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MOLECULAR CANCER MEDICINE

Implications for Integrated Cancer Research and Cancer Care

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UNIVERSITÉ
PARIS-SUD 11

Cancer Worldwide Burden (2008 → 2030)

12.4 million new cases
7.6 million deaths
28 million living with cancer

→

26.4 million new cases
17 million deaths
82 million living with cancer

Courtesy of Peter Boyle. IARC

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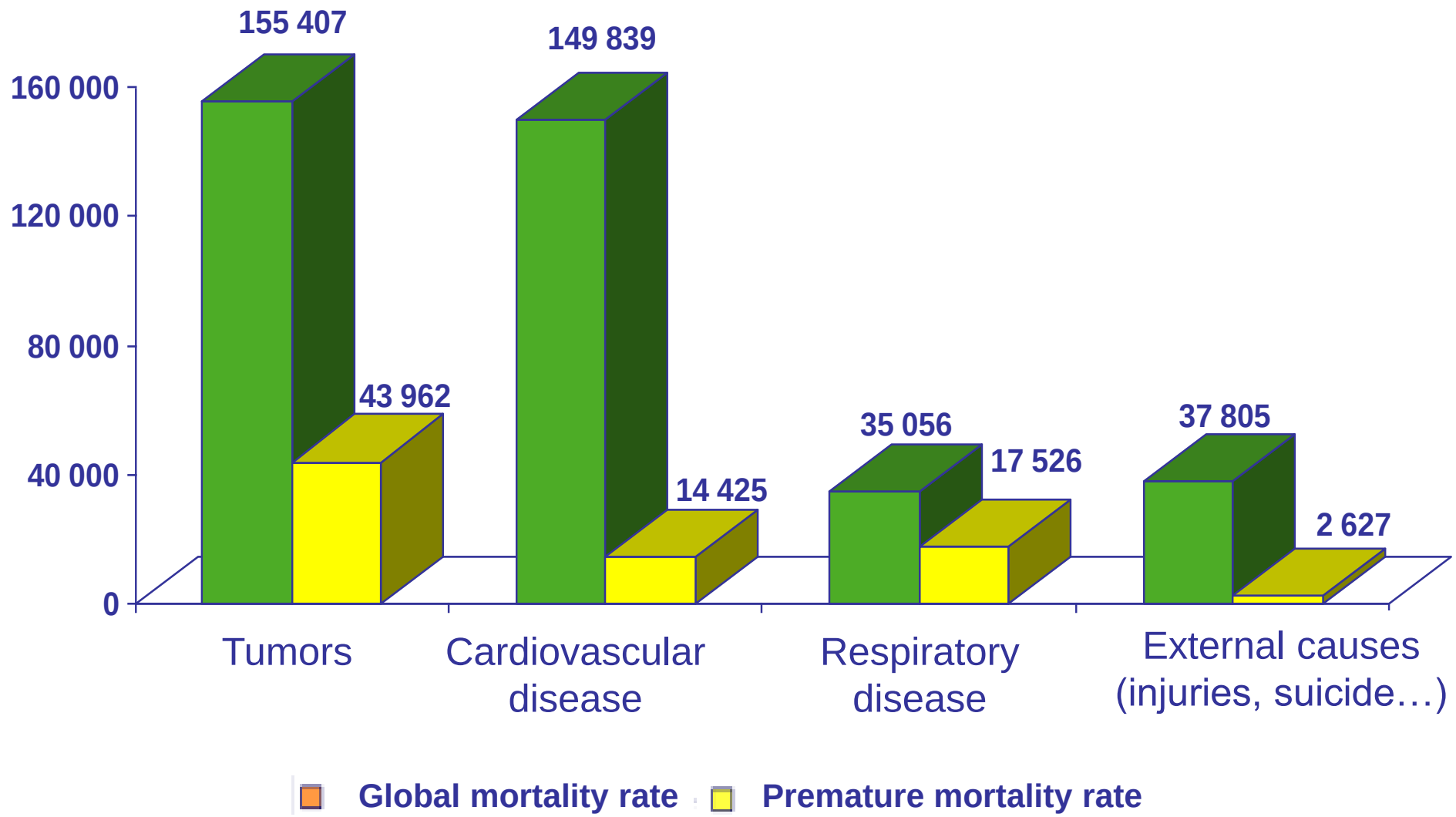
Cancer the leading cause of death over cardiovascular disease

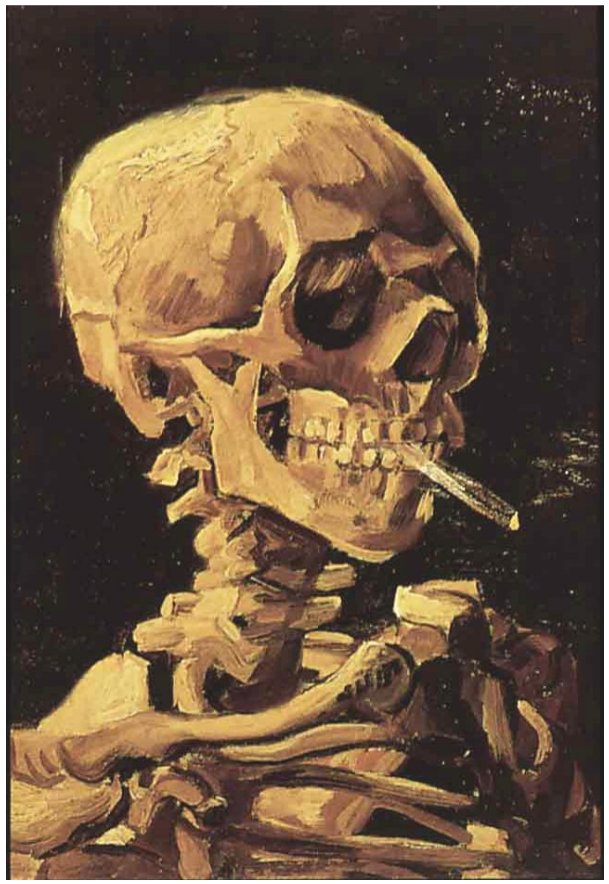
Global and premature mortality rates in France in 2005



Source : CépiDc Database – 2005

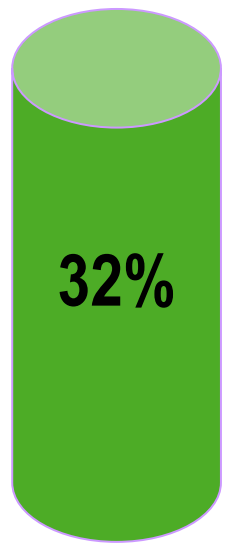
Any obstacles to prevention?

CANCER	France	Europe	World
Incidence	320 000	2 600 000	12 000 000
Mortality	144 000	1 600 000	7 600 000
Prevalence	800 000	8 000 000	28 000 000

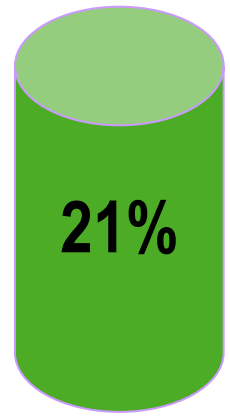


Current smokers in France

Males



Females



IARC 2008; INSERM 2007

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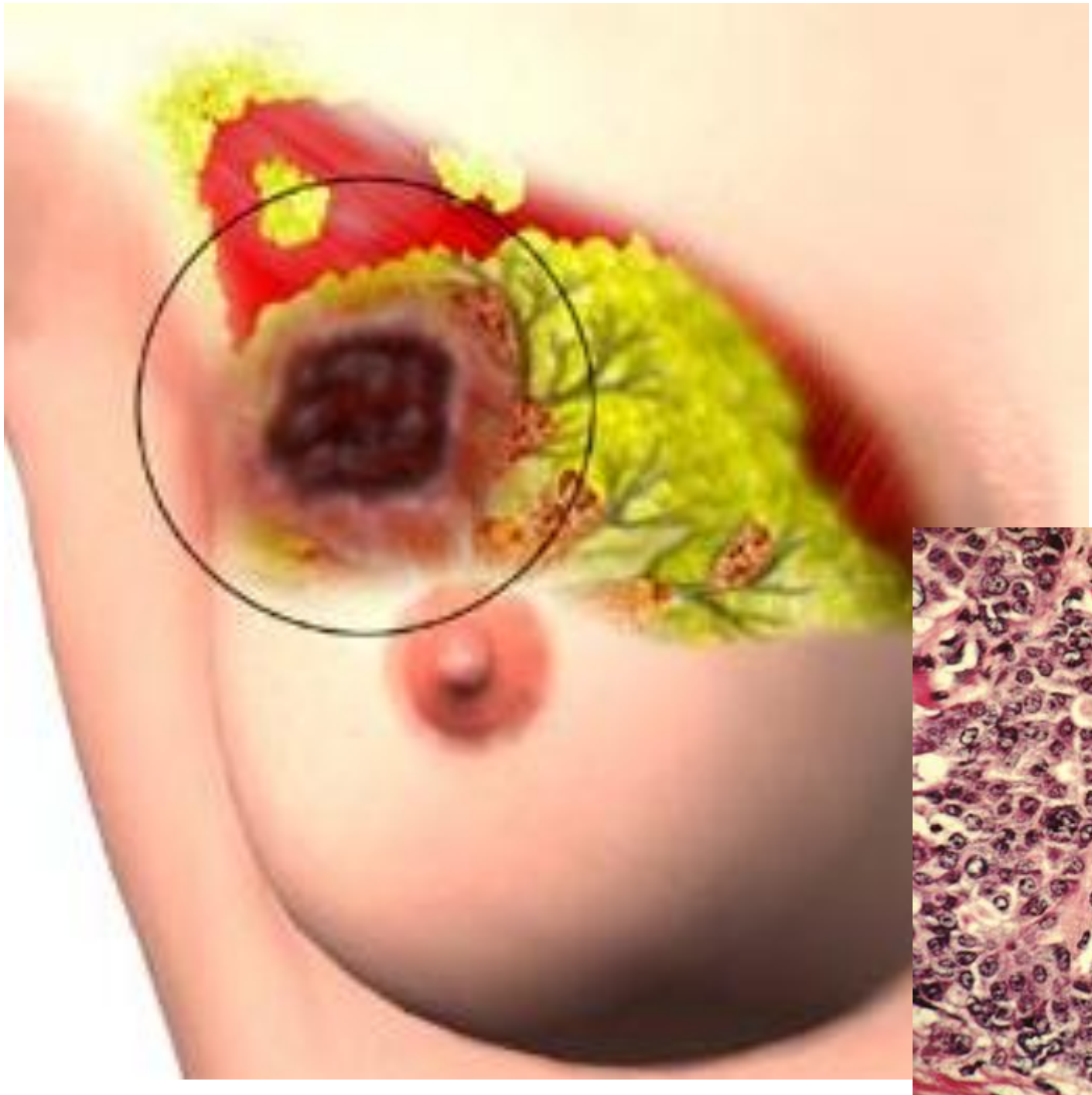
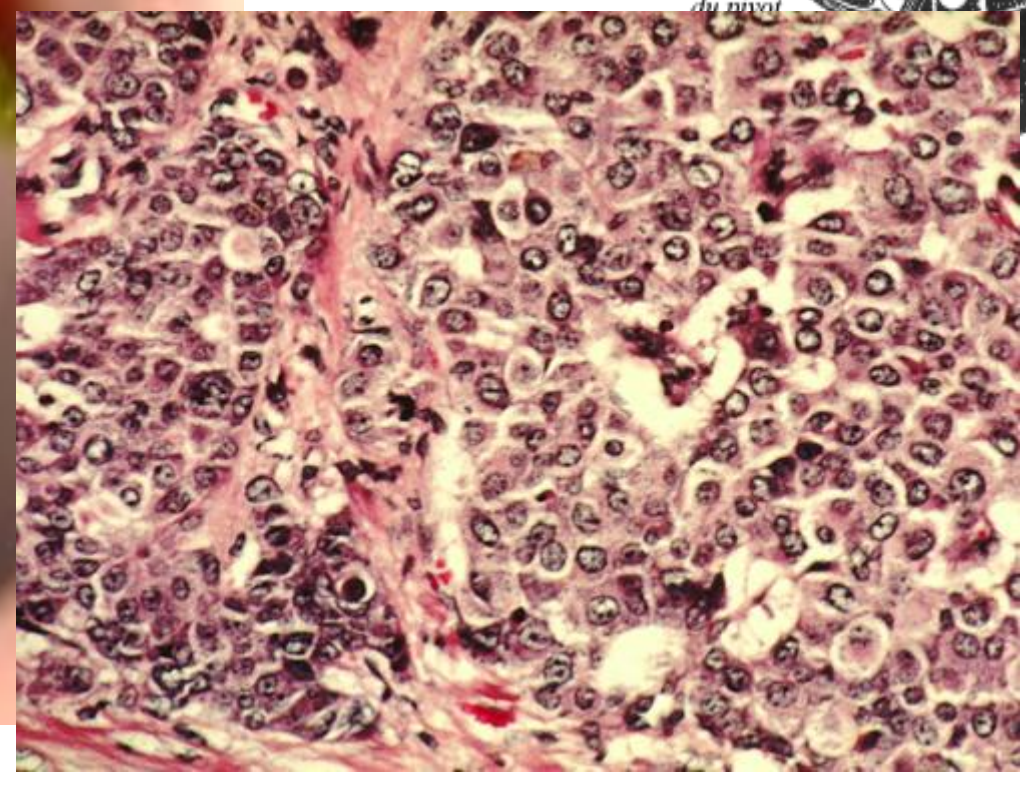
What is breast cancer ? The old perception





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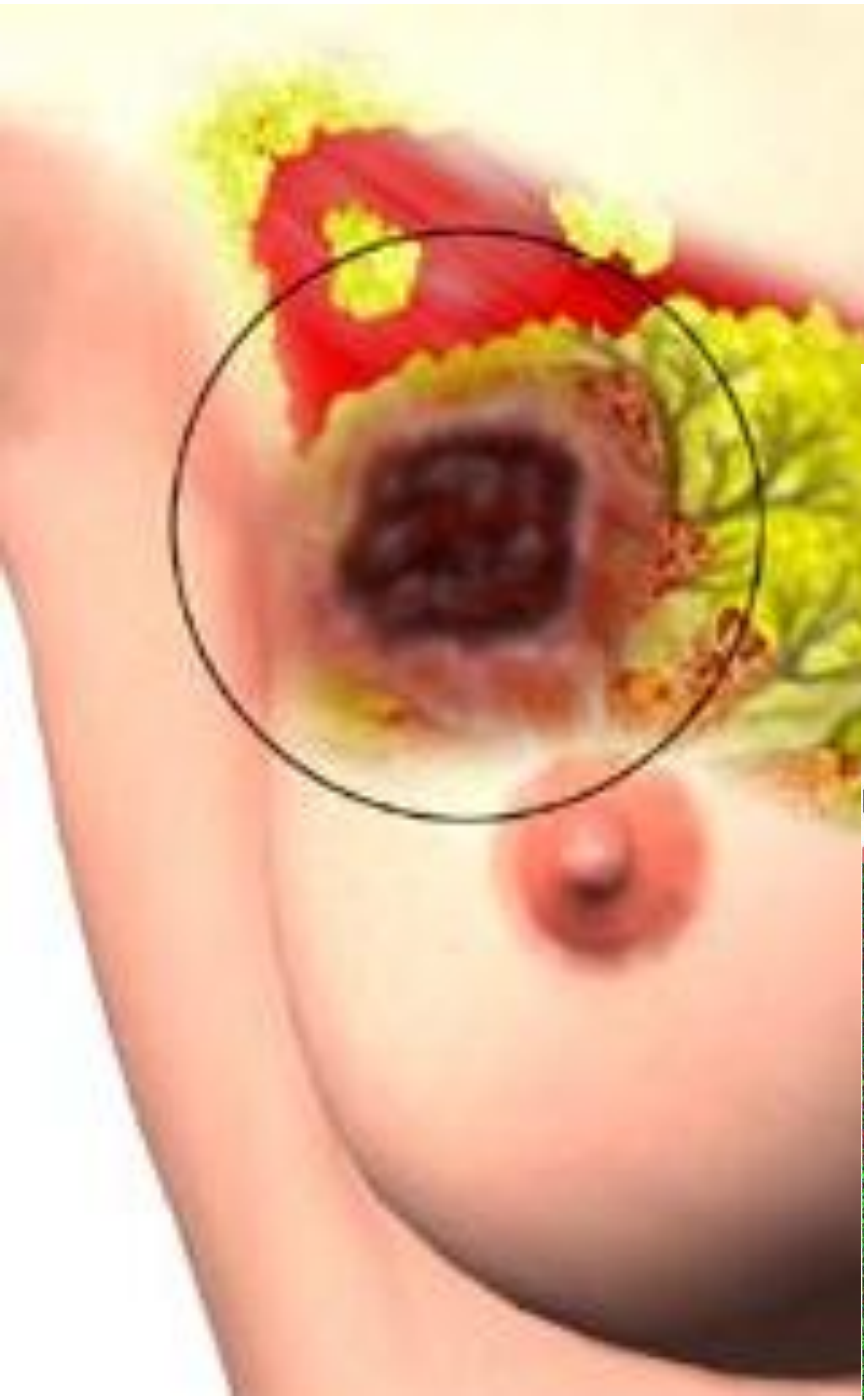
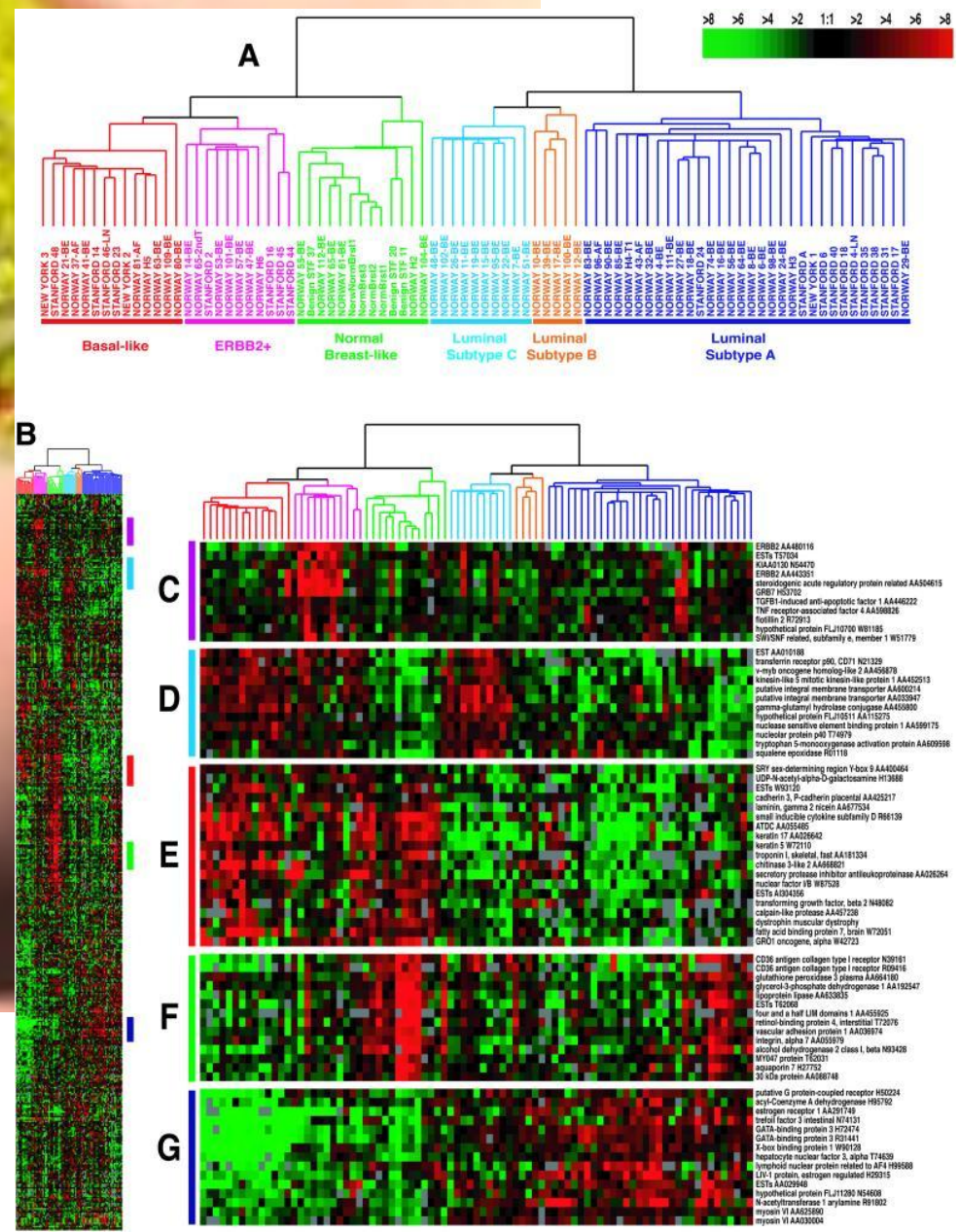
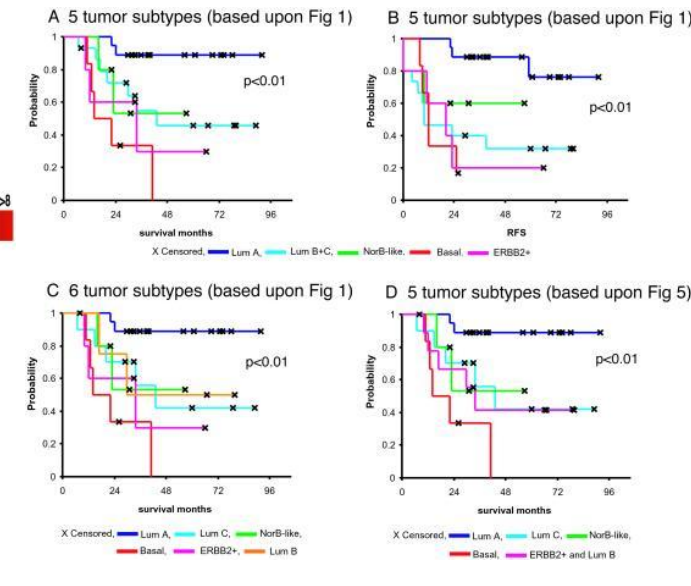
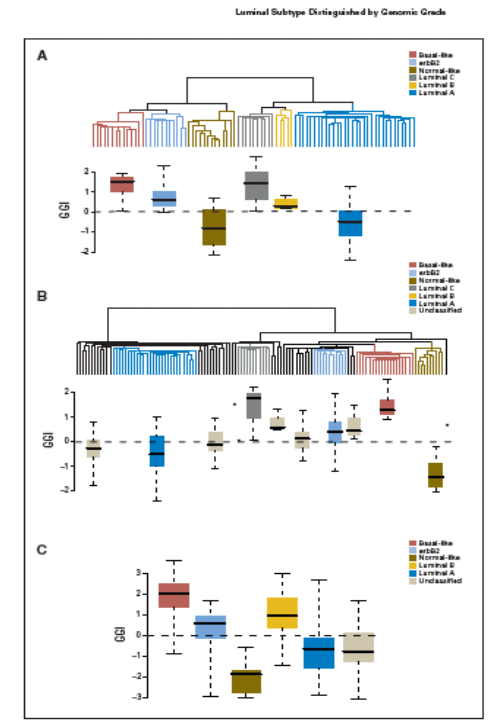
The New Family of Diseases Perception / Molecular Portraits



