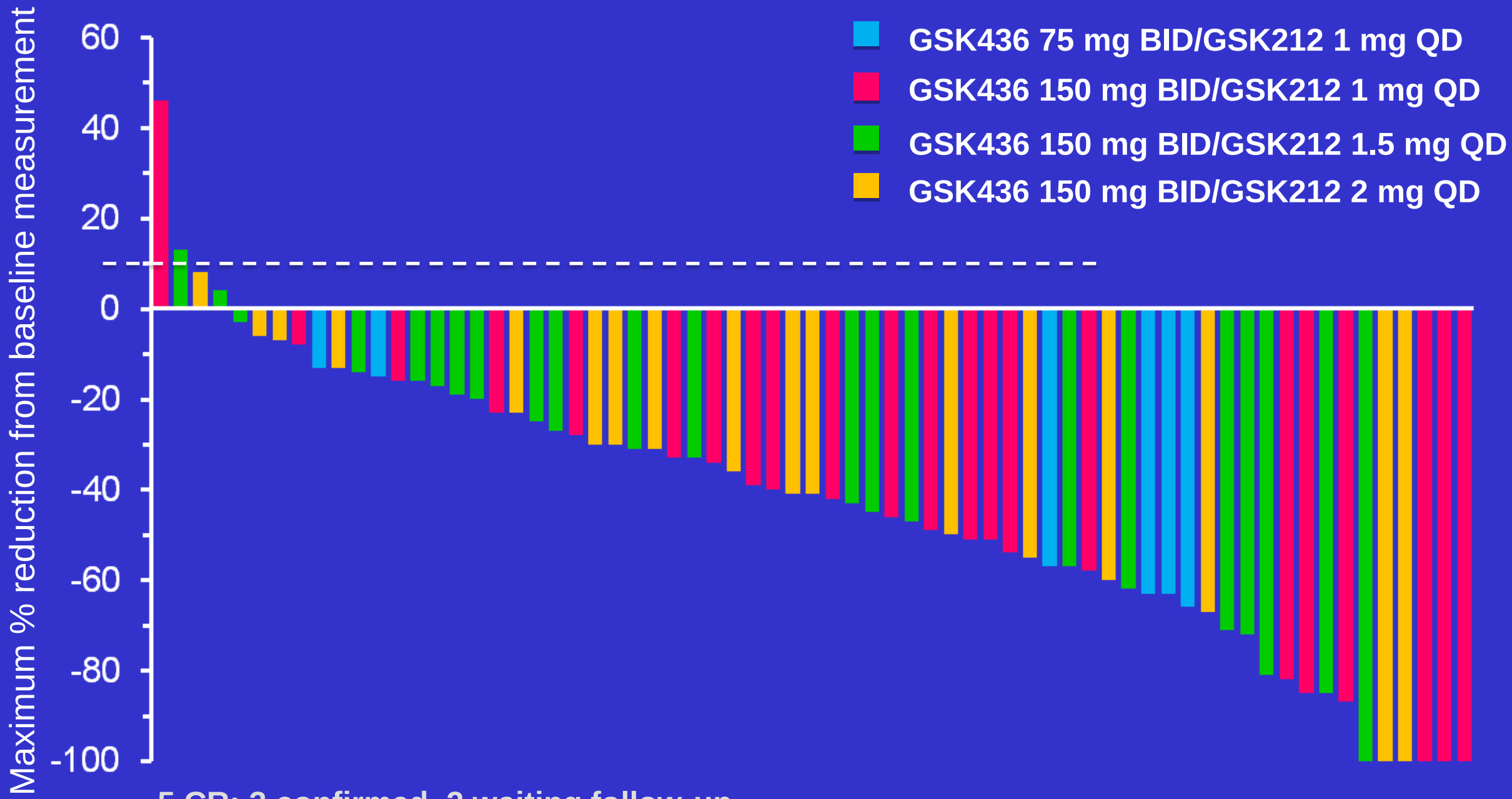
Molecular Alterations in Melanoma

BRAF + MEK Inhibitors (ASCO 2012)



Adapted from Sosman, *Curr. Oncol. Rep*. 11, 405 (2009)