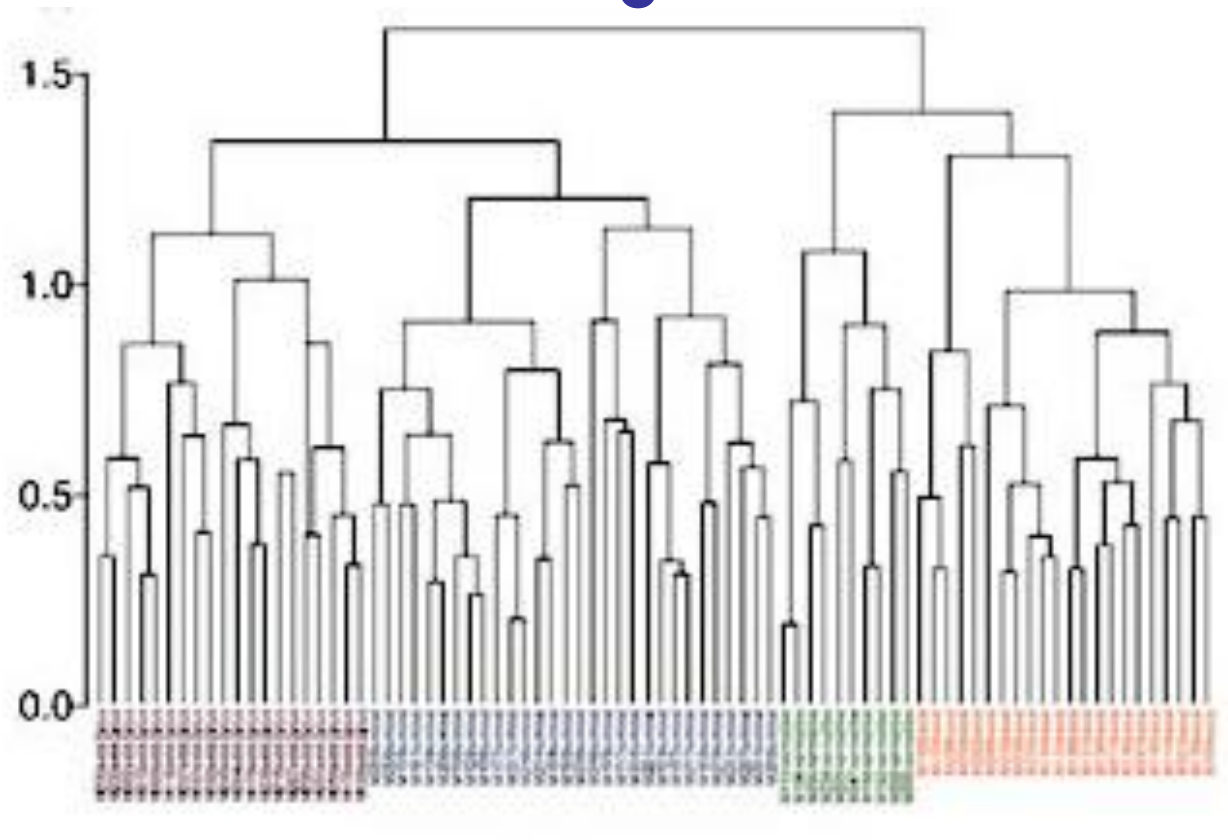






Breast Cancer Molecular Classification: Oncogenic Events

Unsupervised clustering of BC samples (gene expression array)



	HER2+	ER+	HER2–/ER–	
PI3KCA mutations	23%	34%	8%	mTOR
PTEN loss			34%	mTOR
ERBB2 ampli	+++			
FGFR1 ampli		++		
EGFR ampli			+	
IGF1R expression	+	+	+	
BRCA1 mutation			++	
BRCA2 mutations		++		

Andre F. *Nat Clin Pract Oncol* 2006;3:621–32

Breast Cancer 1960

- **Palpable tumor discovered**
- **Tumor biopsy, microscoscopic histopathology**
- **Amputation of the Breast**
  - → **including Axillary Lymphnode Dissection**
- **Radiotherapy to Chest Wall**

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Breast Cancer 2010
Integrative Medicine

- **Chemoprevention ?**
- **Breast Cancer Screening,**
  - → **Stereotactic biopsy – stereotactic excision**
  - → **Breast conserving surgery + Radiotherapy**
- **BRCA1/2 tumors**
  - → **Screening**
  - → **Amputation + Direct Reconstruction**
- **Tumor biopsy, histopathology + molecular portrait**
  - → **ER, PR receptors, Her2Neu positivity,**
- **No More Axillary Lymphnode Dissection? / Less ablations**

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Breast Cancer 2010
Integrative Medicine

- **Larger tumors**
  - → **Induction chemotherapy + breast conserving surgery+ radiotherapy**
- **Adjuvant Therapies**
  - → **Chemo, hormonal, both. Herceptin**
  - → **NEO-adjuvant therapies – future?**
- **Metastatic disease**
  - → **Multiple lines hormonal therapies**
  - → **Multiple lines chemotherapy**
  - → **New targeted therapies (herceptin, PARBinhibitors, etc etc)**

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Breast Cancer Anno 2007……..

- Breast Cancer fragments into many relatively rare tumors
- THIS IS HAPPENING IN MOST TUMORS
- Where national trials used to be able to provide answers in BC and other BIG 4 tumors multinational trials and intergroup trials will be necessary to address the current situation

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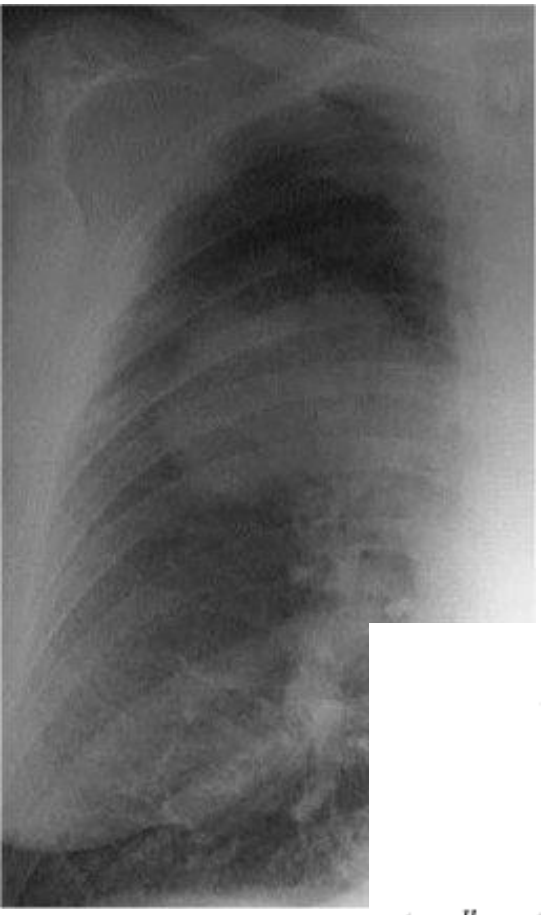
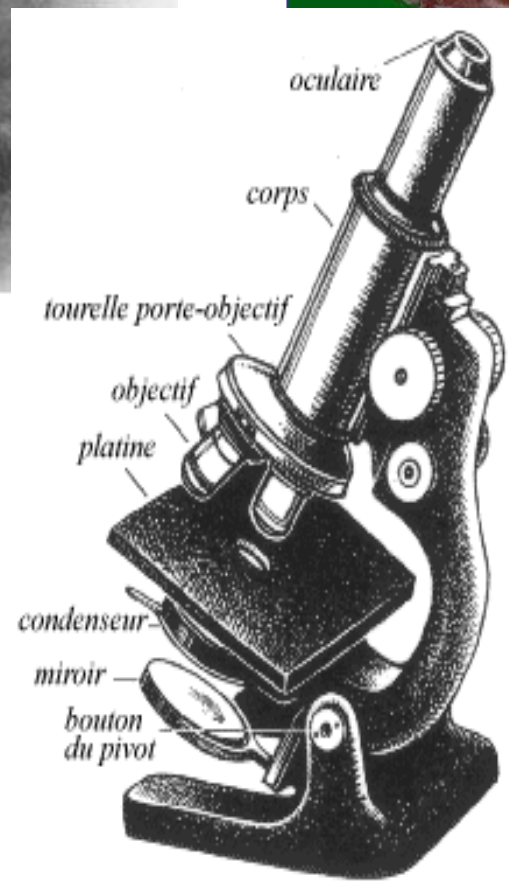
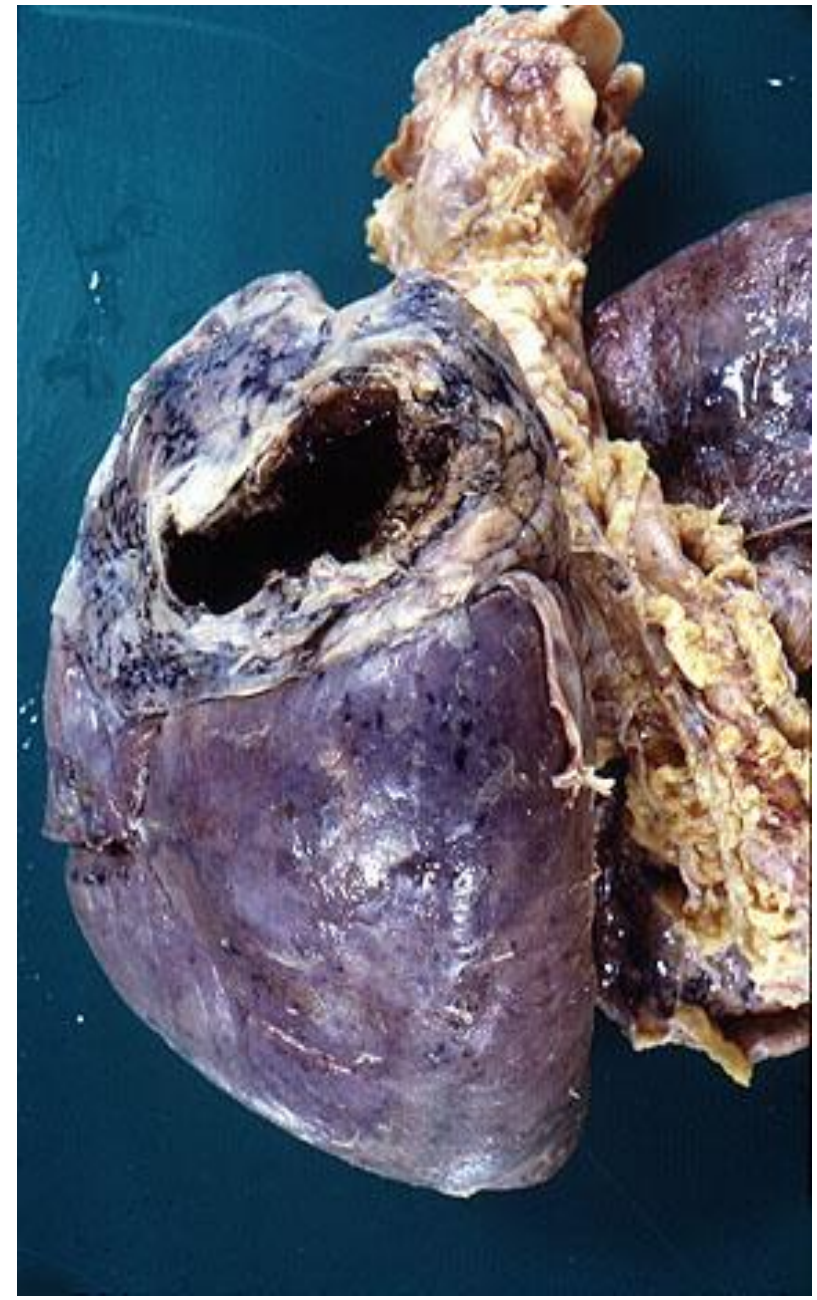
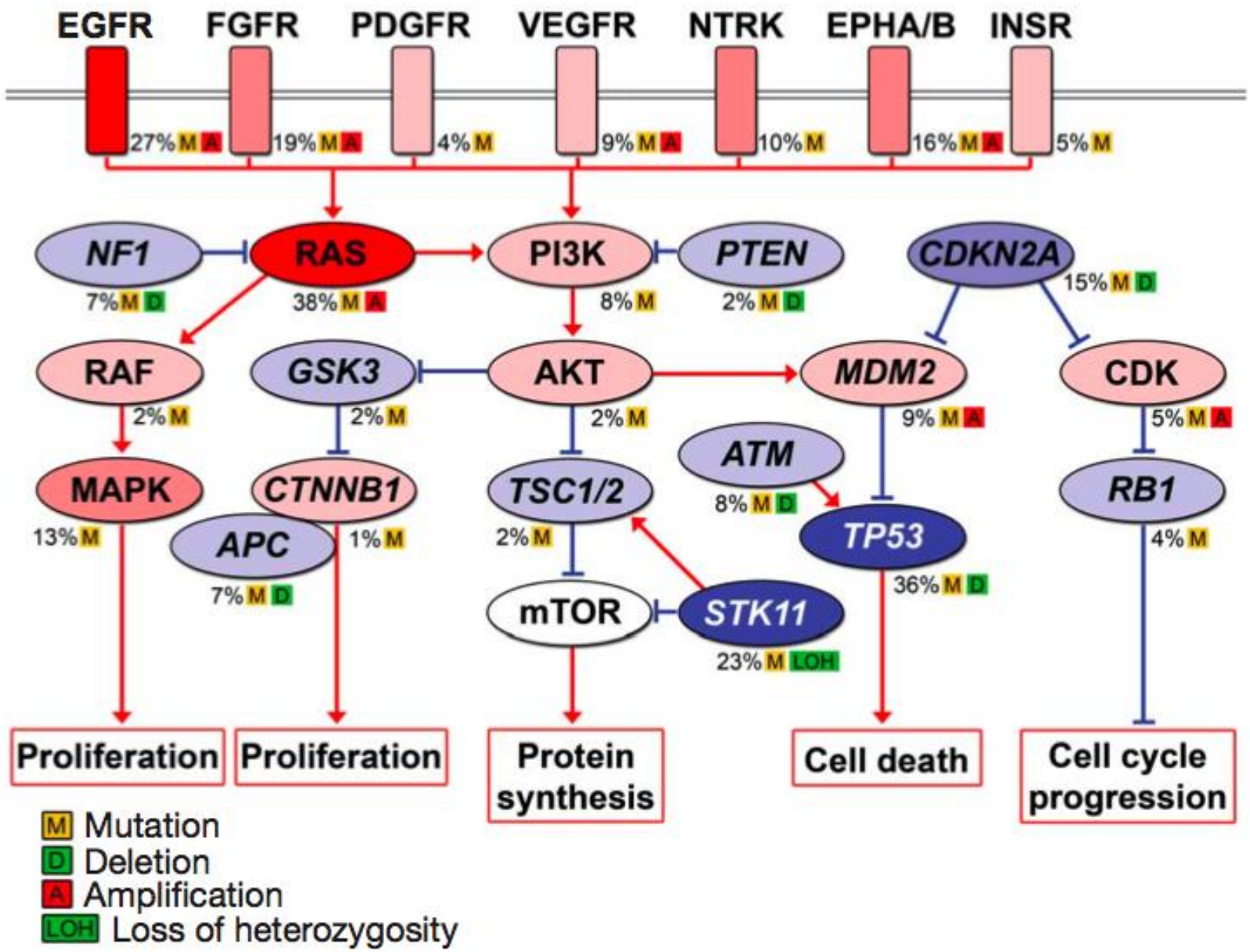
What is lung cancer ? The old perception







Significantly mutated pathways in adenocarcinoma of the lung



Ding et al. Nature 455, 1069, 2008

Common Denominator Driver Genes ....

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 18, 2007 VOL. 356 NO. 3

The Prognostic Role of a Gene Signature from Tumorigenic Breast-Cancer Cells

Rui Liu, Ph.D., Xinhao Wang, Ph.D., Grace Y. Chen, M.D., Ph.D., Piero Dalerba, M.D., Austin Gurney, Ph.D., Timothy Hoey, Ph.D., Gavin Sherlock, Ph.D., John Lewicki, Ph.D., Kerby Shedden, Ph.D., and Michael F. Clarke, M.D.

ABSTRACT

BACKGROUND

Breast cancers contain a minority population of cancer cells characterized by CD44 expression but low or undetectable levels of CD24 (CD44+CD24−/low) that have higher tumorigenic capacity than other subtypes of cancer cells.

METHODS

We compared the gene-expression profile of CD44+CD24−/low tumorigenic breast-cancer cells with that of normal breast epithelium. Differentially expressed genes were used to generate a 186-gene "invasiveness" gene signature (IGS), which was evaluated for its association with overall survival and metastasis-free survival in patients with breast cancer or other types of cancer.

RESULTS

There was a significant association between the IGS and both overall and metastasis-free survival (P<0.001, for both) in patients with breast cancer, which was independent of established clinical and pathological variables. When combined with the prognostic criteria of the National Institutes of Health, the IGS was used to stratify patients with high-risk early breast cancer into prognostic categories (good or poor); among patients with a good prognosis, the 10-year rate of metastasis-free survival was 81%, and among those with a poor prognosis, it was 57%. The IGS was also associated with the prognosis in medulloblastoma (P=0.004), lung cancer (P=0.03), and prostate cancer (P=0.01). The prognostic power of the IGS was increased when combined with the wound-response (WR) signature.

CONCLUSIONS

The IGS is strongly associated with metastasis-free survival and overall survival for four different types of tumors. This genetic signature of tumorigenic breast-cancer cells was even more strongly associated with clinical outcomes when combined with the WR signature in breast cancer.

From the Departments of Internal Medicine (R.L., G.Y.C., P.D., M.F.C.) and Statistics (K.S.), University of Michigan, Ann Arbor; Oncomed Pharmaceuticals, Mountain View, CA (X.W., A.G., T.H., J.L.); the Stanford Institute for Stem Cell Biology and Regenerative Medicine, Palo Alto, CA (P.D., M.F.C.); and the Department of Genetics, Stanford University School of Medicine, Stanford, CA (G.S.).

Drs. Liu and Wang contributed equally to this article, and Drs. Chen and Dalerba contributed equally to this article.

N Engl J Med 2007;356:217-26.

Table 1. Classification of the 186 Genes in the Invasiveness Gene Signature (IGS).

Class	Genes
Apoptosis	*DPF2, CASP8, BCL2*
Calcium-ion binding	*SCGN, SWAP70, KIAA0276*
Cell cycle	*C10orf9, C10orf7, ALKBH, TOB2*
Cell-surface receptor	*XPR1, CD59, LRP2*
Chemotaxis	*PLP2, MAPK14, CXCL2*
Collagen catabolism	*MMP7*
Differentiation	*MGP, MLF1, FLNB*
Ion-channel activity	*SCNM1*
Membrane protein	*HSPC163, C5orf18, MGC4399, CDW92, TMC4, ZDHHC2, TICAM2, KDELR3*
Metabolism	*GNPDA1, THEM2, DBR1, FLJ90709, FLJ10774, C16orf33, GAPD, LDHA, MR-1, LARS, GTPBP1, PRSS16, WFDC2, AIM1, DHRS6, DHRS4, MGC15429, MGC45840, ECHDC2, GOLGIN-67, AFURS1, KIAA0436, CYP4V2, JTV1*
Methyltransferase	*ICMT, DNMT3A, HNMT, METTL7A, METTL2*
Morphology	*VIL2, TPD52, ARPC5*
Nucleotide binding	*NOL8, NSF, RAD23B, SRP54, HSPA2, PBP, THAP2, CIRBP, SNRPN, KIAA0052*
Phosphatase	*DUSP10*
Proliferation	*SSR1, ERBB4, EMP1, CHPT1, LRPAP1*
Protein binding	*FLJ11752, CSTF1, KLHL20, DNAJC13, APLP2, ARGBP2, DNAJB1, NEBL, SH3BGRL, NUDT5, GABARAPL1, MAPT, DCBLD1*
Protein kinase	*STK39, PAK2, CSNK2A1, PILRB, ERN1, SGKL, WEE1, MAST4, C11orf17*
Protein transport	*NUP37, CLTC, COPB2, SLC25A25*
Signal transduction	*ECOP, PDE8A, STAM, TUBB, SNX6, RAB23, PLAA, STC2, LTF*
Transcription factor	*ISGF3G, ATXN3, GTF3C3, GSK3B, KLF10, ELL2, ZBTB20, IRX3, ETS1, SERTAD1, MGC4251, MAFF, SFPQ, CITED4, CEBPD, EIF4E2*
Transferase	*HS2ST1, AGPS, PGK1, ATIC, ETNK1, ALG2*
Ubiquitination	*NCE2, MARCH8, CNOT4, RNF8, PSMA5, DPF2*
Function unknown	*AMMECR1, KIAA1287, LOC144233, LOC286505, PNAS-4, FLJ20530, THUMPD3, MGC45564, CAP350, ETAA16, HAN11, DNAPTP6, C7orf25, FLJ37953, FLJ10587, C7orf36, ELP4, NDEL1, NPD014, DKFZP564D172, FAM53C, IER5, LOC255783, KIAA0146, KIAA0792, LOC439994, LOC283481, CG018, LOC130576, NGFRAP1L1, KIAA1217, C4orf7, C21orf86, C9orf64, FLJ13456, KIAA1600, B7-H4, LOC80298, C7orf2, NUCKS, DKFZP566D1346, LOC388279, FLJ31795, C6orf107, FLJ12439, FLJ12806, FLJ39370*

182 Genes Signature for BC also relevant for Other Tumors

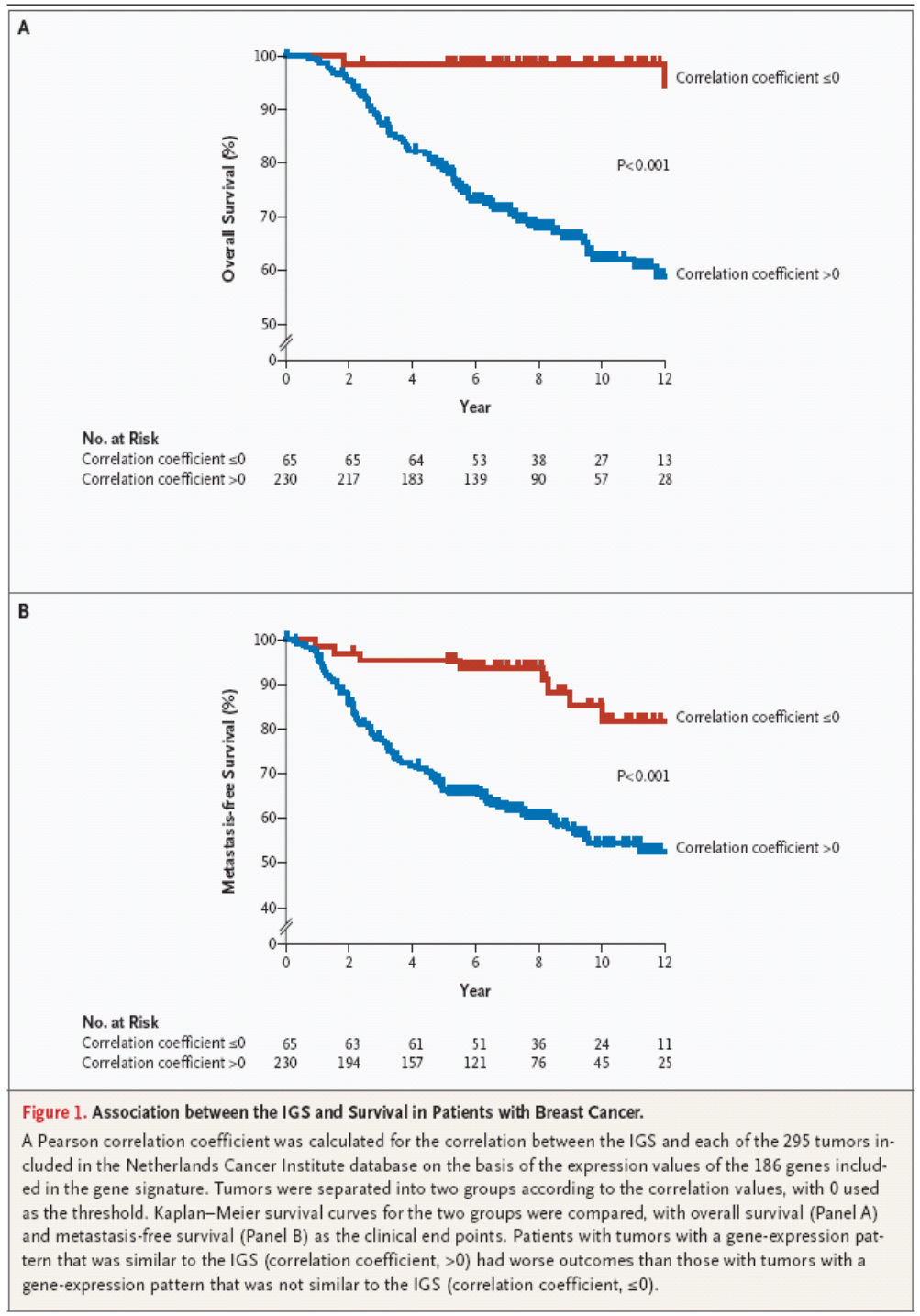
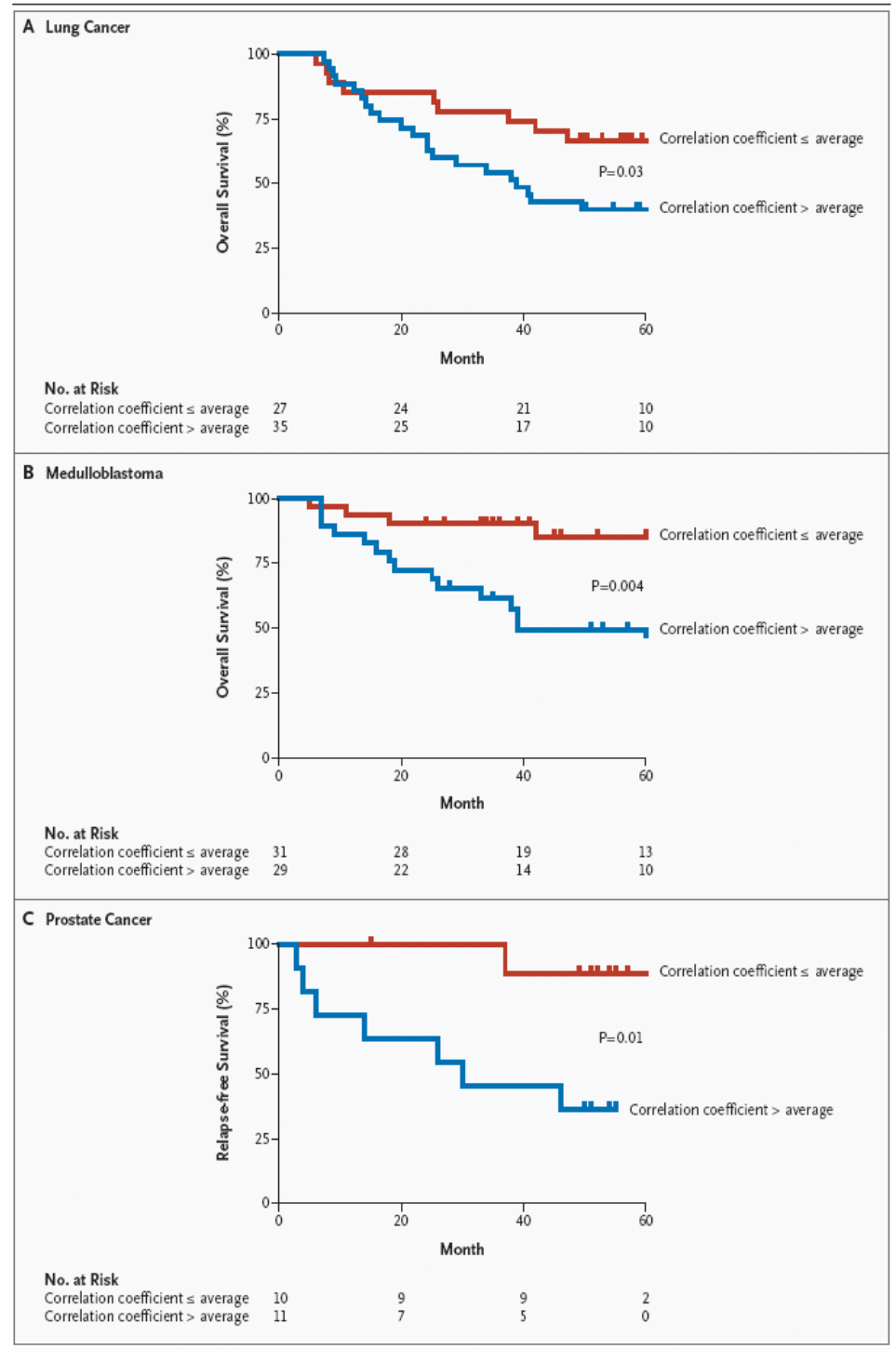


Figure 1. Association between the IGS and Survival in Patients with Breast Cancer.

A Pearson correlation coefficient was calculated for the correlation between the IGS and each of the 295 tumors included in the Netherlands Cancer Institute database on the basis of the expression values of the 186 genes included in the gene signature. Tumors were separated into two groups according to the correlation values, with 0 used as the threshold. Kaplan–Meier survival curves for the two groups were compared, with overall survival (Panel A) and metastasis-free survival (Panel B) as the clinical end points. Patients with tumors with a gene-expression pattern that was similar to the IGS (correlation coefficient, >0) had worse outcomes than those with tumors with a gene-expression pattern that was not similar to the IGS (correlation coefficient, ≤0).



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even the BIG 4 become a collection of many different 'rare' cancers

Implications for internationalizing trials

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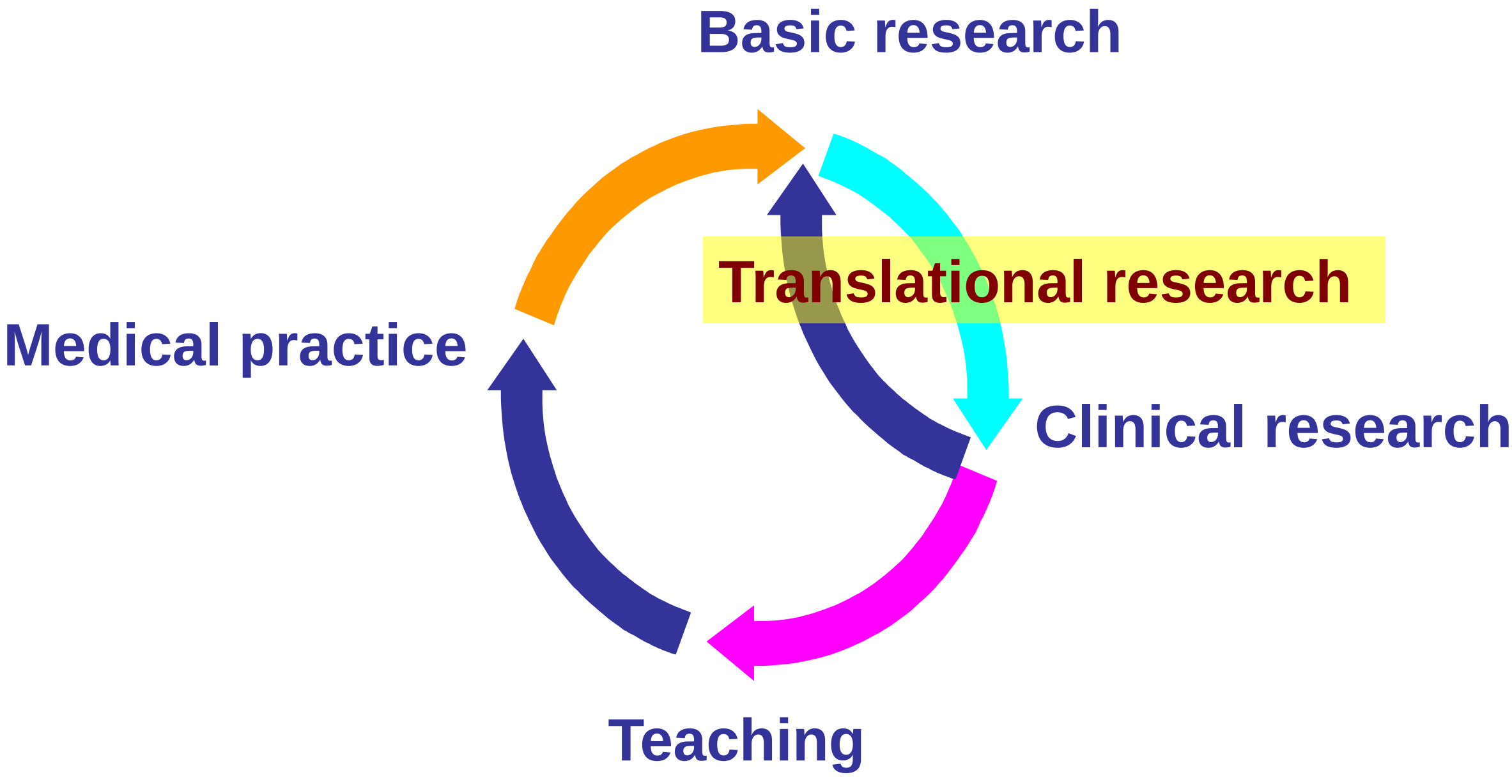
TRANSLATIONAL RESEARCH CRUCIAL COMPONENT OF CLINICAL TRIALS



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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 (intra / interpathway)**
- **Fewer and Smaller Phase III trials**

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THE MELANOMA PARADIGM

- MUTATION DRIVEN DRUG DEVELOPMENT
- INNOVATIVE IMMUNOMODULATION

Alexander M.M. Eggermont, MD, PhD
Cancer Institute Gustave Roussy, Villejuif/Paris, France

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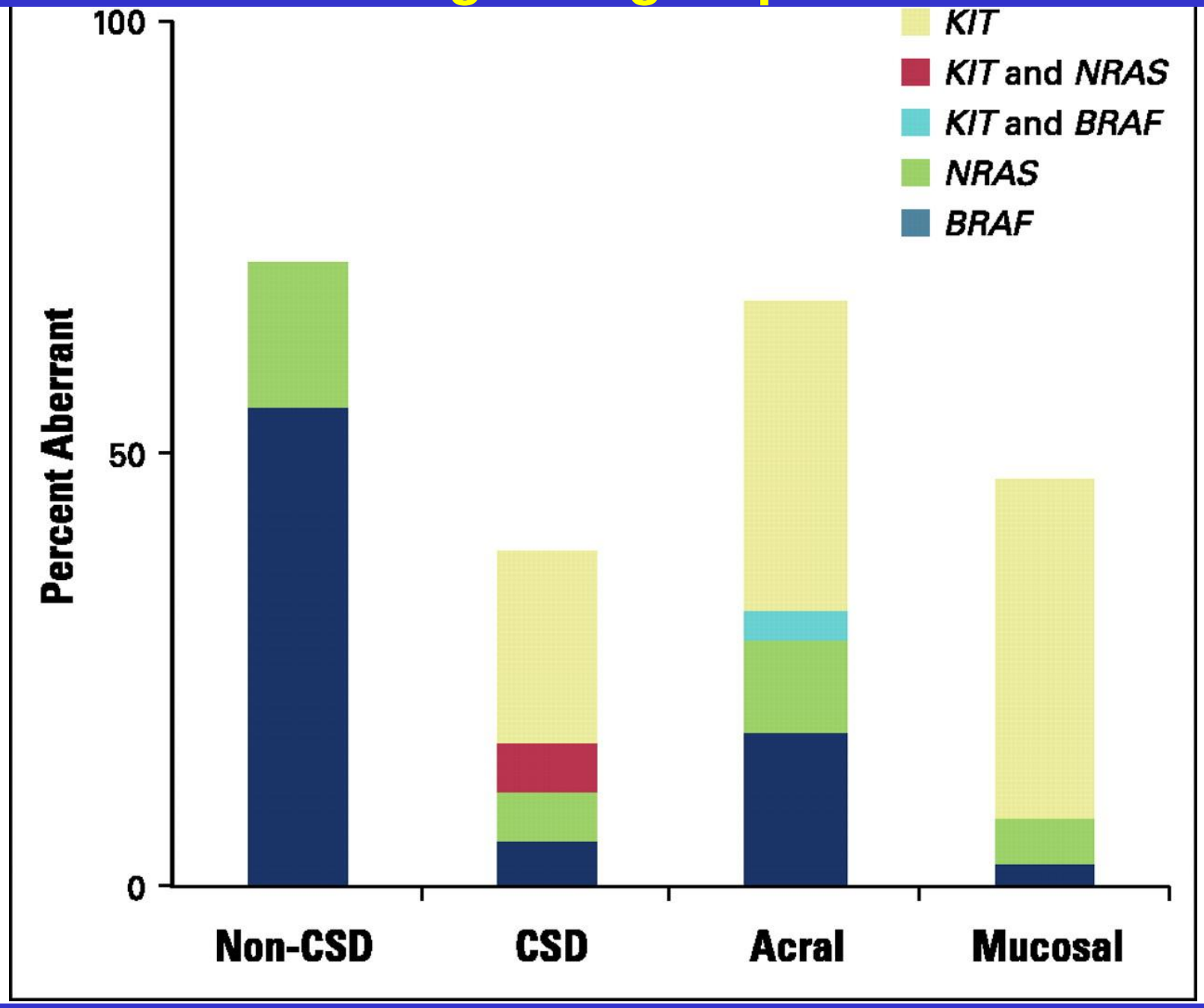
Frequency distribution of genetic alterations in BRAF, NRAS, and KIT among four groups of melanoma



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

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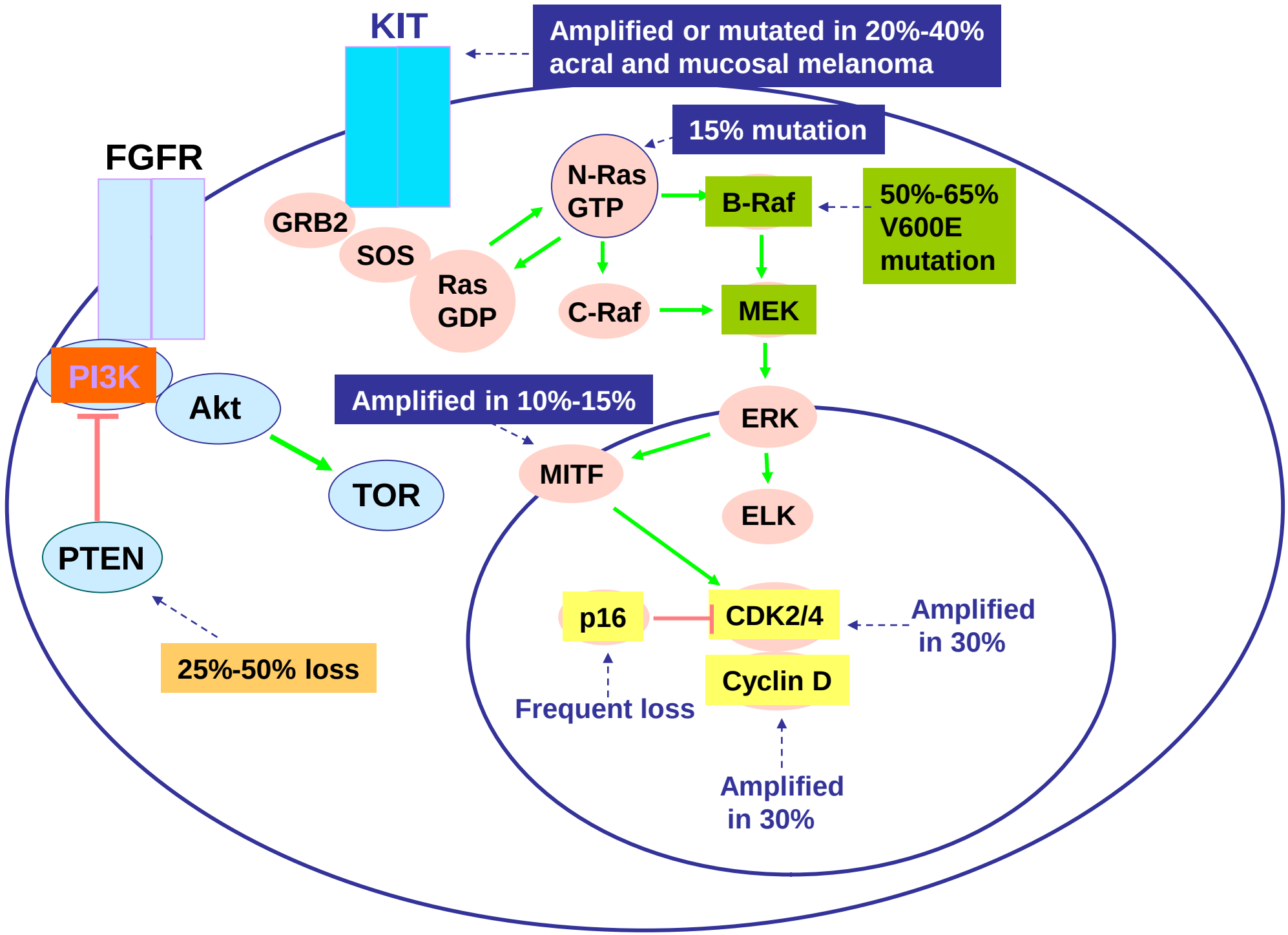
Molecular Alterations in Melanoma