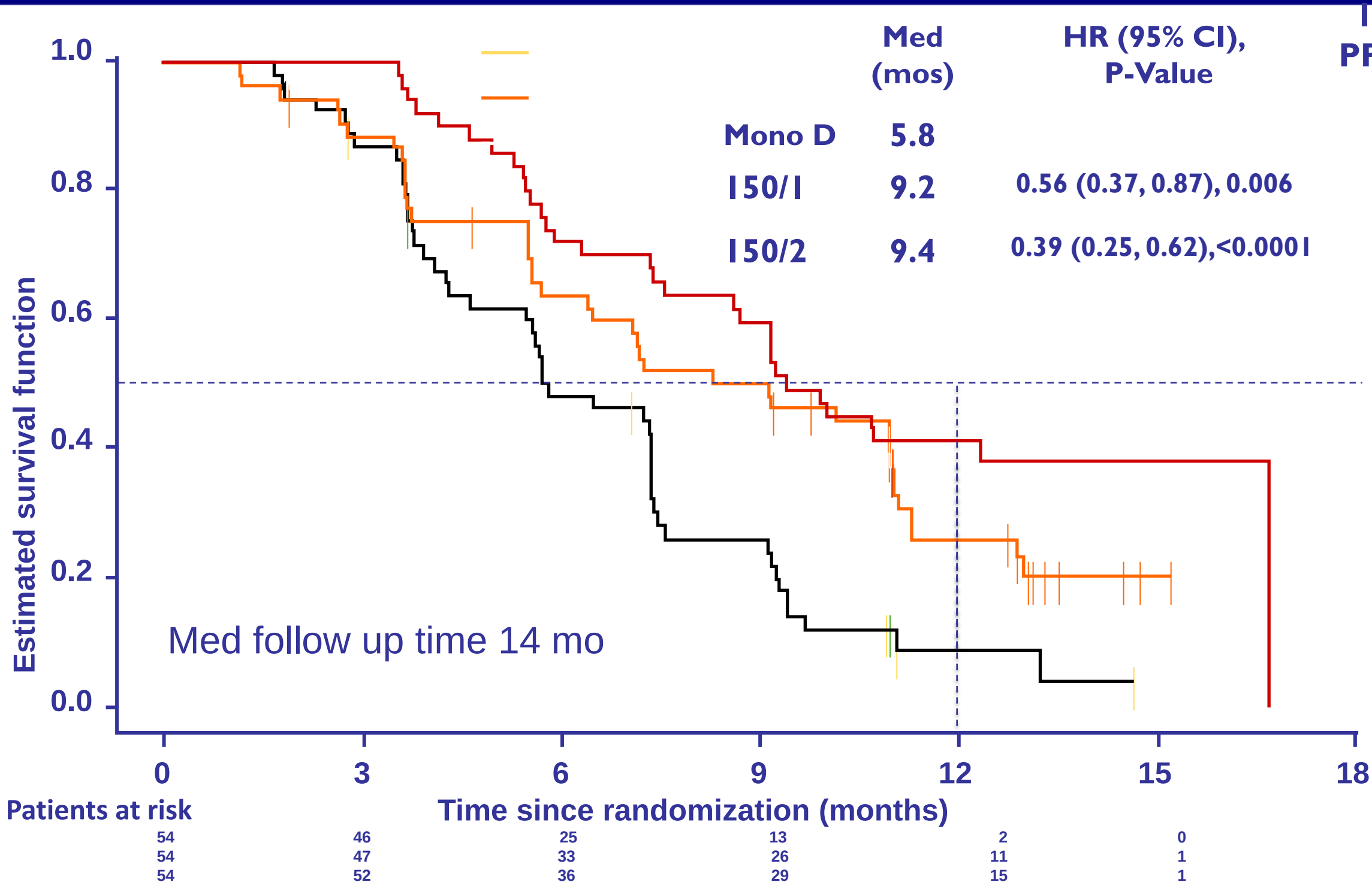
Combination: BRAF (GSK436) plus MEK inhibitor (GSK212)