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

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B-RAF INHIBITOR

PLX4032/RG7402

veramufenib

Keith Flaherty et al
NEJM 2010

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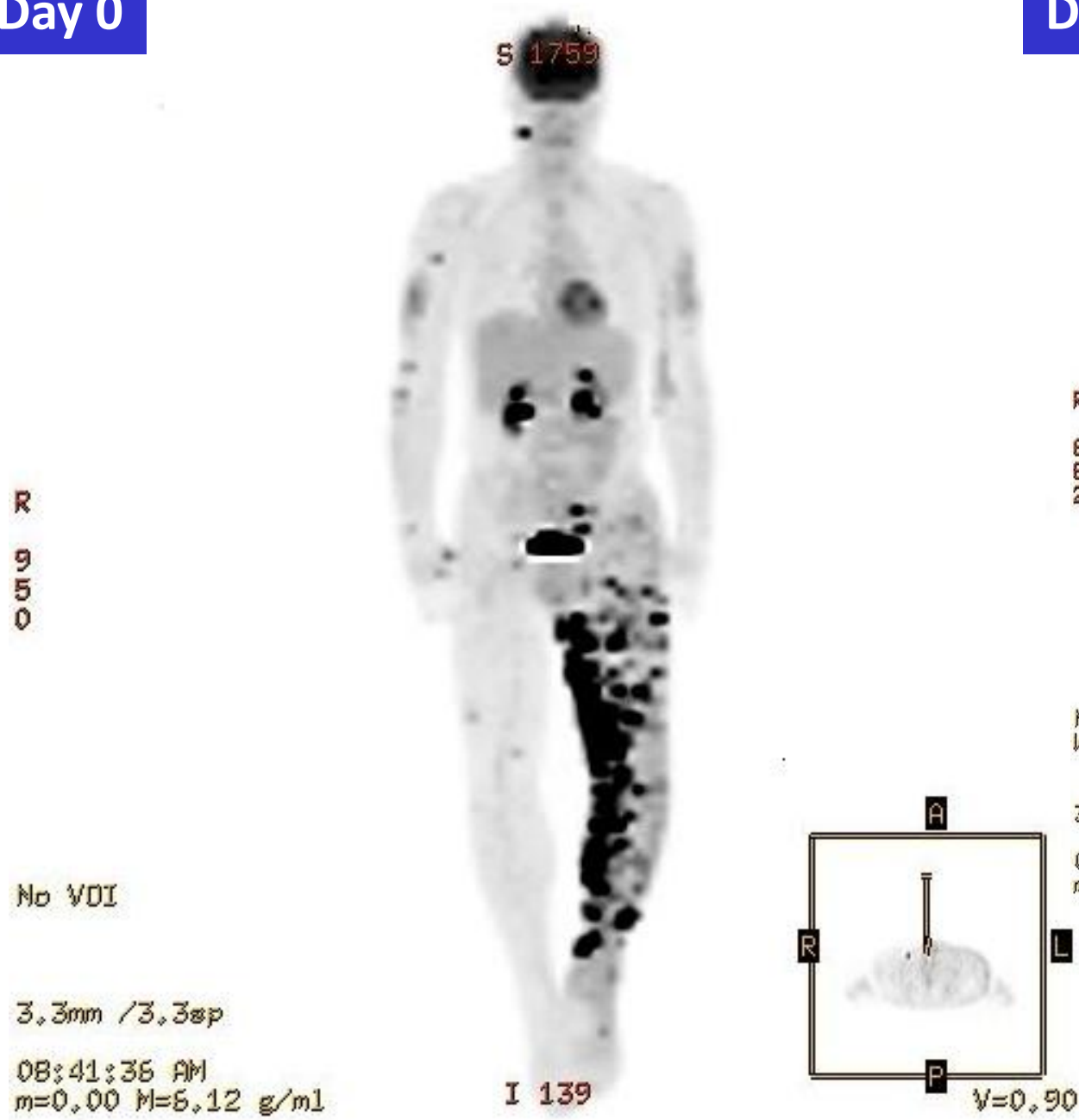
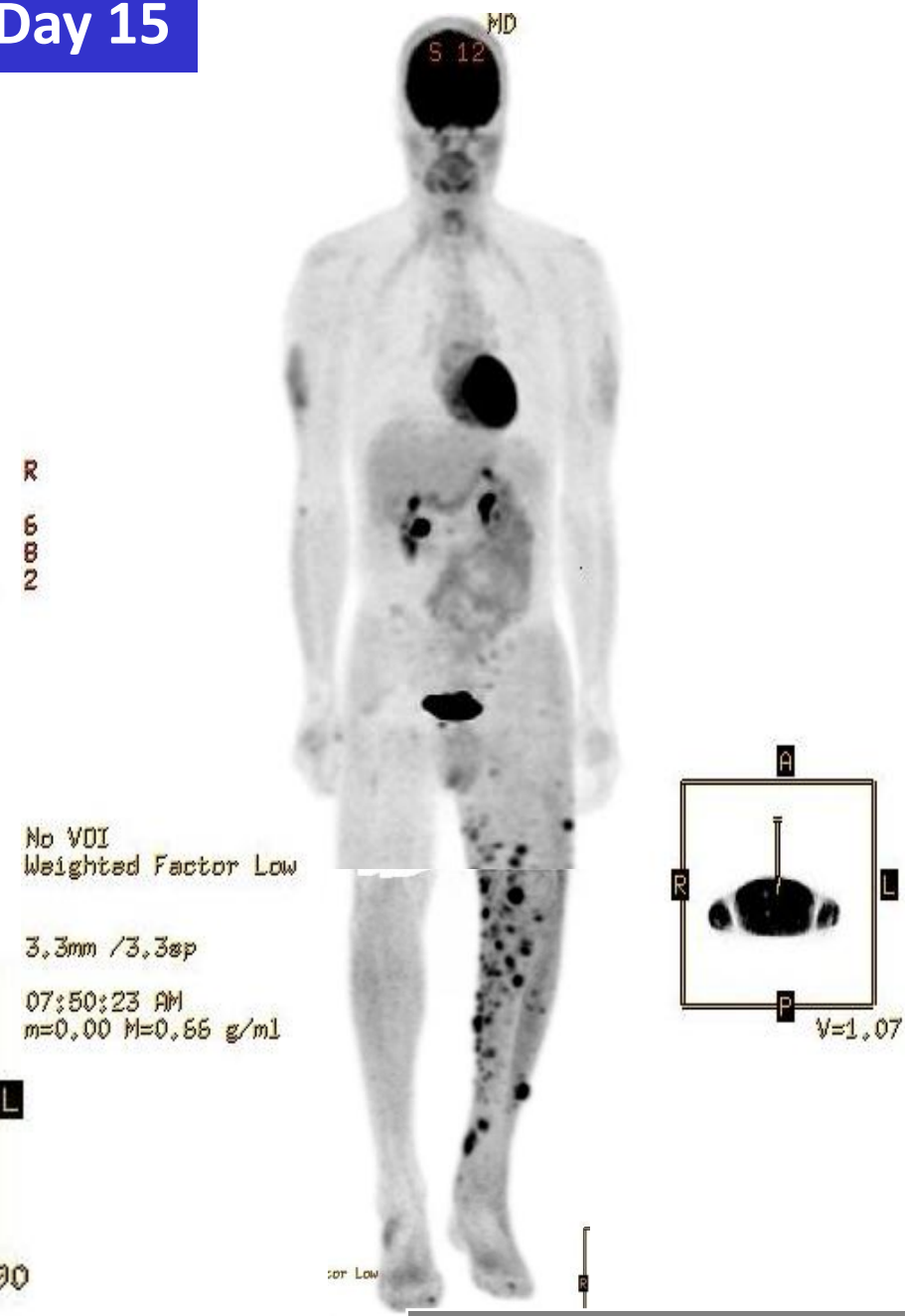
$BRAF^{V600E}$ melanoma patient PET scan at baseline and day +15 after PLX4032 treatment at 320 mg BID

Day 0



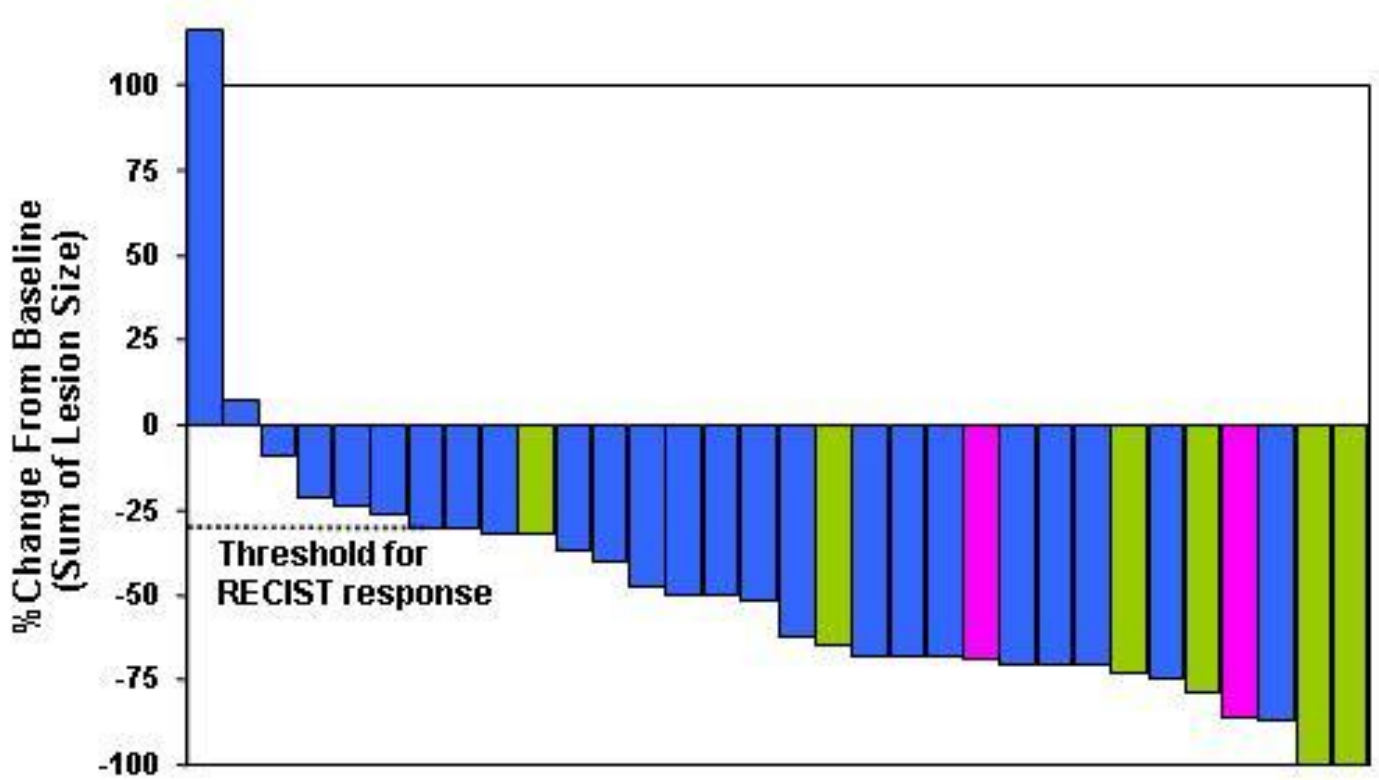
Day 15



Pt 45 – MD Anderson

BRIM I: PLX4032 in stage IV melanoma
81 % RR

Figure 3a



Flaherty et al., NEJM 2010

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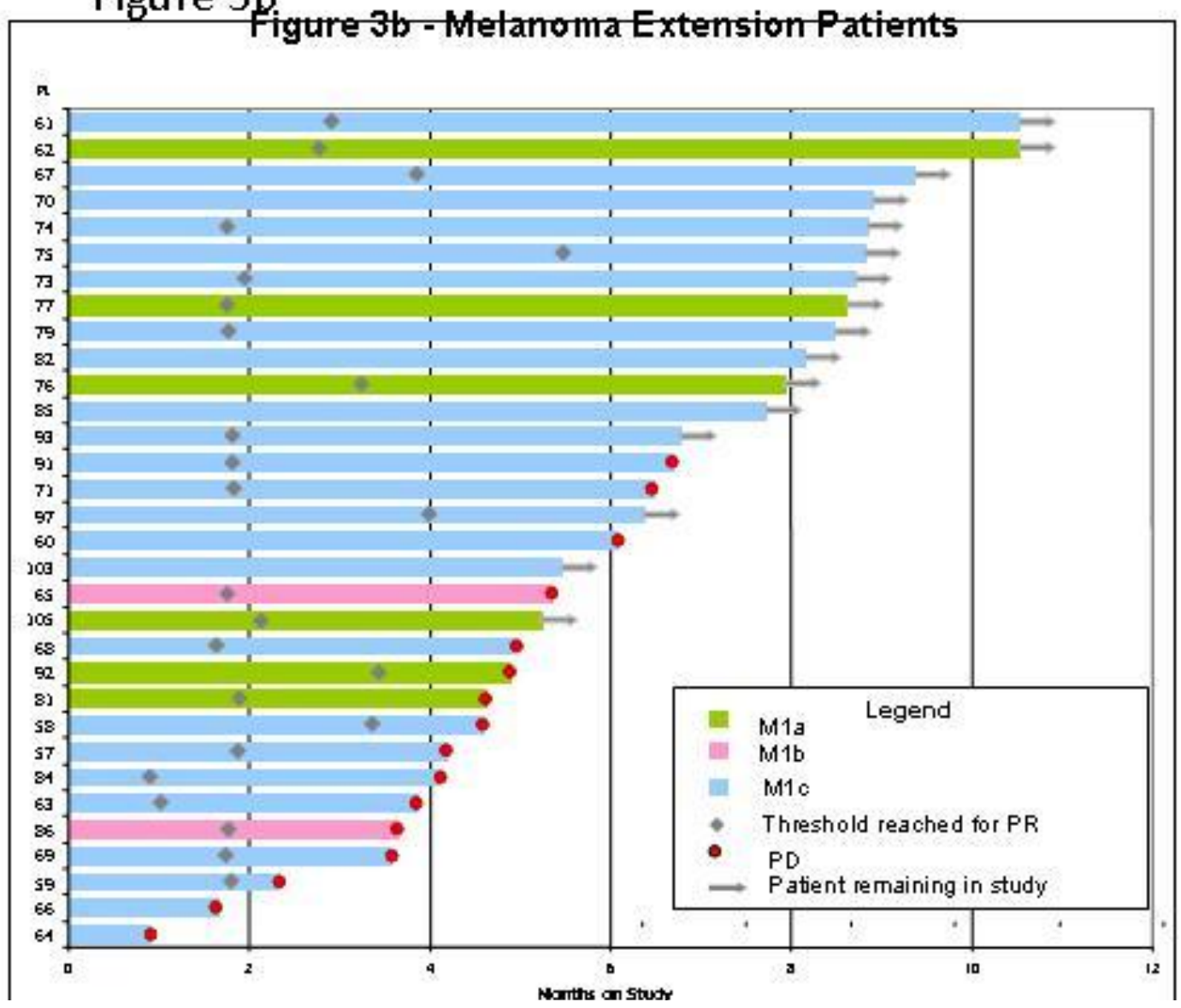
BRIM I : PLX4032 in stage IV Melanoma

PFS > 6 months

Figure 3b

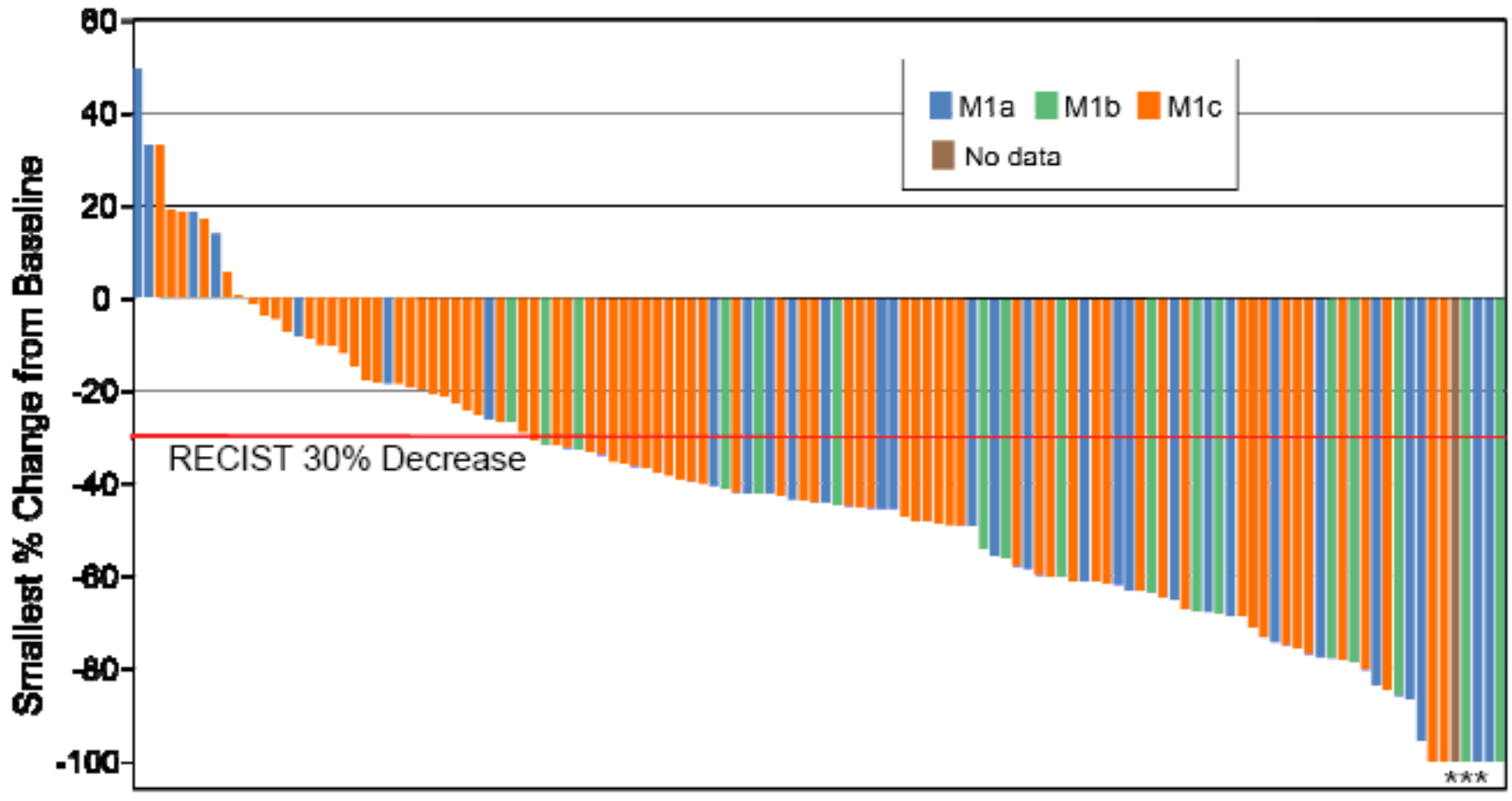


Flaherty et al, NEJM 2010

BRIM-2

PHASE 2, 2ND LINE

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



*** 7 patients had 100% tumor shrinkage, **3 of which had confirmed CR**;
1 patient had unconfirmed CR and 3 patients had non-target lesions present

- 122 patients had baseline and ≥ 1post-baseline scan with measurable disease

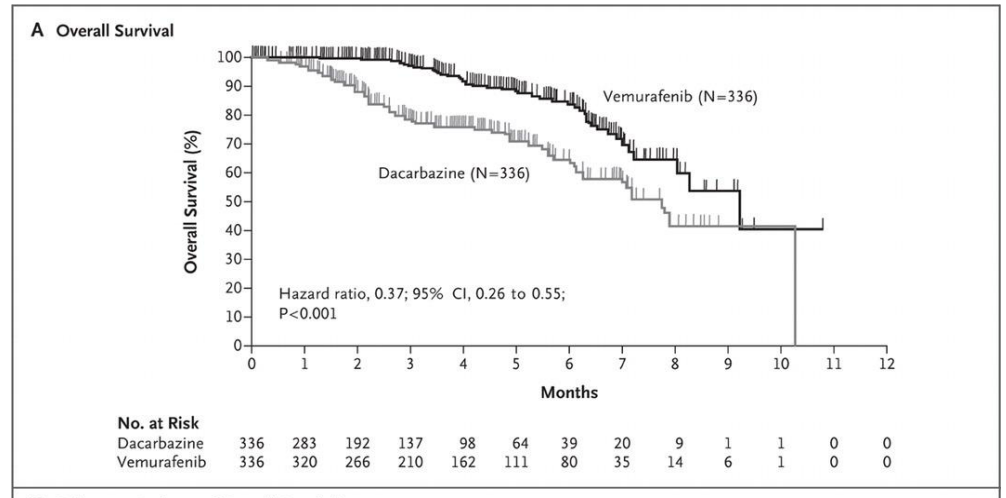
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

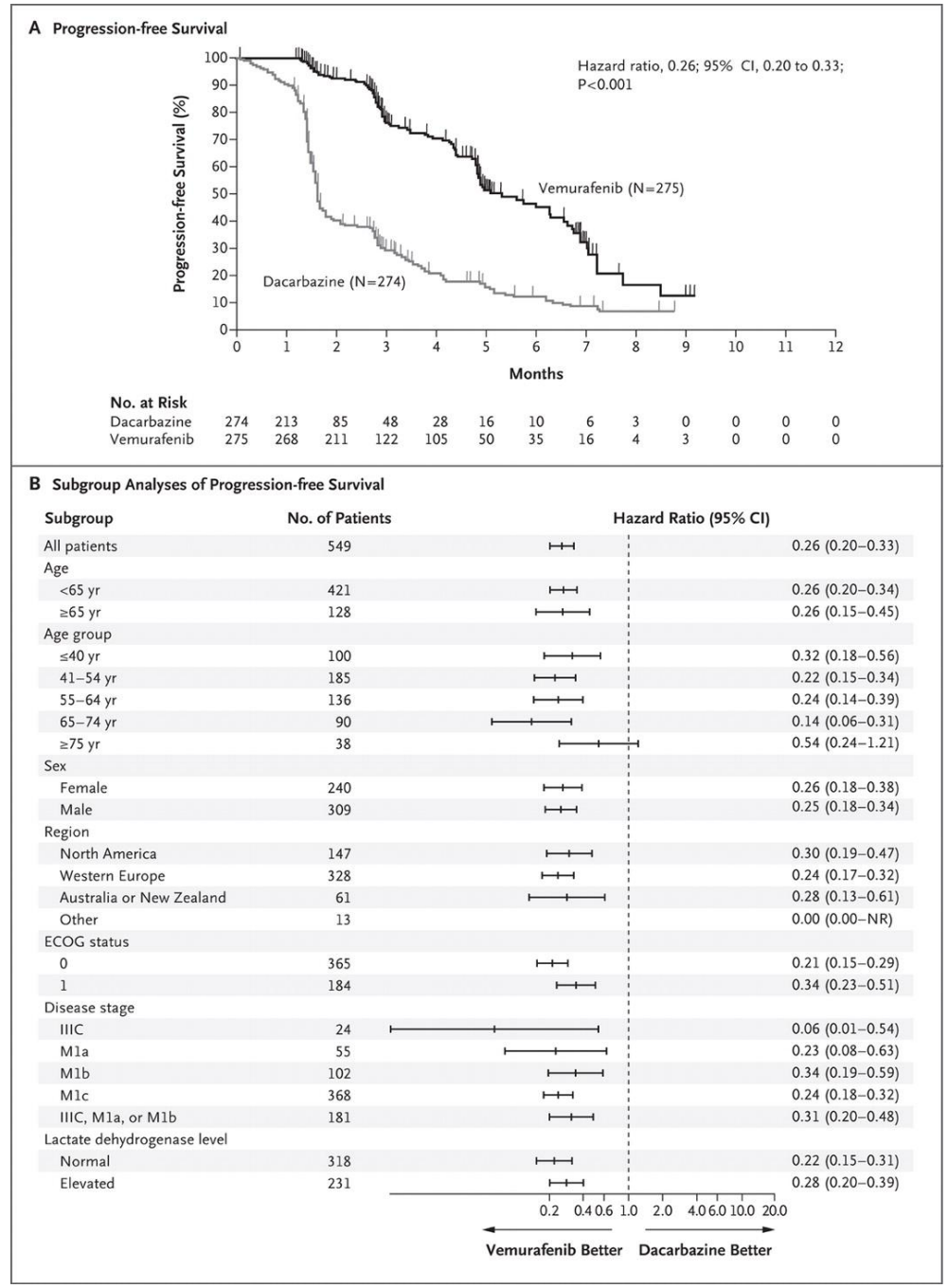
Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

Overall Survival.



Chapman PB et al. N Engl J Med 2011. DOI: 10.1056/NEJMoa1103782

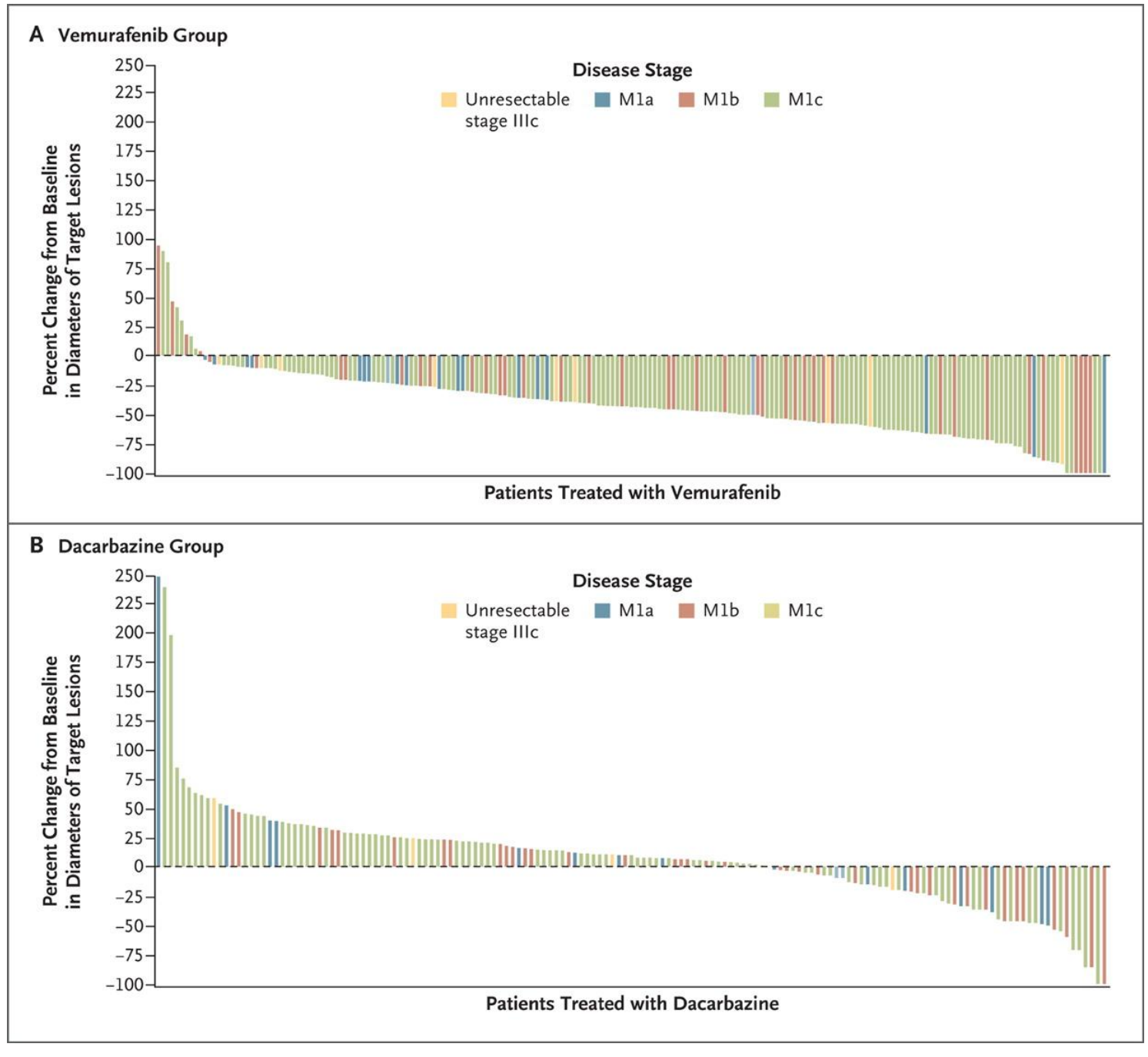
Progression-free Survival.



Subgroup	No. of Patients	Hazard Ratio (95% CI)
All patients	549	0.26 (0.20–0.33)
Age		
<65 yr	421	0.26 (0.20–0.34)
≥65 yr	128	0.26 (0.15–0.45)
Age group		
≤40 yr	100	0.32 (0.18–0.56)
41–54 yr	185	0.22 (0.15–0.34)
55–64 yr	136	0.24 (0.14–0.39)
65–74 yr	90	0.14 (0.06–0.31)
≥75 yr	38	0.54 (0.24–1.21)
Sex		
Female	240	0.26 (0.18–0.38)
Male	309	0.25 (0.18–0.34)
Region		
North America	147	0.30 (0.19–0.47)
Western Europe	328	0.24 (0.17–0.32)
Australia or New Zealand	61	0.28 (0.13–0.61)
Other	13	0.00 (0.00–NR)
ECOG status		
0	365	0.21 (0.15–0.29)
1	184	0.34 (0.23–0.51)
Disease stage		
IIIC	24	0.06 (0.01–0.54)
M1a	55	0.23 (0.08–0.63)
M1b	102	0.34 (0.19–0.59)
M1c	368	0.24 (0.18–0.32)
IIIC, M1a, or M1b	181	0.31 (0.20–0.48)
Lactate dehydrogenase level		
Normal	318	0.22 (0.15–0.31)
Elevated	231	0.28 (0.20–0.39)

Chapman PB et al. N Engl J Med 2011. DOI: 10.1056/NEJMoa1103782

Best Tumor Response for Each Patient.



Chapman PB et al. N Engl J Med 2011. DOI: 10.1056/NEJMoa1103782

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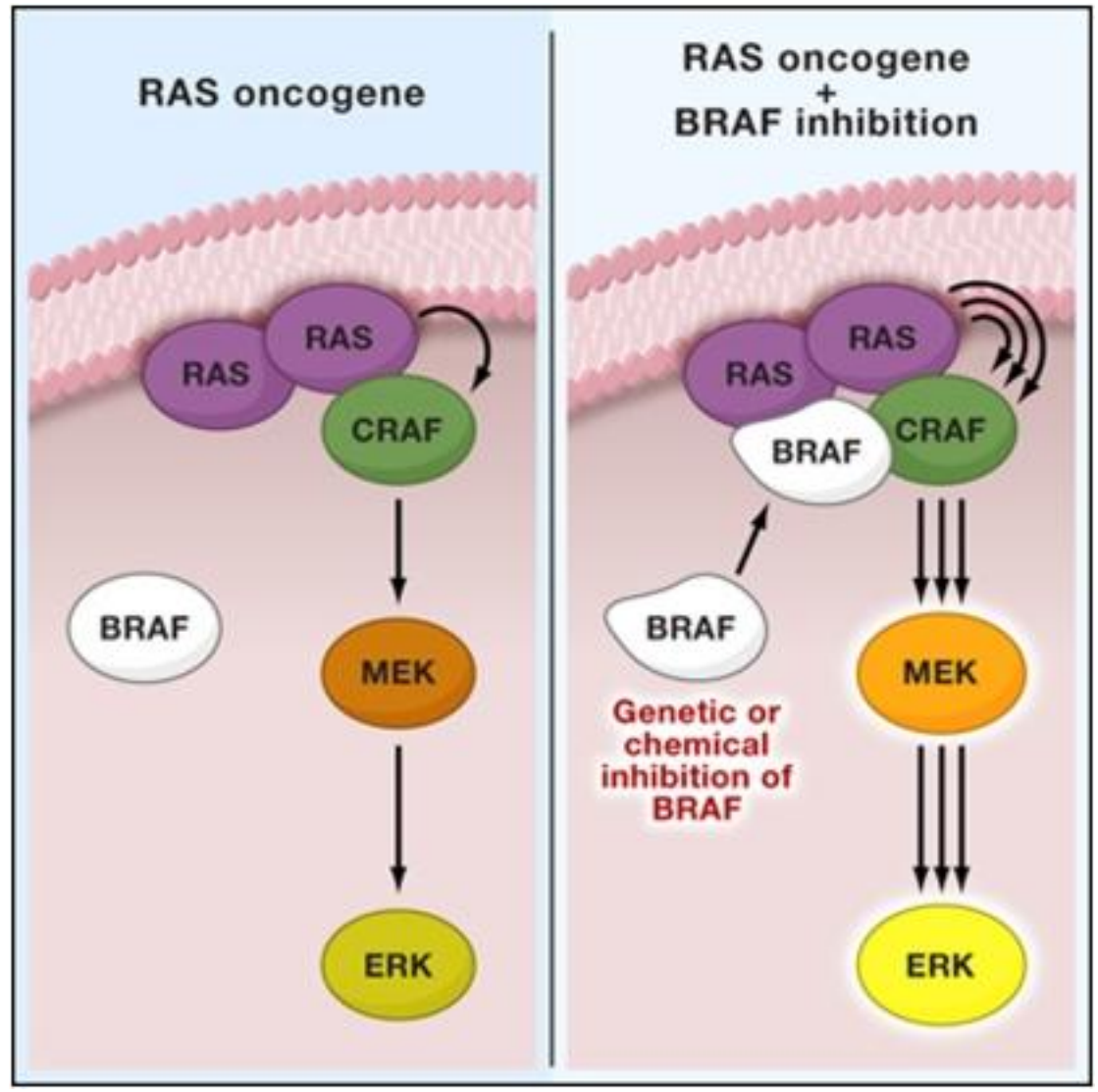
Kinase-Dead BRAF and Oncogenic RAS Cooperate to Drive Tumor Progression through CRAF



Cell. 2010 January 22; 140(2): 209–221

Sonja J. Heidorn,…….and Richard Marais1.

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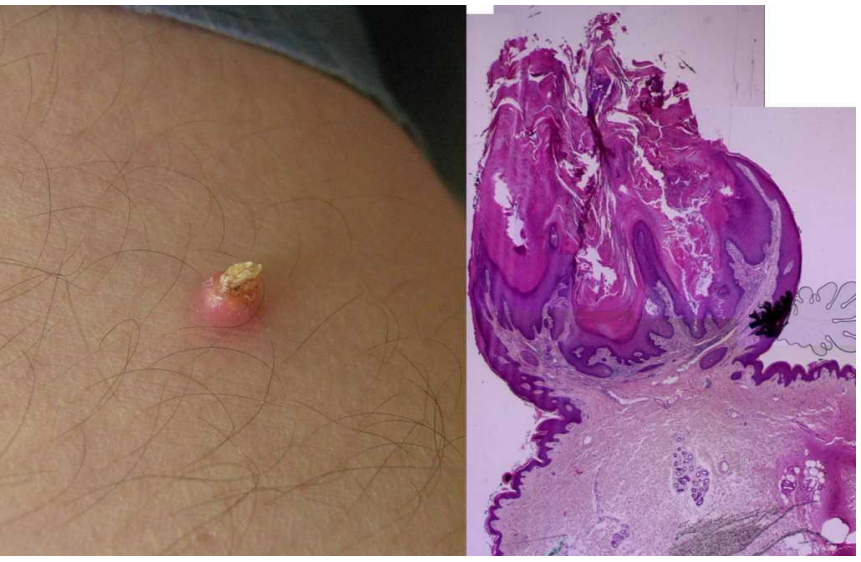
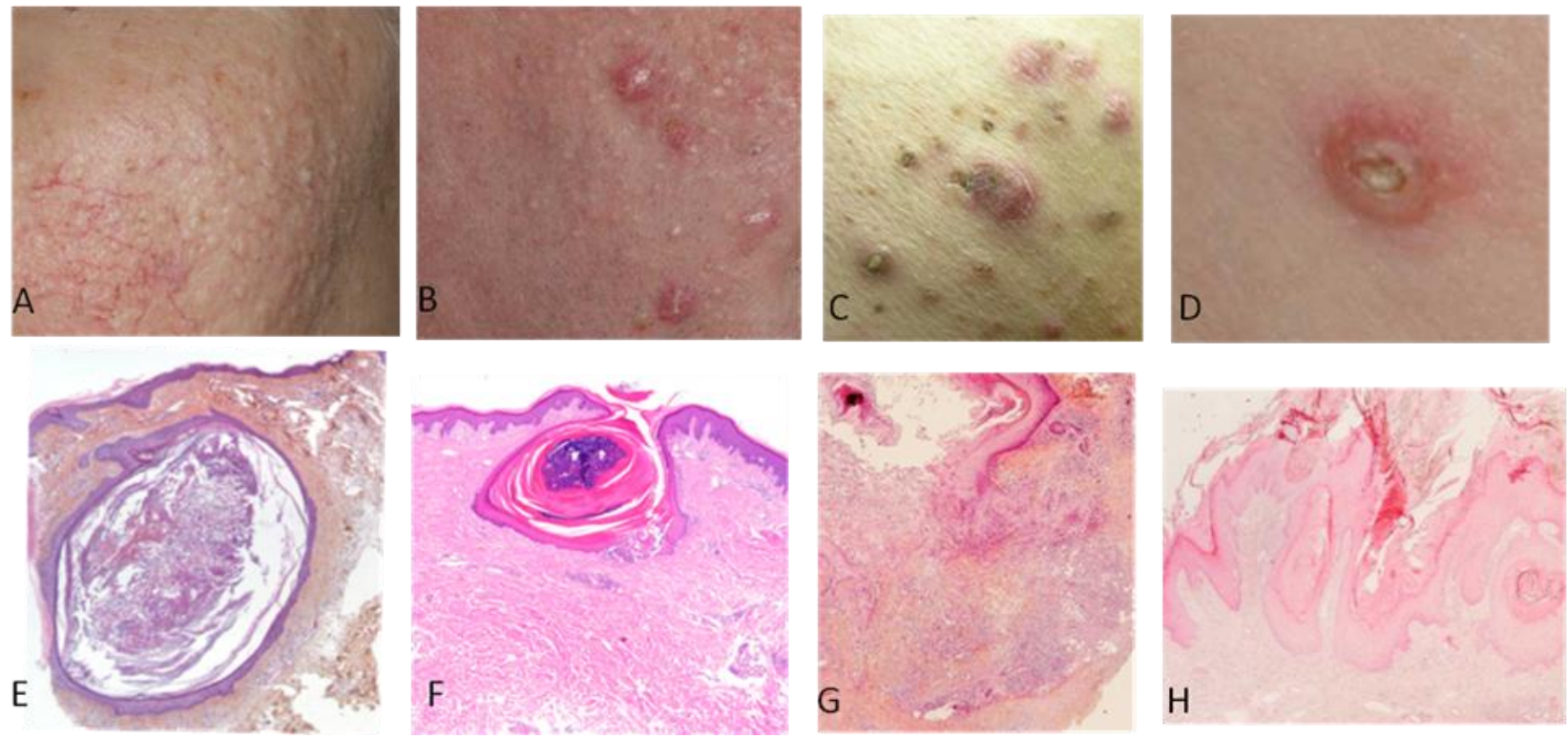
Variety of Skin Lesions with MKPI