5 CR: 3 confirmed, 2 waiting follow-up
4 pts not shown on plot: 2 PR, 1 SD, 1 PD

ASCO 2011 Kefford et al

Dabrafenib vs Dabrafenic+Trametinib
Progression-Free Survival



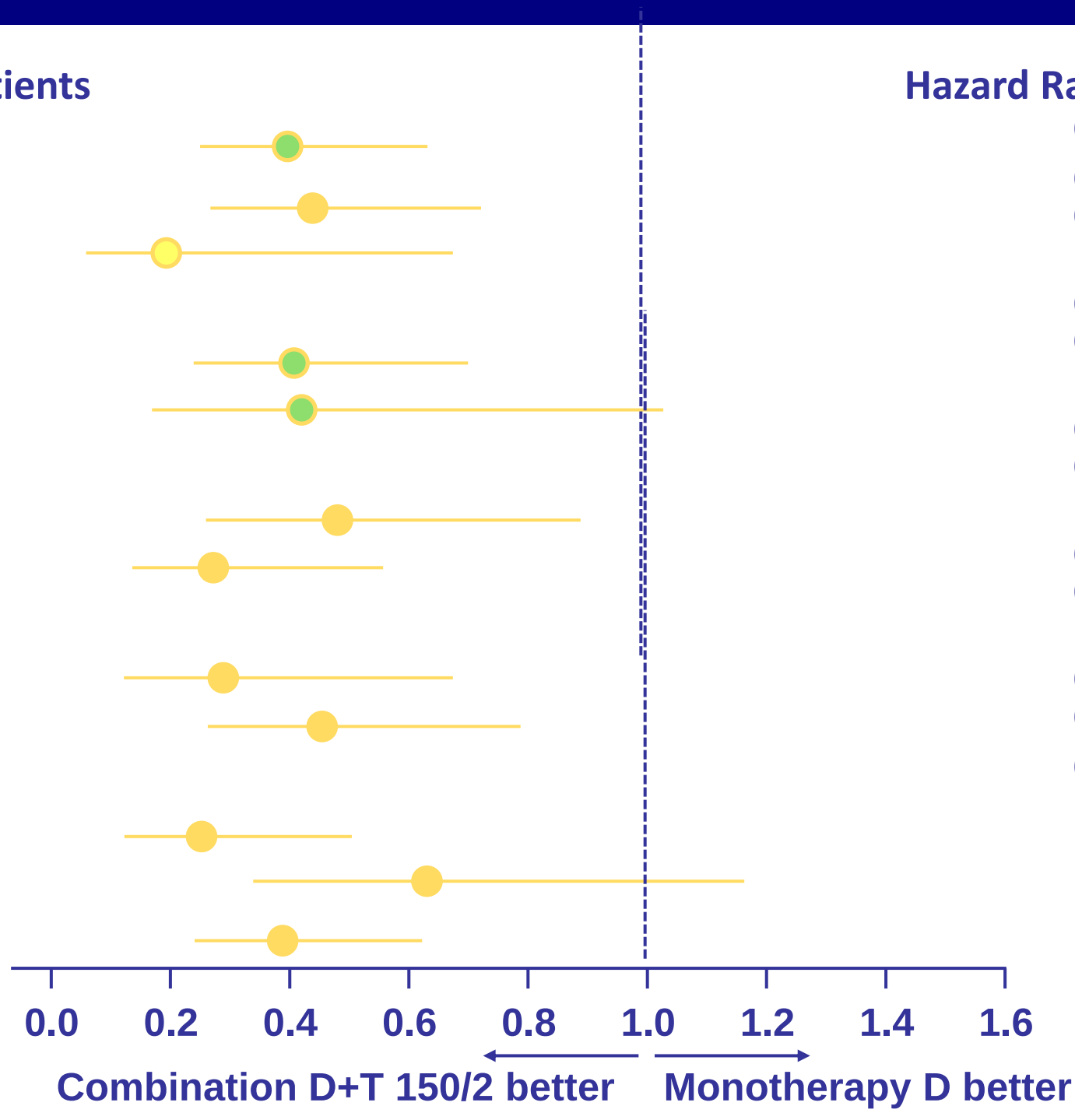
	Med (mos)	HR (95% CI), P-Value	12 mo. PFS rate
Mono D	5.8		9%
150/1	9.2	0.56 (0.37, 0.87), 0.006	26%
150/2	9.4	0.39 (0.25, 0.62),<0.0001	41%

Patients at risk

54	46	25	13	2	0
54	47	33	26	11	1
54	52	36	29	15	1

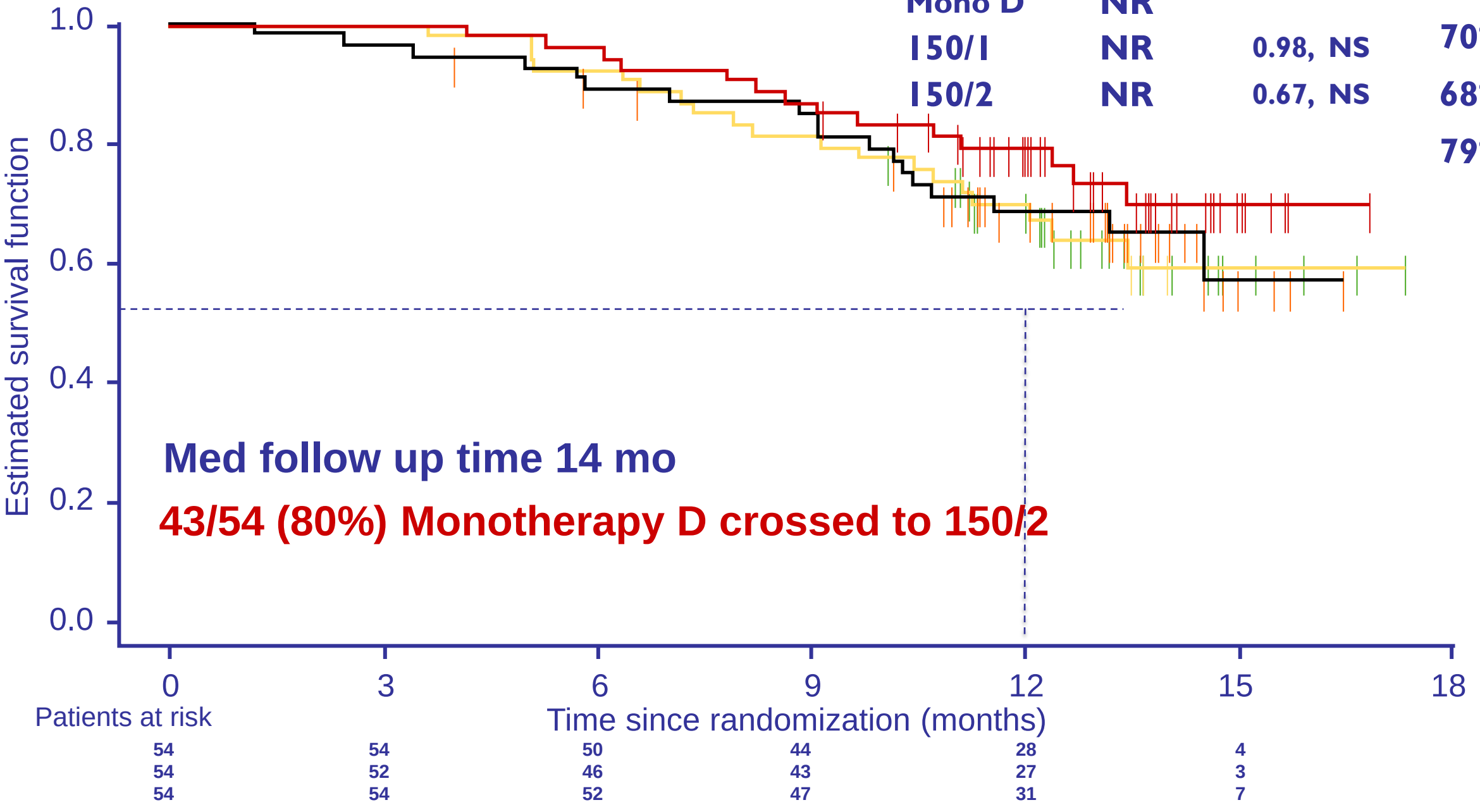
PFS Subgroup Analyses
Combination D+T 150/2 vs Monotherapy D