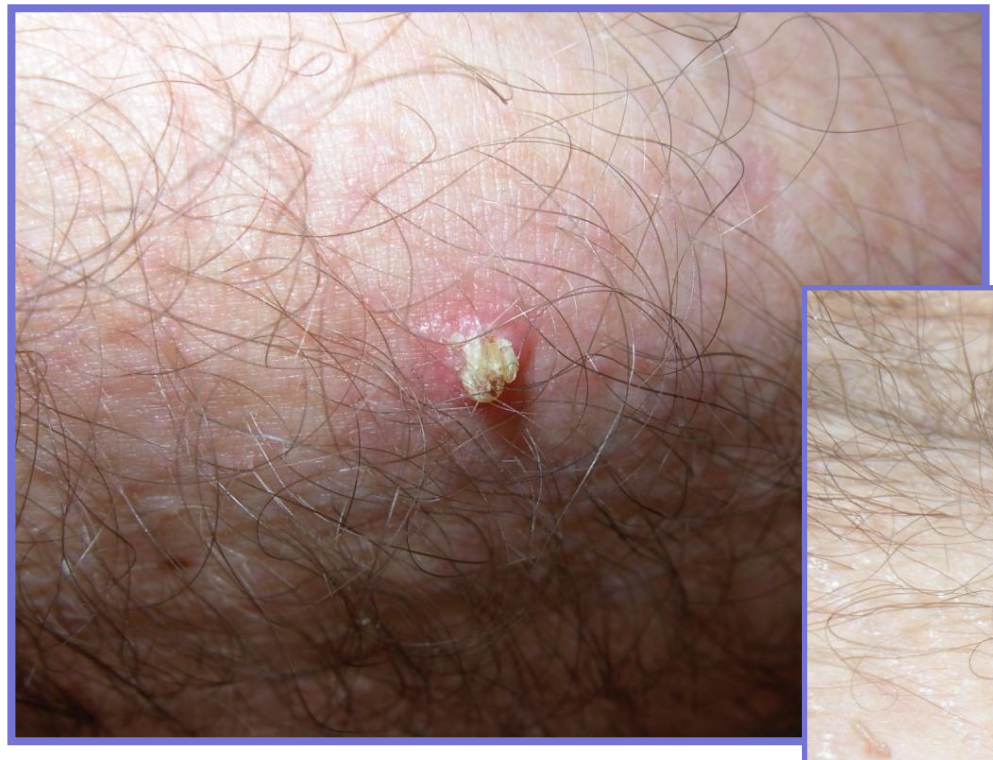


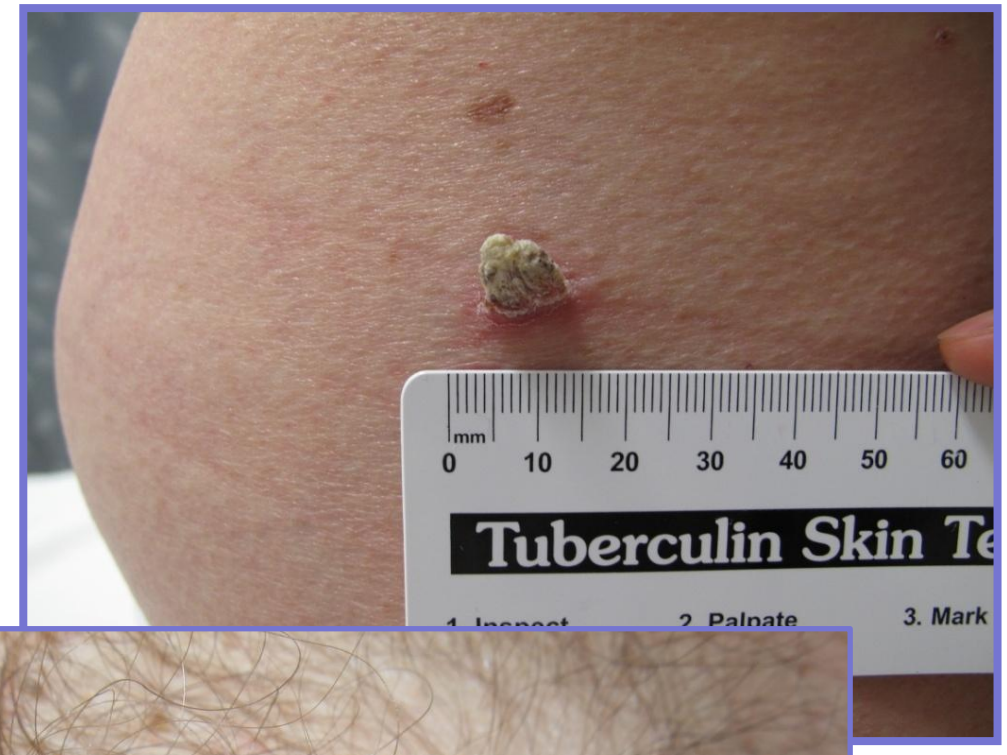


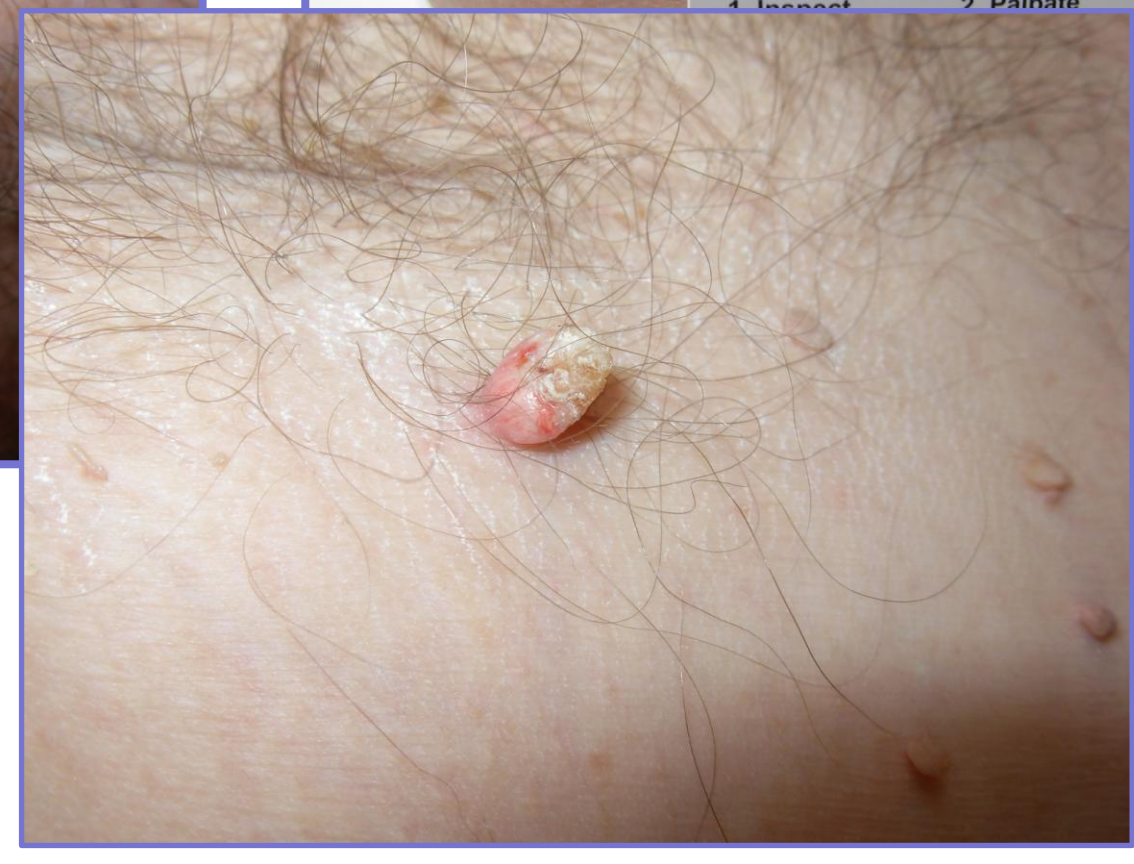
Caroline Robert, JCO 2009

Caroline Robert, 2010 submitted

Keratotic Lesions

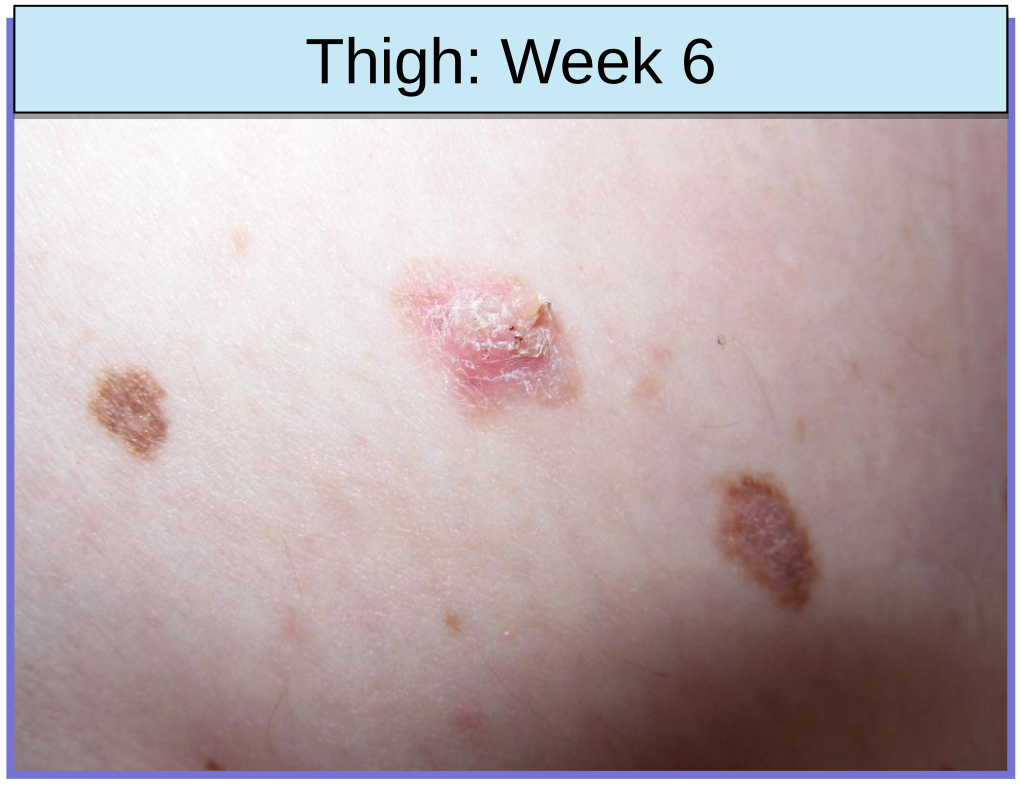




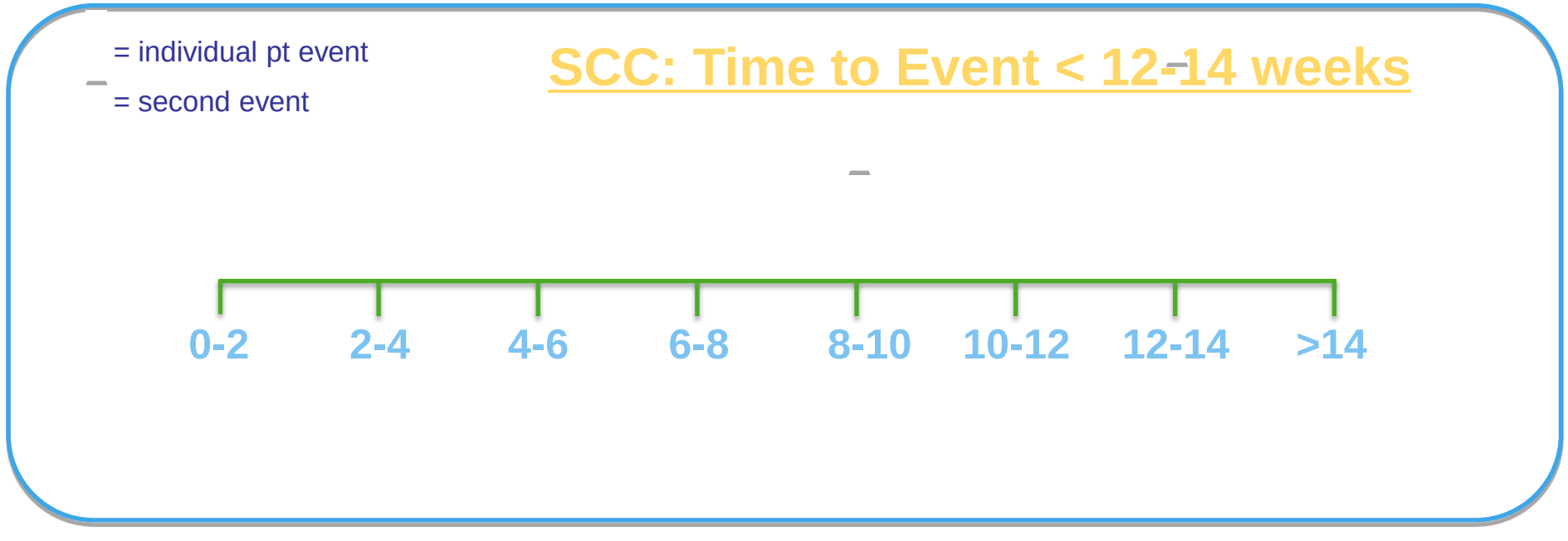


Kefford et al, Sydney 2010

Squamous Cell Carcinoma (Skin)



- **Histopathology: Low-grade squamous cell carcinoma**



Kefford et al, Sydney 2010

BRIM3: PLX4032/RG7402 vs. DTIC

Stratify:

- AJCC M stage
- LDH (normal vs. high)
- ECOG PS

R A N D O M I Z E

Arm A

PLX4032/RG7402
960 mg PO BID

Arm B

DTIC 1,000 mg/m² IV q 21 days

N = 680 patients with treatment-naïve metastatic melanoma
Primary endpoint = **overall survival (HR ≤ 0.75)**

STOPPED AT FISRT INTERIM ANALYSIS !!

BRF113683: Phase III trial
GSK2118436 vs DTIC

Stratify:

AJCC M stage

LDH (normal vs. high)

ECOG PS

R A N D O M I Z E

Arm A

GSK2118436 150 mg PO BID

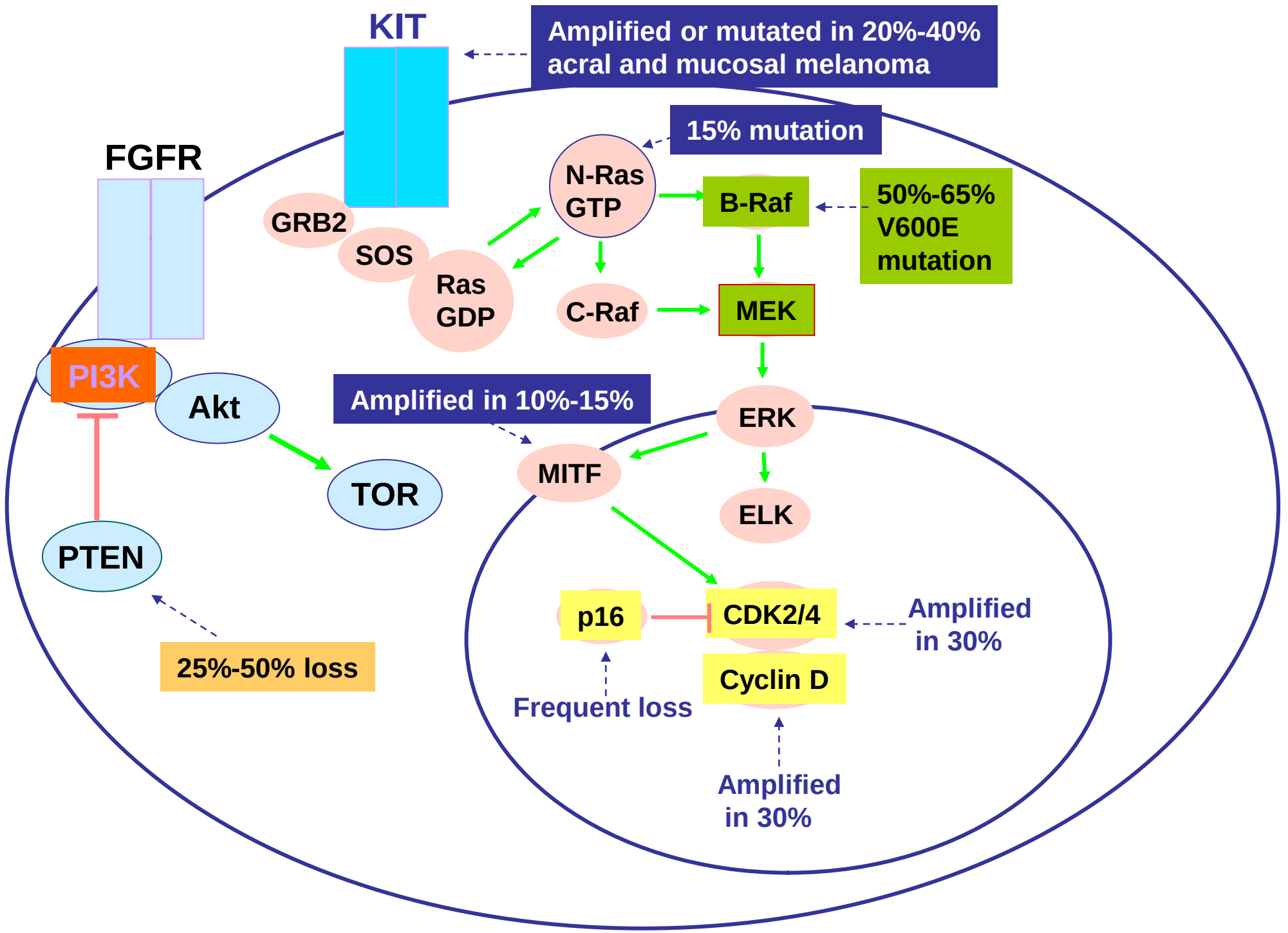
Arm B

DTIC 1,000 mg/m² IV q 21 days

N = 200 patients with treatment-naïve metastatic melanoma

Primary endpoint = **progression-free survival (HR ≤ 0.33)**

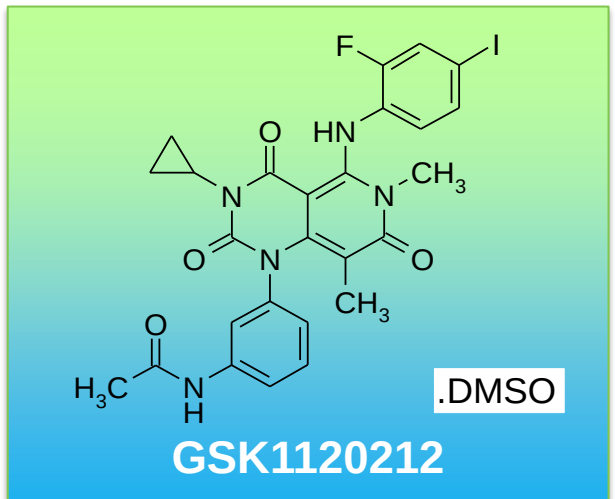
Molecular Alterations in Melanoma
MEK Inhibitors



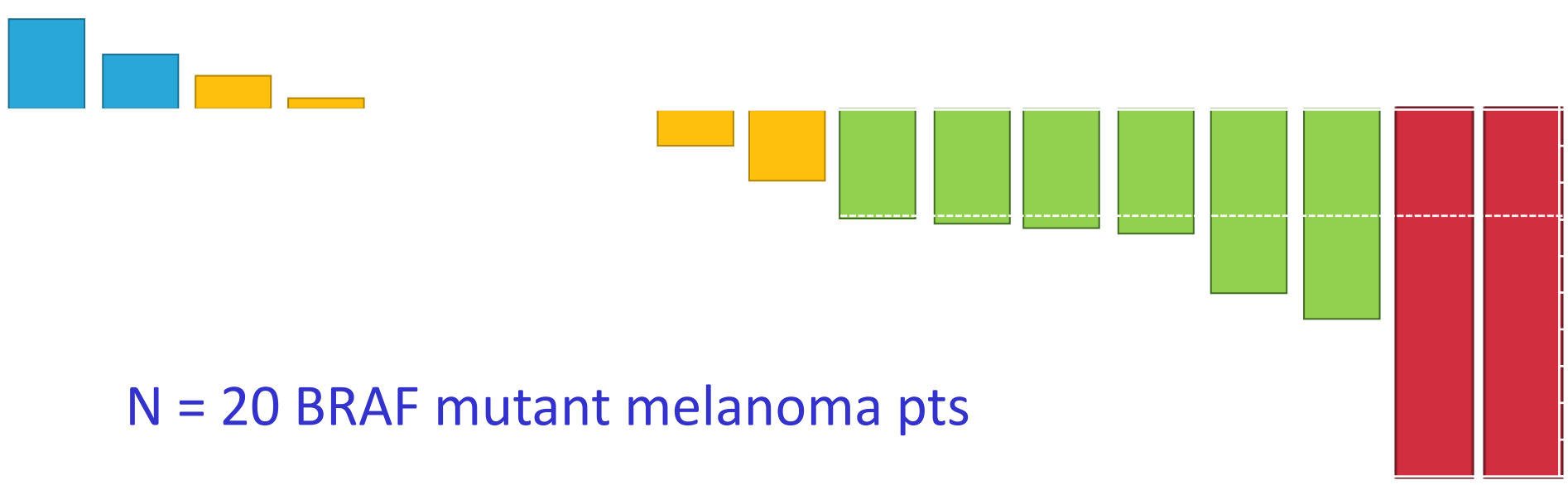
Adapted from Sosman, *Curr. Oncol. Rep*. 11, 405 (2009)

GSK1120212: best-in-class activity among MEK inhibitors

Infante J et al ASCO 2010, abs 2503



IC50 (nM)	MEK1	0.7
	MEK2	0.9
Inhibition of pERK (nM)	SKMEL28 (B-RAF^{V600E})	0.92
Inhibition of proliferation (nM)	SKMEL28 (B-RAF^{V600E})	2.5
	Colo205 (B-RAF^{V600E})	1
	A375P (B-RAF^{V600E})	1.3
	HCT116 (K-Ras^{G13N})	42
	HN5 (wt Ras/Raf)	106



MEK114267: Phase III trial
GSK1120212 vs DTIC or Paclitaxel

Stratify:

Prior therapy

LDH (normal vs. high)

R A N D O M I Z E

Arm A

GSK2118436 150 mg PO BID

Arm B

DTIC 1,000 mg/m² IV q 21 days
or
paclitaxel 175 mg/m² IV q 21 days

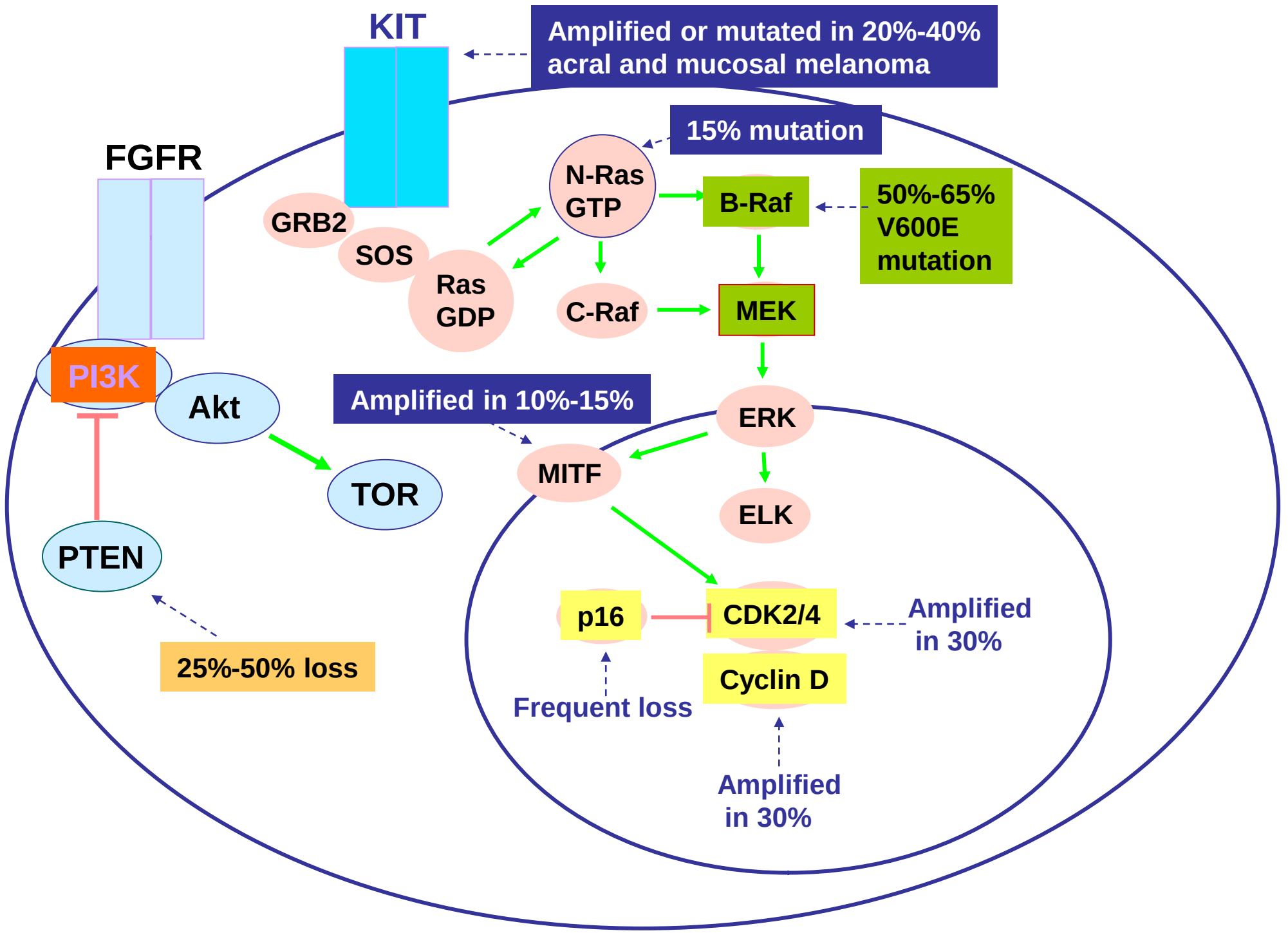
N = 549 patients

PFS (HR ≤ 0.33) & OS (HR ≤ 0.70) (220 or 550 patients ???????)

New Landscape, revise SPAs ?

Molecular Alterations in Melanoma

BRAF + MEK Inhibitors



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

BRAFi + MEKi

Phase I-II studies ongoing

Phase III planned

BRAFi + MEKi vs BRAFi

Veramufenib vs Ipilimumab vs COMBI

NEXT: BRAFinh + MEKinh + Ipilimumab $$$$$$$

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THE MELANOMA PARADIGM

- MUTATION DRIVEN DRUG DEVELOPMENT
- INNOVATIVE IMMUNOMODULATION

IMMUNOTHERAPY ESTABLISHED

"targeted therapy"

ANTI-CTLA4

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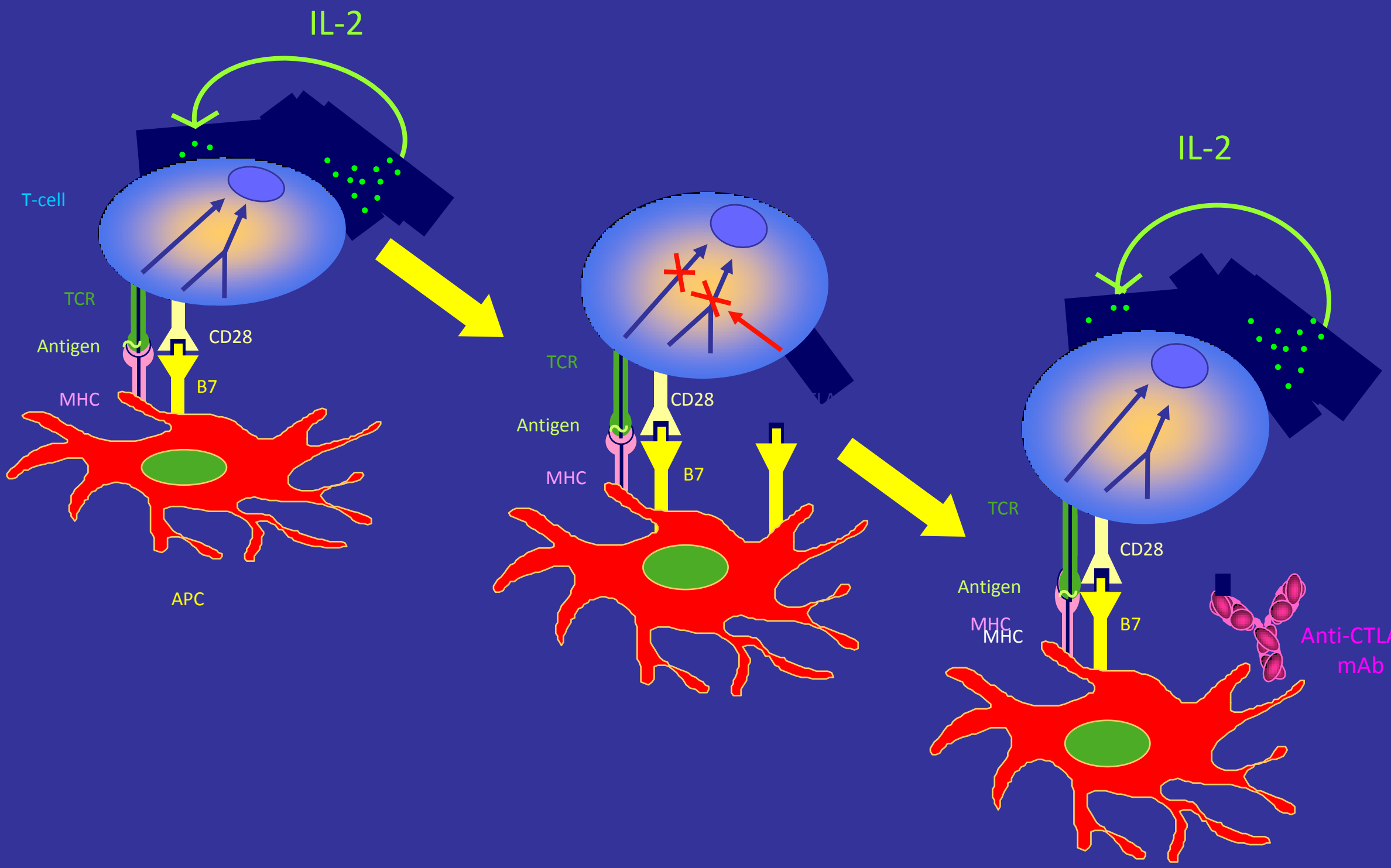
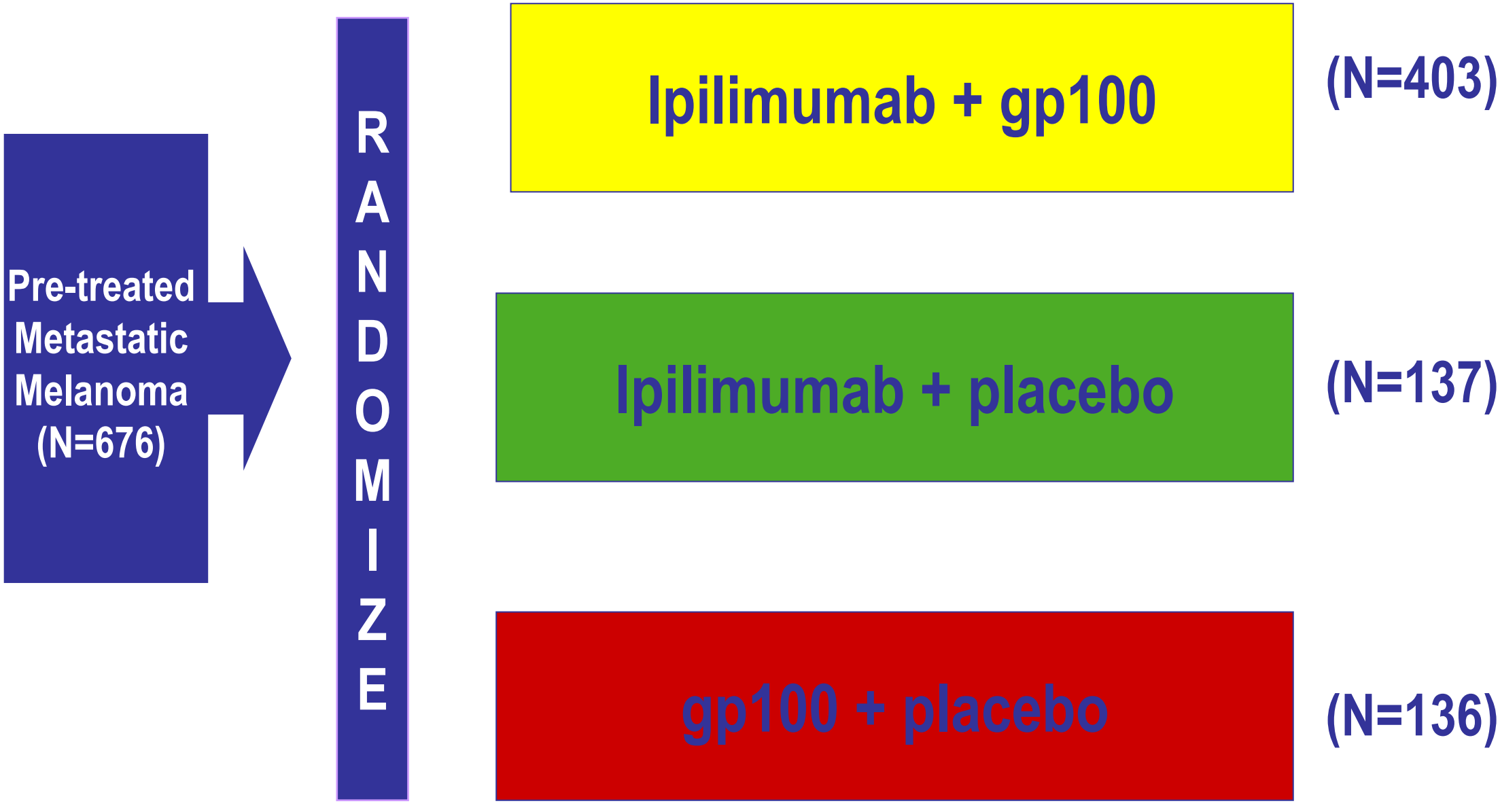
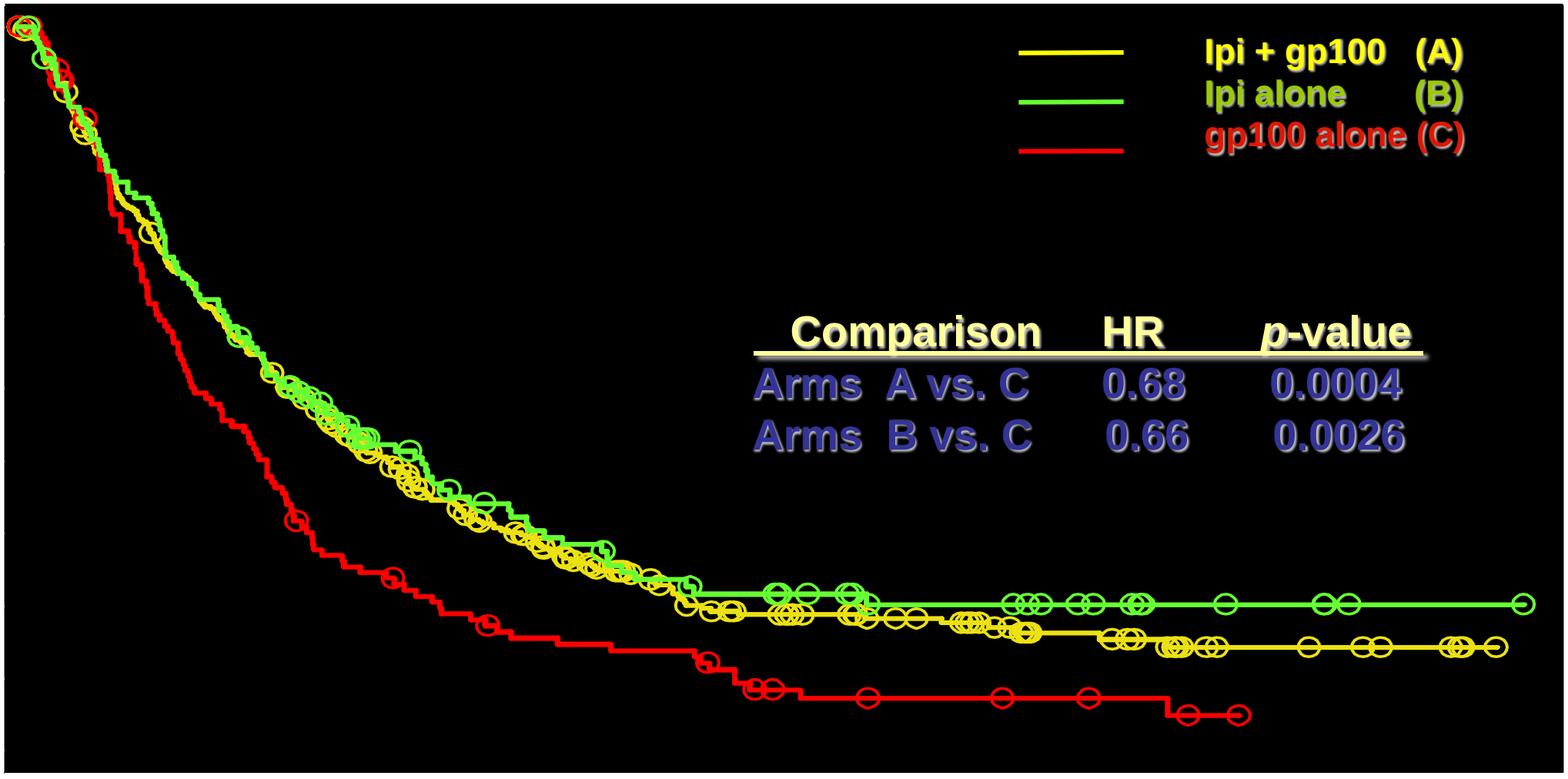
Anti CTLA-4 Monoclonal Antibodies Perpetuate T Cell Activation



MDX010-20: Study Design

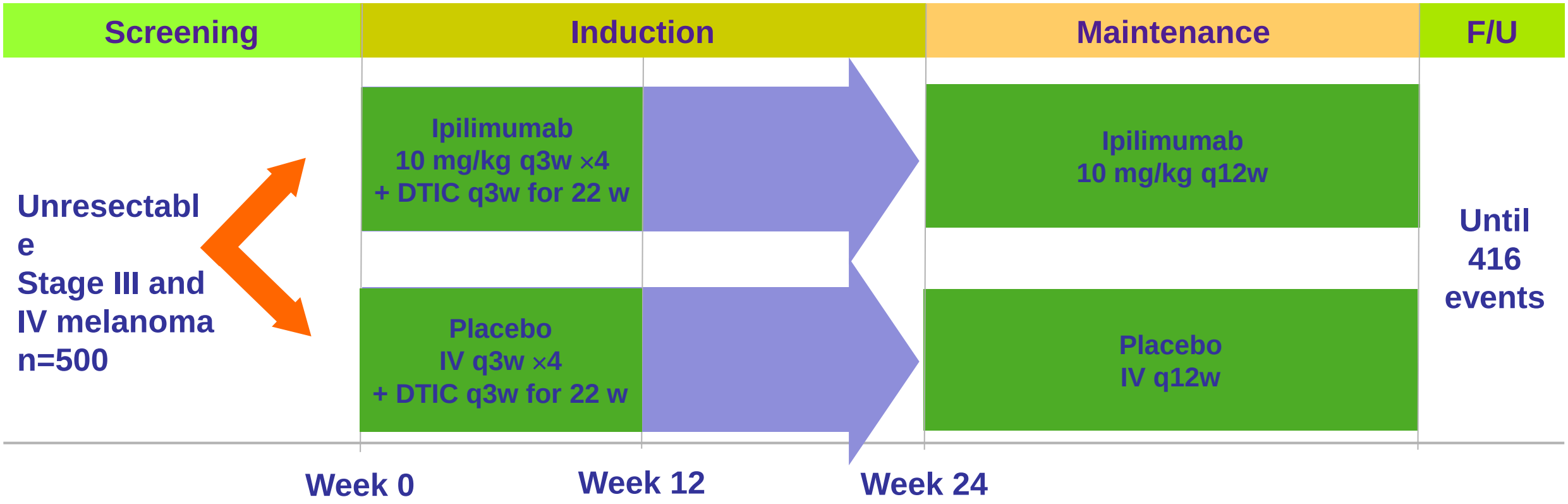


Kaplan-Meier Analysis of Survival



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

Study CA184-024: Randomized, Double-blind Phase III Trial
ipilimumab vs. ipilimumab with dacarbazine



- Primary endpoint: Overall survival
- Secondary objectives: PFS, DCR, BORR, survival rates, safety profile, time to response, duration of response, health-related QoL, Population PK

PFS: progression-free survival; DCR: disease control rate (CR+PR+SD); BORR: best objective response rate (CR+PR); QoL: quality of life

www.clinicaltrials.gov

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Immunotherapy 'forever'
For 120.000 $ for 4 injections

- **Ipilimumab for MULTIPLE TUMORS**
  - → Melanoma, Renal Cell Cancer,
  - → NSCLC, Prostate (+vax)
  - → CRC, etc ???

- **In MELANOMA a SYNERGY with**
  - → BRAFinh etc

- **RESCUE of VACCINE Field**
  - → Prostate
  - → Lymphoma vaccines
  - → CRC vaccines
  - → NCSLC (mage3 etc..)

- **IMMUNOGENIC DEATH Chemotherapies (zitvogel, kroermer)**

Drug Development 2011

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

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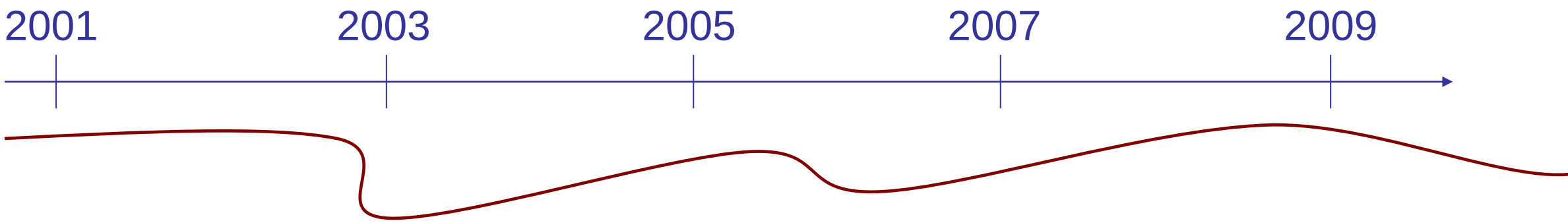
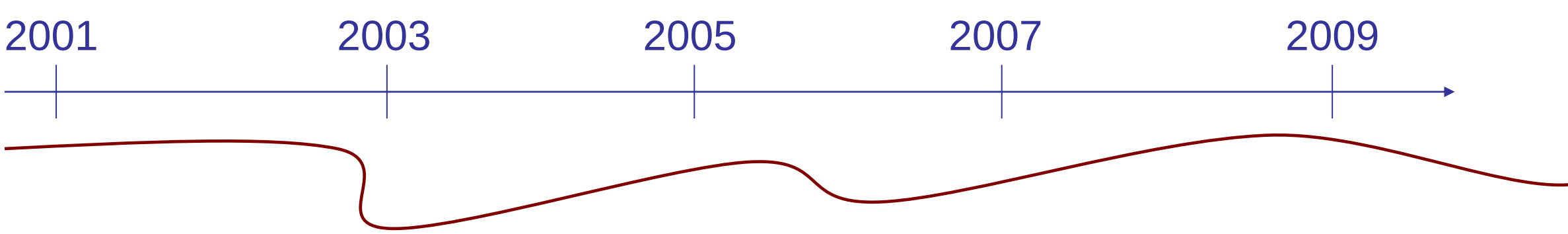
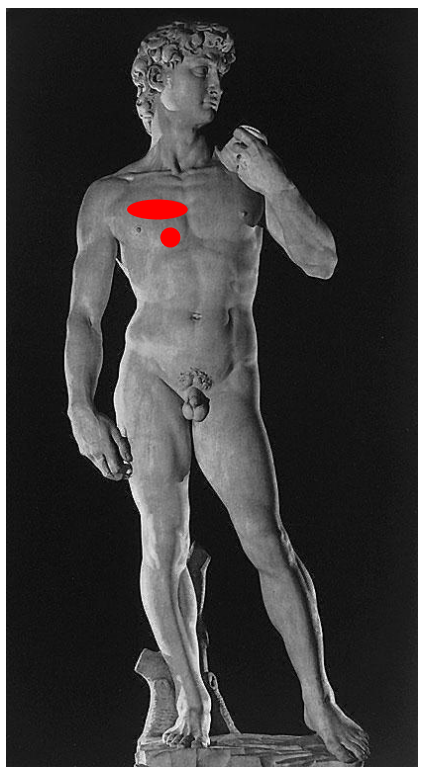
MOLECULAR MEDICINE