Subgroup	No. of patients	Hazard Ratio (95% CI)
Overall	108	0.39
V600E	92	0.43
V600K	16	0.19
Age		
<65	85	0.40
≥65	23	0.41
Sex		
Male	63	0.48
Female	45	0.27
Baseline disease stage		
IIIcM0/IVM1a/IVM1b	33	0.28
IVM1c	75	0.45
Baseline LDH		
<ULN	59	0.25
≥ULN	49	0.63
No brain met history	102	0.38



D vs D+T Overall Survival

	Median	HR, P-Value	12 mo. OS rate
Mono D	NR		70%
150/1	NR	0.98, NS	68%
150/2	NR	0.67, NS	79%



Drug Development 2011

- Tumor by evolution is "moving target" which requires repeated portraits and thus sequential biopsies
  - Heterogeneity and innate resistance
  - Acquired resistance
  - Additional mutations

  - MONO-DIMENSIONAL THINKING ABOUT PATHWAYS

A map of human cancer signaling

Qinghua Cui[1], Yun Ma[2], Maria Jaramillo[3], Hamza Bari[1], Arif Awan[1], Song Yang[4], Simo Zhang[2], Lixue Liu[2], Meng Lu[2], Maureen O'Connor-McCourt[3], Enrico O Purisima[1,5] and Edwin Wang[1,5,*]

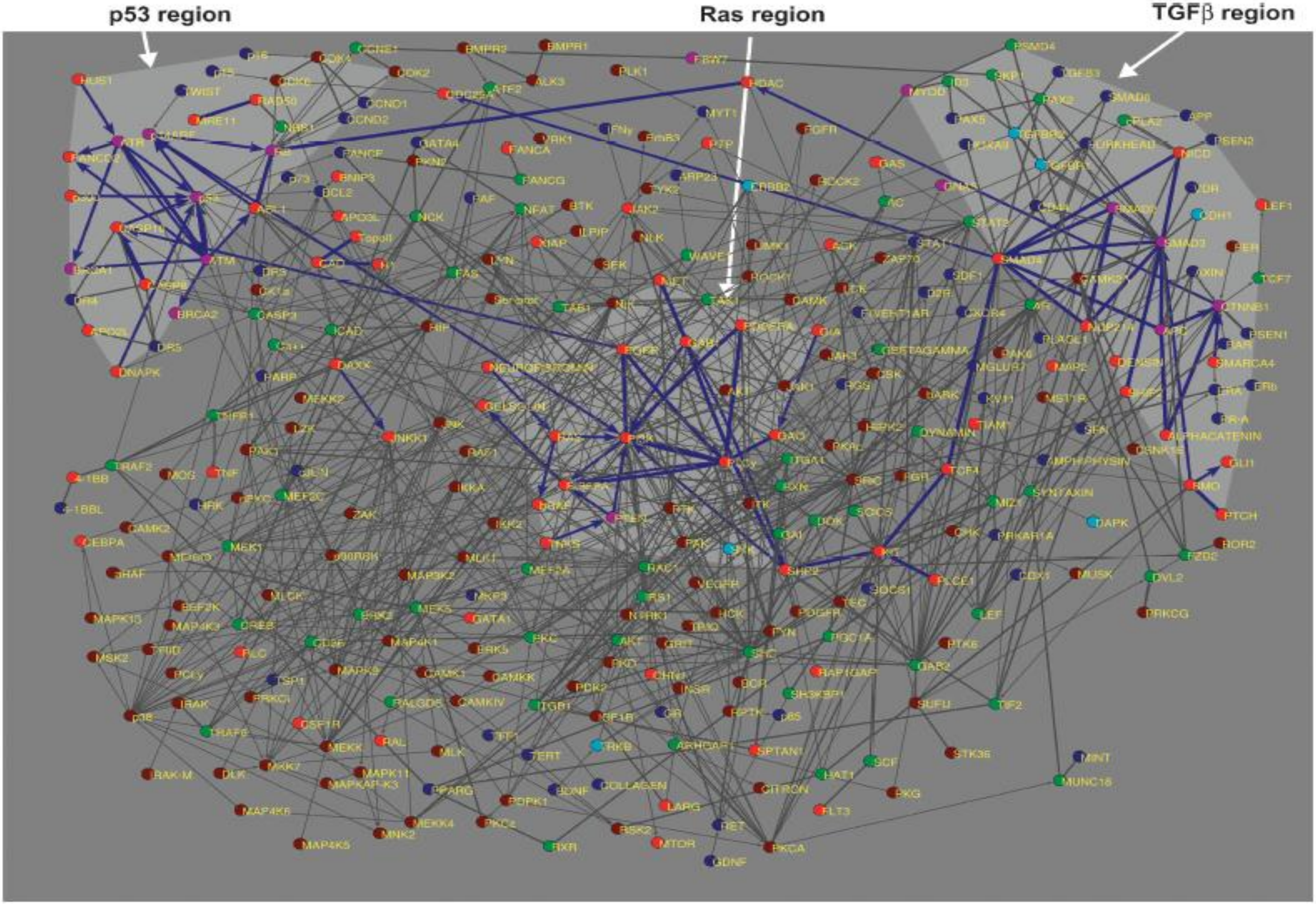


Figure 3 Human oncogene-signaling map. The human cancer-signaling map was extracted from the human signaling network, which was mapped with cancer

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THE MELANOMA PARADIGM

MUTATION DRIVEN DRUG DEVELOPMENT

INNOVATIVE IMMUNOMODULATION

IMMUNOTHERAPY ESTABLISHED
"targeted therapy"

ANTI-CTLA4

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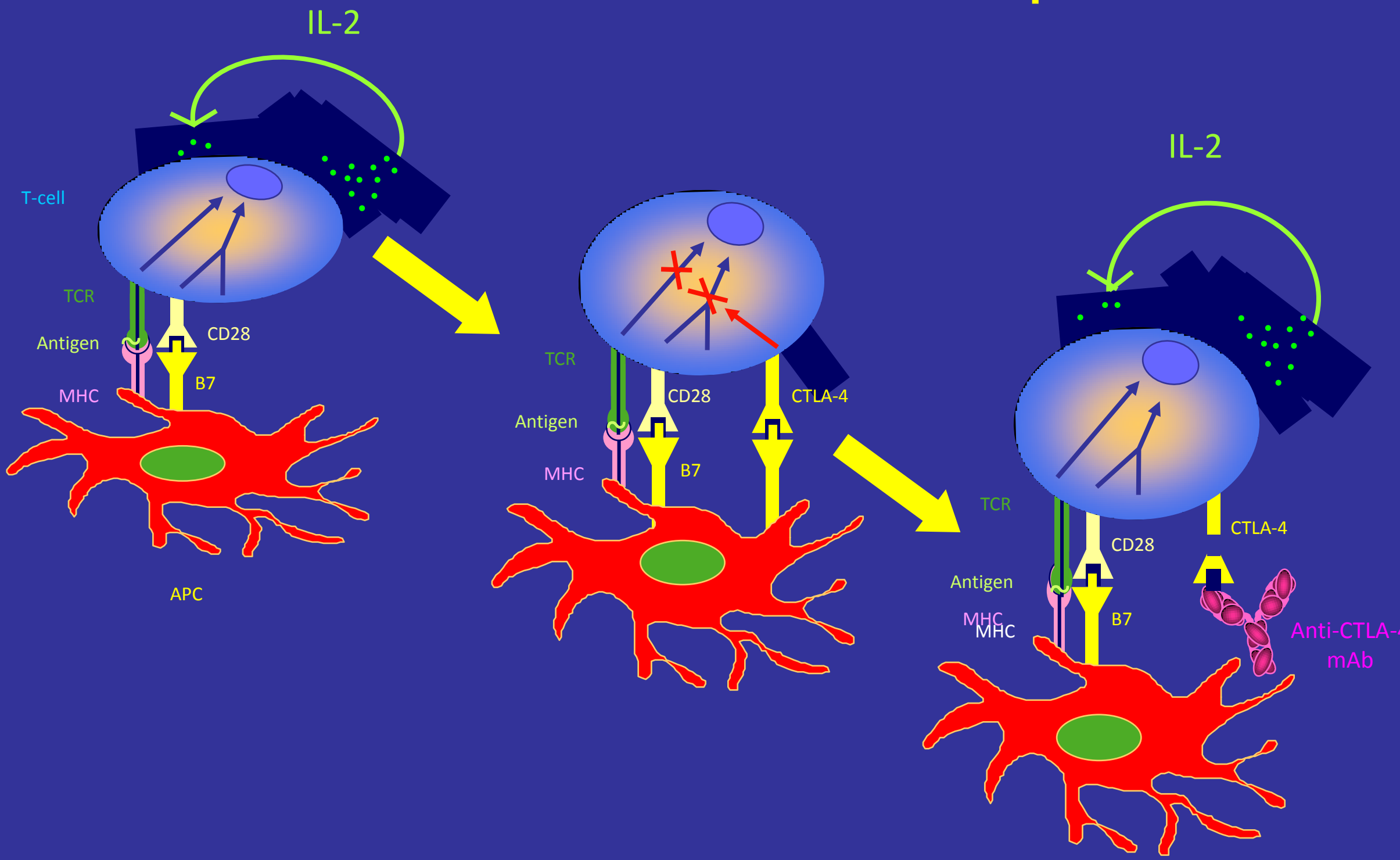
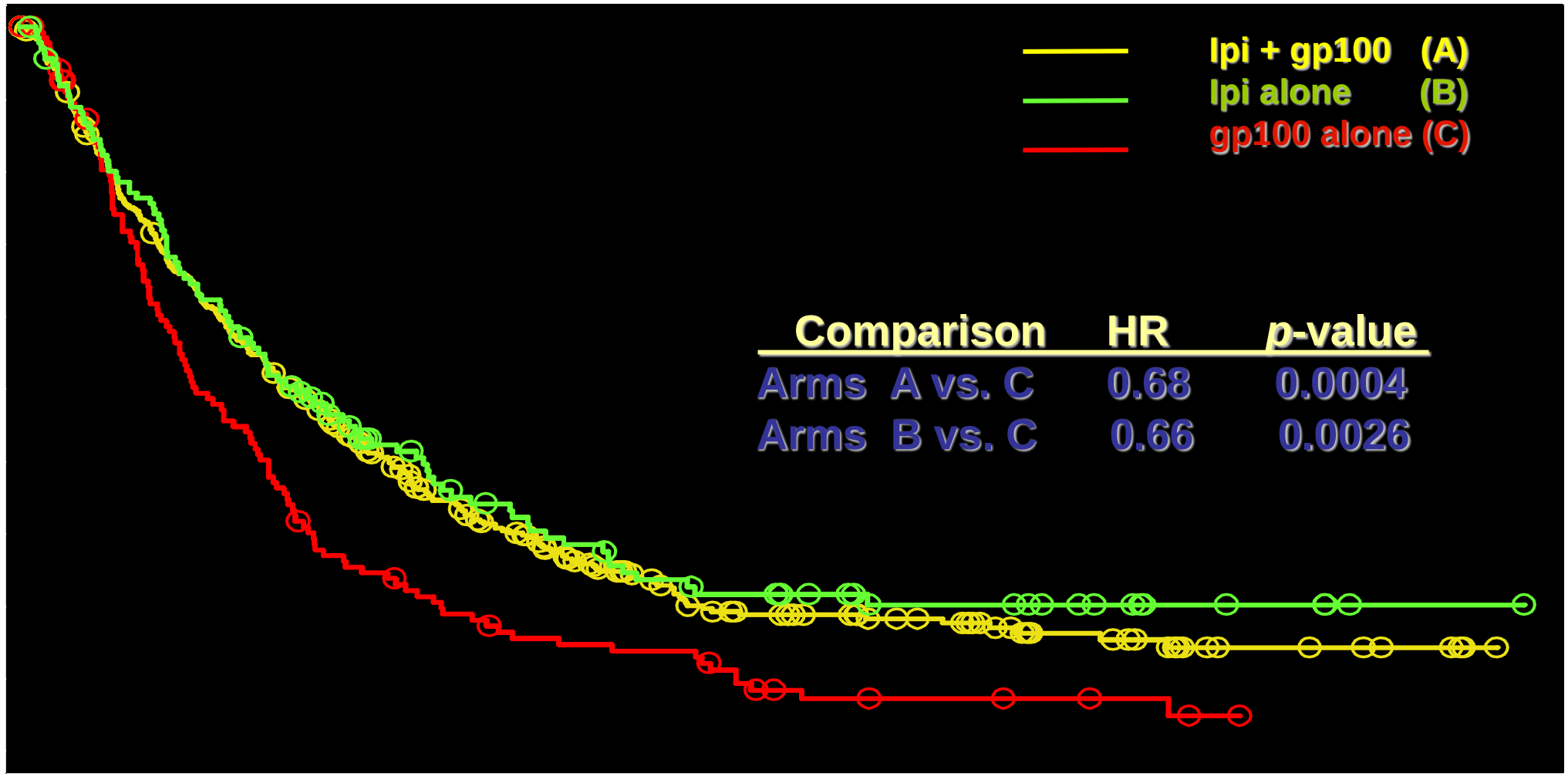
Anti CTLA-4 Monoclonal Antibodies Perpetuate T Cell Activation Reawaken silenced Immune Response

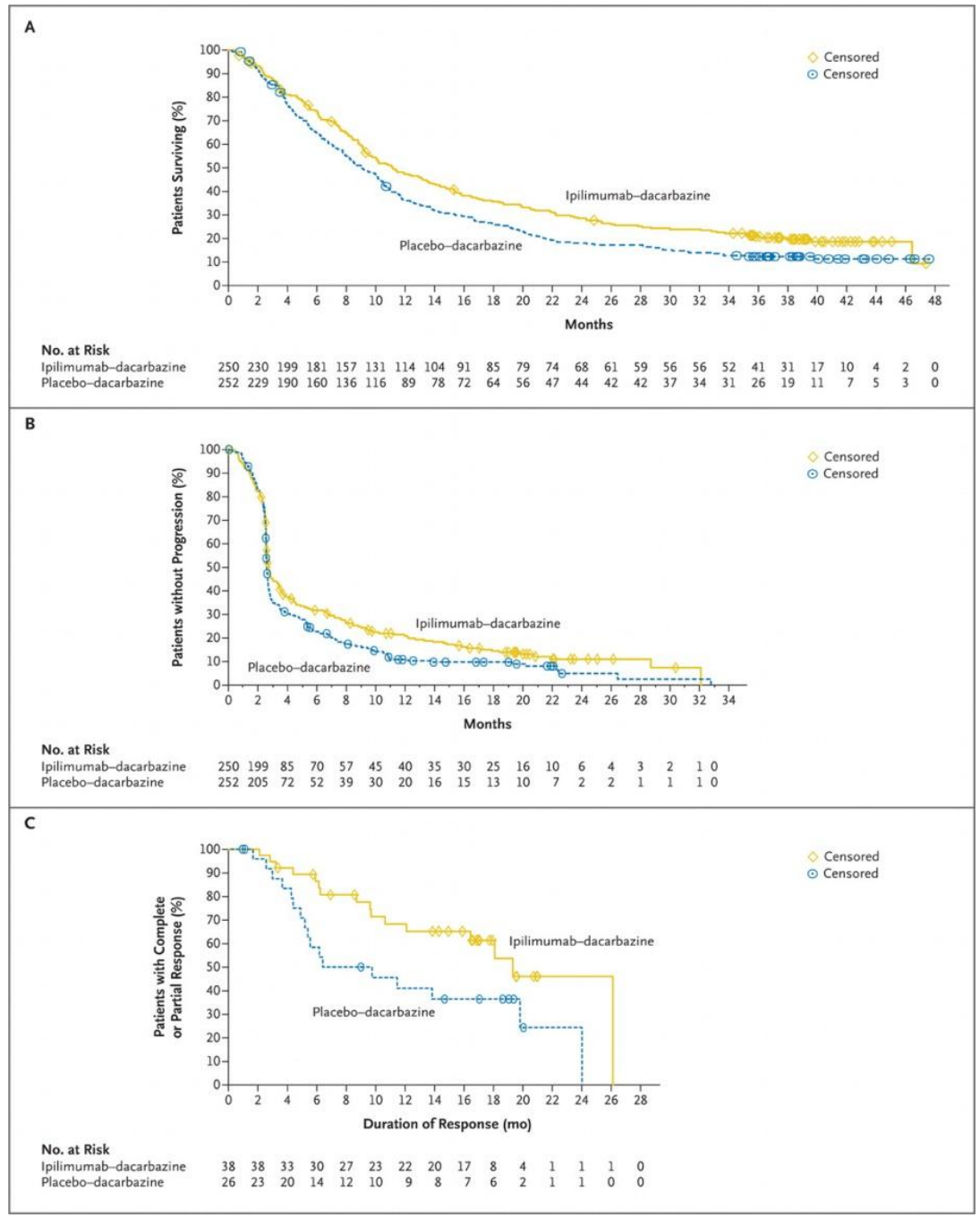


Ipilimumab in Melanoma in 2nd line



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

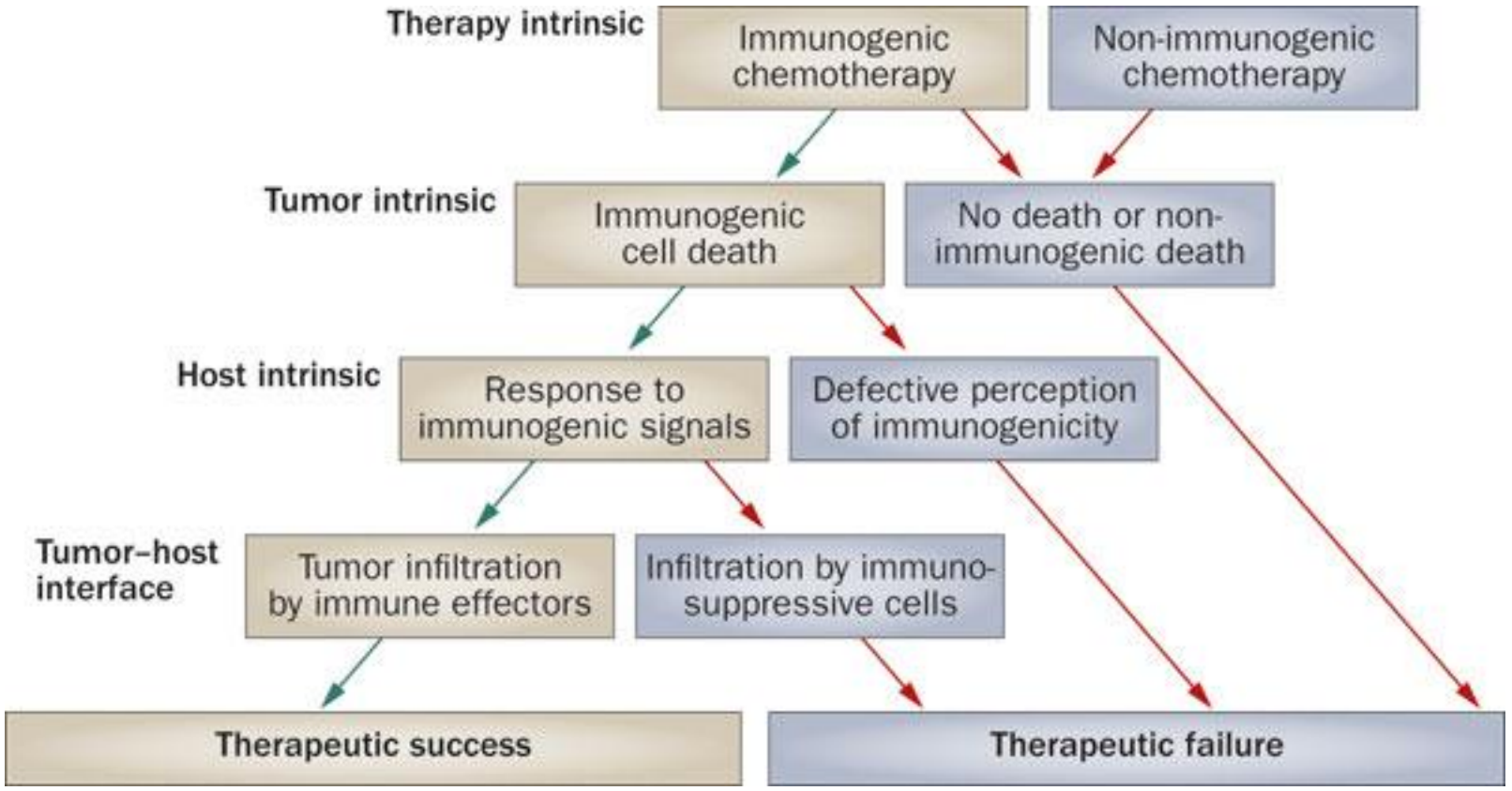
Ipilimumab + DTIC in Melanoma in 1st line.
IMPACT MEDIAN SURVIVAL 2.1 MONTHS



Robert C et al. N Engl J Med 2011.

ZITVOGEL AND KROEMER

IMMUNOGENIC vs TOLEROGENIC CELL DEATH A CRITICAL DETERMININANT FOR TUMOR CONTROL



Zitvogel, L. *et al.* (2011)
Immune parameters affecting the efficacy of chemotherapeutic regimens
Nat. Rev. Clin. Oncol.

nature REVIEWS CLINICAL ONCOLOGY

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COSTS : a major issue

- **Ipilimumab: 4 injections in 3 months: 88.000 EUROS**
  - → **All melanoma patients are candidate**
  - → **At least 80% will get this : NO BIOMARKER**

- **Vemurafenib for BRAF-mutated: 6 months 56.000 EUROS**
  - → **50% will not progress: another 3 months: 81000 EUROS**
  - → **50% will not progress: another 3 months 112.000 EUROS**
  - → **At progression: eligible for reinduction ipilimumab?: add 88.000**

- BRAFinh +MEKinh: price??
- BRAFinh + Mekinh + Ipilimumab Price ???

- **Vemurafenib + Ipilimumab:**
  - → **> 170.000 - >200.000 EUROS**

The Disneyland Paradigm

- In entertainment and in health care you pay up front
- Everybody should have the right to go to Disneyland during the last year of life
- Disneyland tickets are 150.000 Euros
- What will society do?
  - → Provide tickets at this price with equal access for all
  - → Demand price that would allow equal access for all

Of note: in 2022 the whole health care budget in India could be spent on dealing with diabetes type II management alone

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NOW WHAT ?

BIG IMPACT

in (small) well defined populations

(newly defined diseases)

will decide drug development processes

economic models of molecular medicine

are uncertain

especially if we fail to create CURES

(requests involvement immune system)

Duplication of Effort
Fragmentation of Research
No single institute/nation can do it all

Networking/Consortia is a Must

Noci EORTC
EUROCAN Translational Research Platform
German TR Network
WIN Consortium
etc, etc

THANK YOU

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