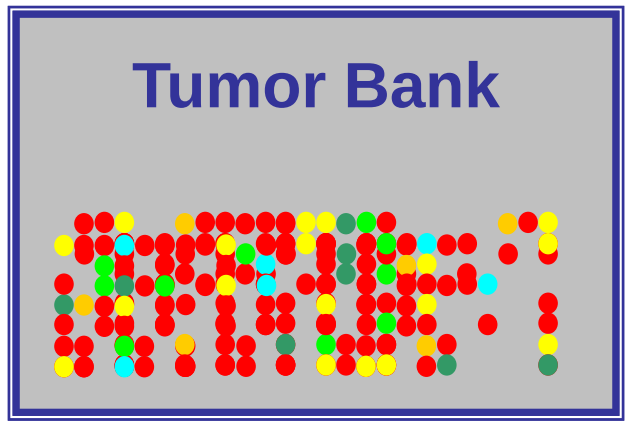
CANCER is a MOVING TARGET

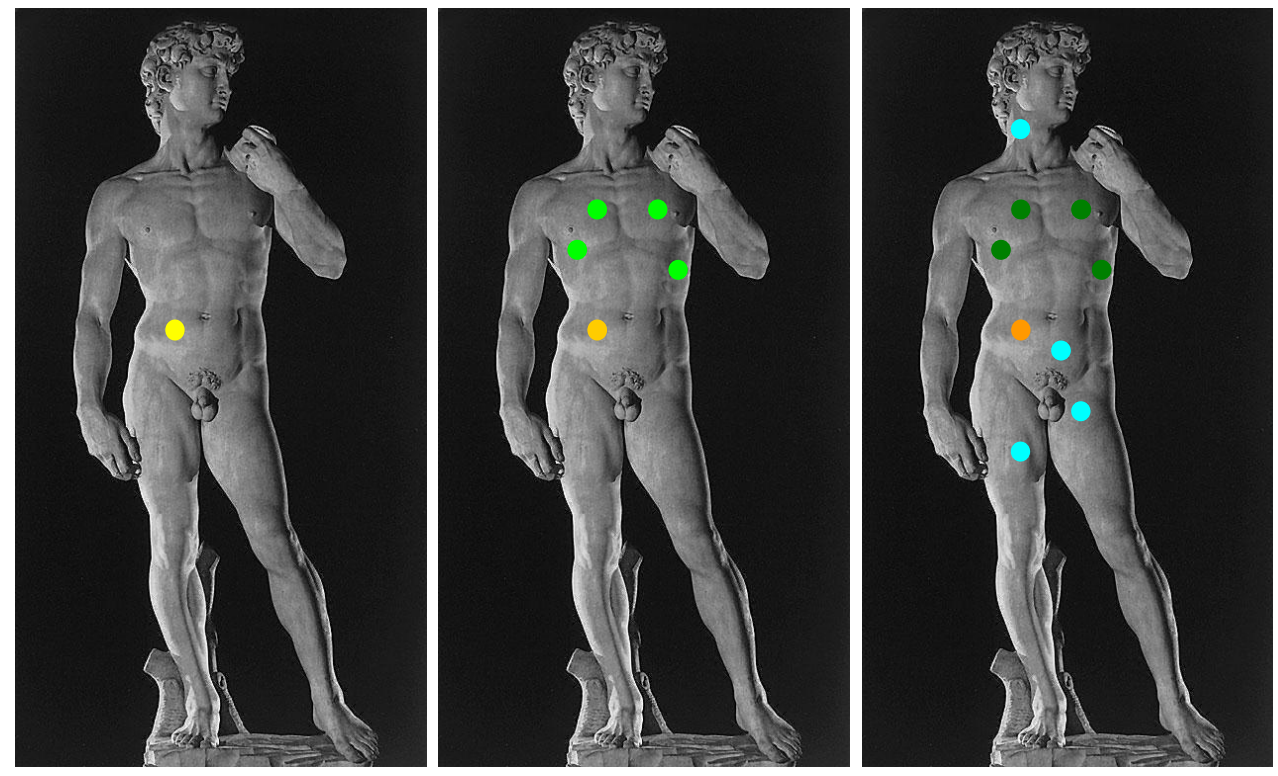


Whole tumor	***Tissue***	Adrenal gland biopsy	-	-
Vinorelbine cisplatinum	***Treatment***	Taxol Carbo bevacizumab	Pemetrexed	Biology guided ?









Whole tumor	***Tissue***	Adrenal gland biopsy	-	-
Vinorelbine cisplatinum	***Treatment***	Taxol Carbo bevacizumab	Pemetrexed	Biology guided ?

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INFRASTRUCTURAL REQUIREMENTS

RESEARCH MENTALITY

RESEARCH LABS

BIOBANKING

Quality SOPs

Interventional Radiology

FUNCTIONAL IMAGING

TRIAL OFFICE

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INFRASTRUCTURAL REQUIREMENTS

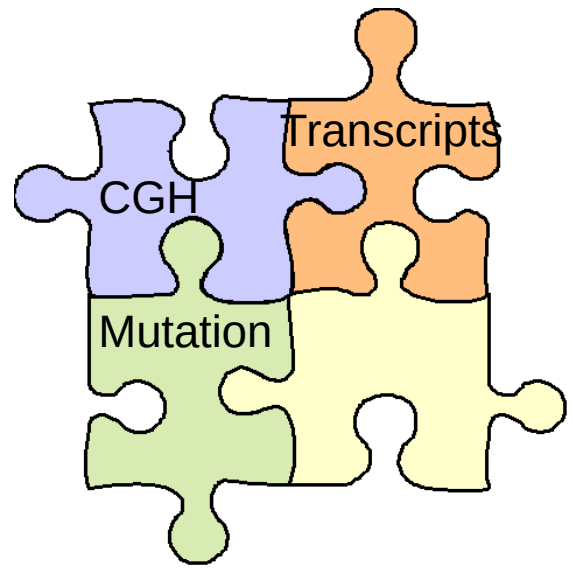
Molecular Diagnostics Devision
Broad Array of Technologies
Sequencing (various levels)
CTC capcity
Immunologic Array Capacities
(sorting, cloning, kine-arrays, etc)
All OMICS

BIO-INFORMATICS

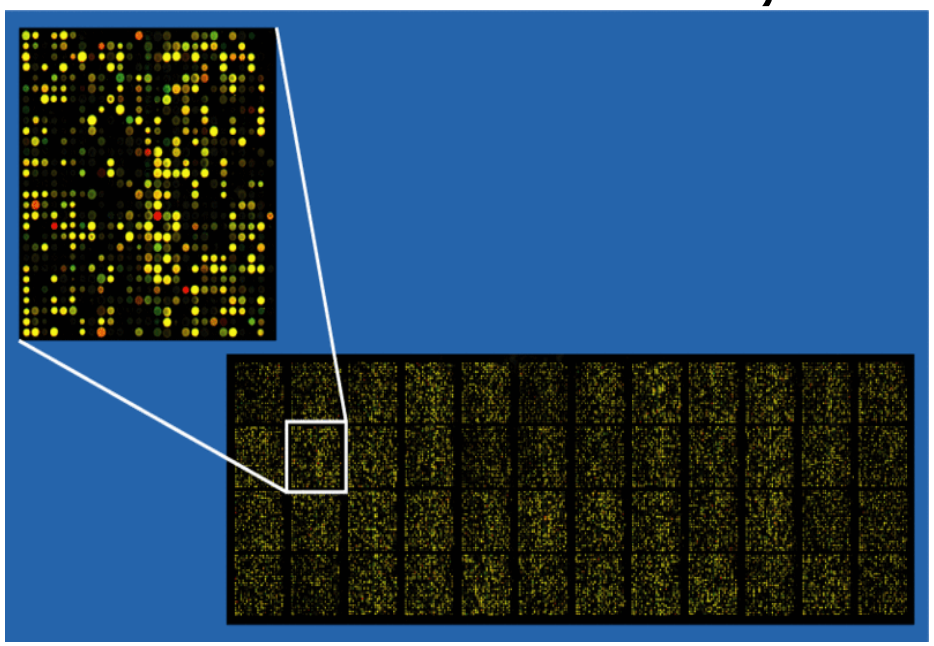
MOLECULAR PORTRAIT OF CANCER ARRAYS

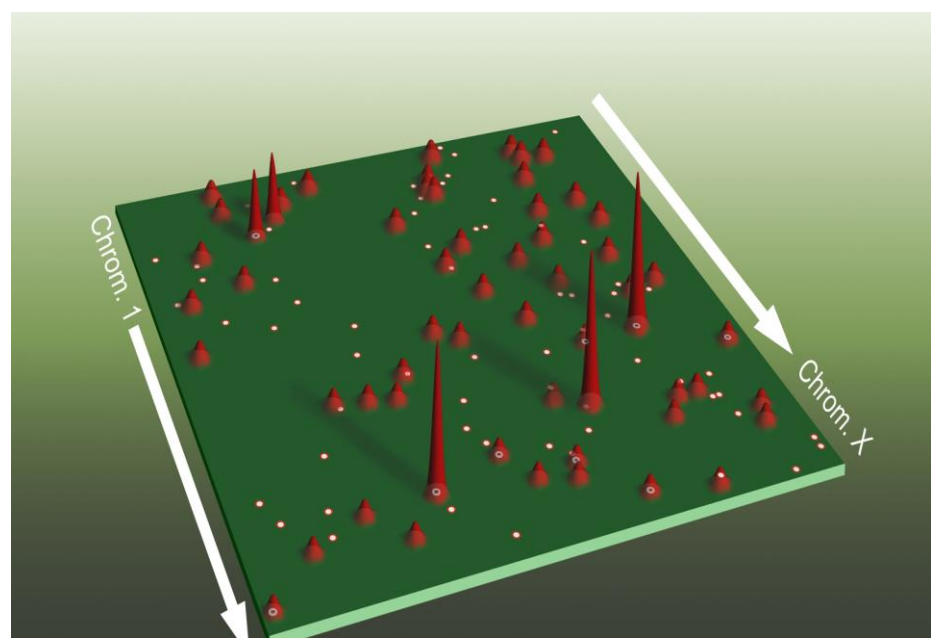
A system biology approach:

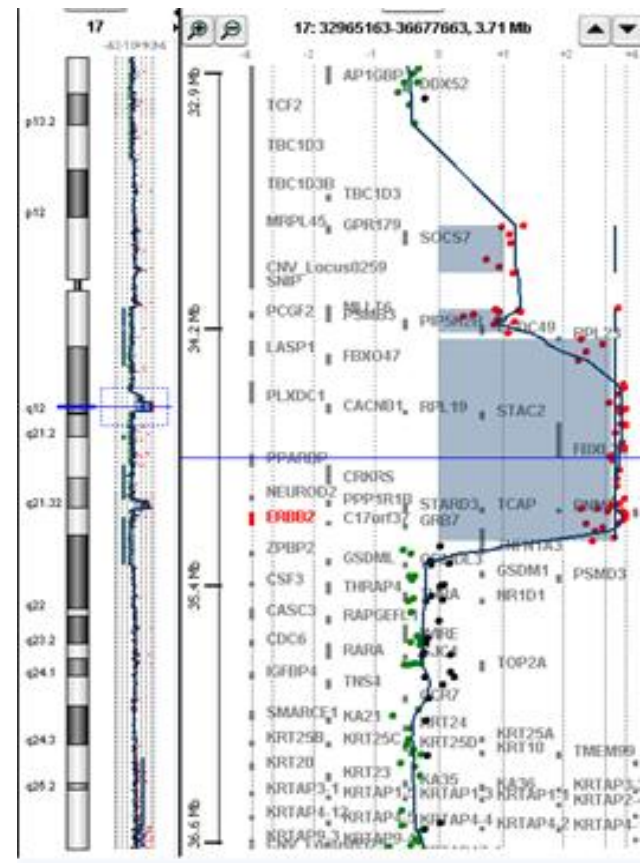
- **Sequencing**
- **CGH**
- **siRNA**
- **transcriptome**



+/- splicosome, methylome, acetylome, metabolome,







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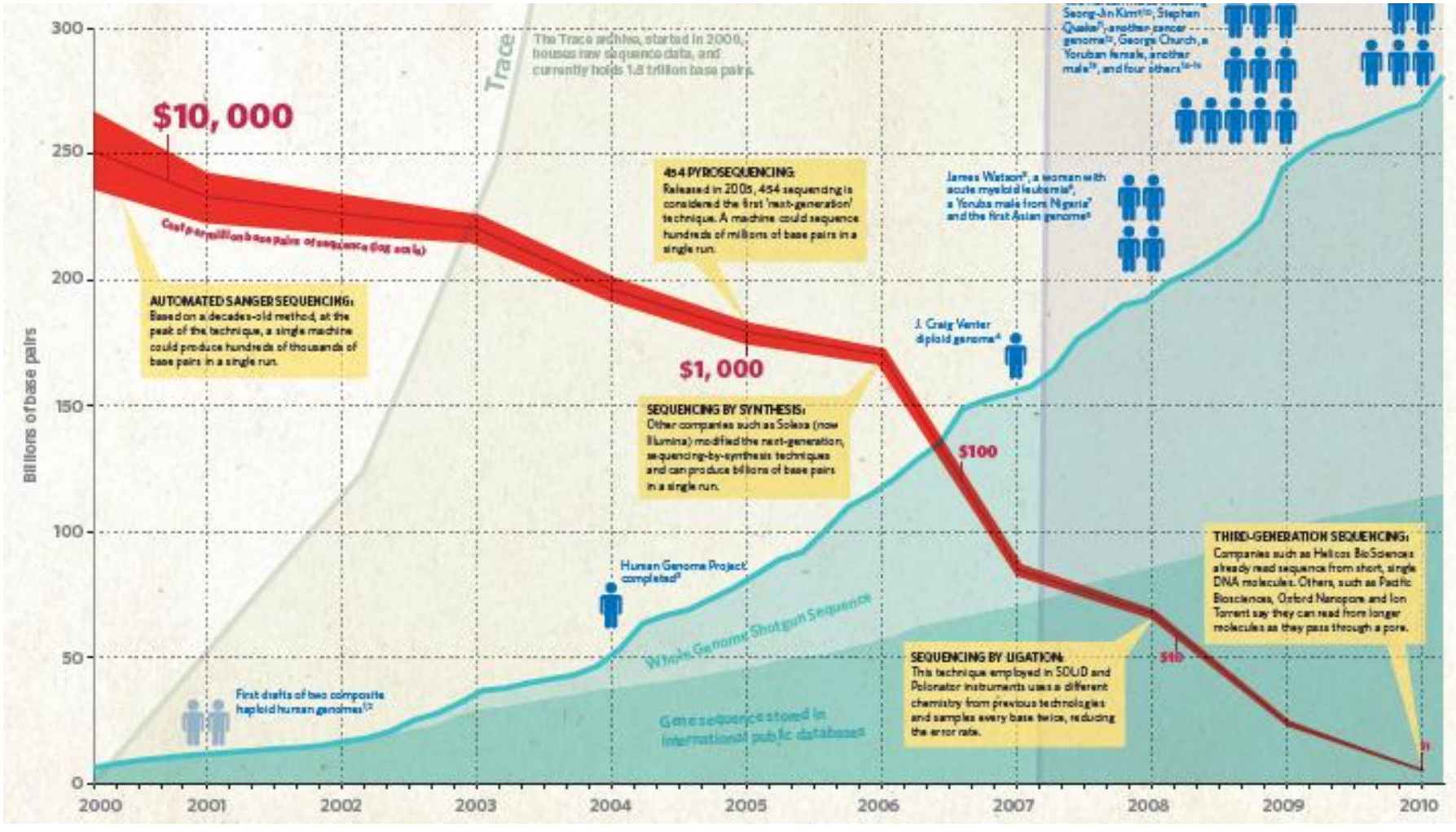
Sequencing gets cheaper but increasing complexity poses fundamental and computational problems that are very costly
1 patient becomes a series of projects over time



- **Challenge: integrating multiple read-outs**

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

- Integration of Basic Research and Clinical Research
- Networks of Clinical and Basic Research Institutes

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

Networking is a Must

Regional (Canceropole, etc)
National (INCA, FNCLCC, etc)

International
Bilateral
Multicentric

Consortia
Descartes, Pentagon/Hexagon
EORTC, OECI, EU-FP7/8
WIN

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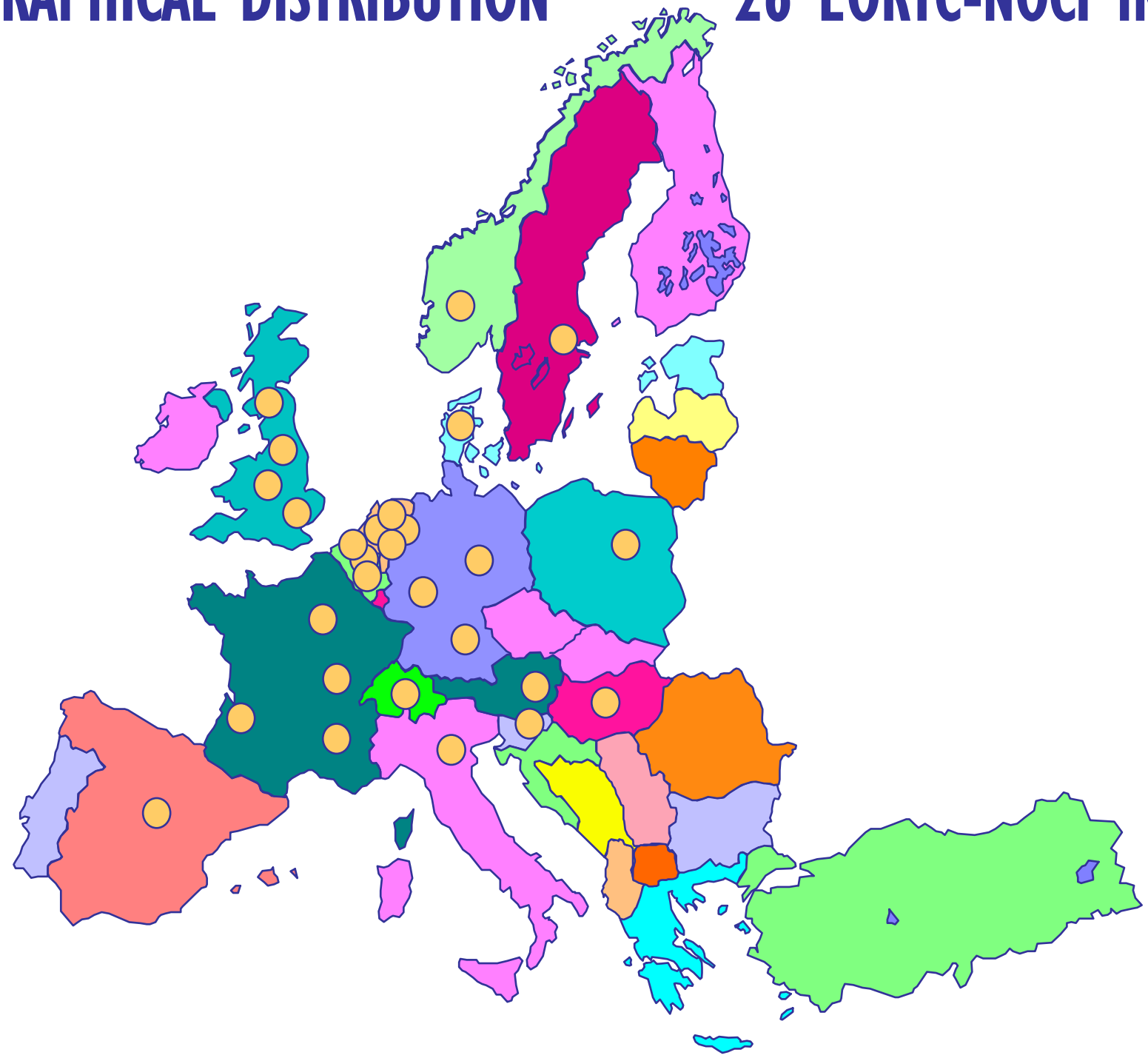
GEOGRAPHICAL DISTRIBUTION 26 EORTC-NOCI INSTITUTIONS



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Comprehensive ERA-net like structure for Fundamental-Translational-Clinical Research EUROCAN PLATFORM for TCR

Eurocan Plus

Feasibility Study for Coordination of National Cancer Research Activities

MOLECULAR ONCOLOGY XXX (2008) 1–2

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/molonc

Letter to the Editor

The Stockholm Declaration☆

European cancer research, when looked at in a global perspective, has a number of unique strengths, such as a strong foundation in biomedical science, good patient registries and biobanks. However, research is still fragmented and lacks the critical mass needed to translate basic research discoveries into a clinical setting for the diagnosis and treatment of cancer patients.

Oncology is a unique discipline which is increasingly depending on multidisciplinarity. The concept was progressively defined during the 20th century and developed around clinical considerations in order to have surgeons, radiologists, pathologists, radiation- and medical oncologists working together in concord.

The current explosion of new concepts and technologies emerging from molecular- and cellular biology has made it necessary to bridge the gap between the various fields of basic and clinical research. No single European cancer institution has the critical mass to deliver in all cancer areas. As a result, European institutions must work together to create a world-class infrastructure in which all disciplines are integrated with the aim of innovating in cancer care and prevention.

A Comprehensive Cancer Center (CCC) is a facility in which care and prevention is integrated with research and education. The concept of a CCC arose as a consequence of the increasing complexity of cancer activities and increasing needs for innovation. The translational cancer research continuum, in which the patients are always in focus, stands at the heart of a CCC where all components of the research process, from basic to clinical to outcome research are fully integrated with each other. This structure should ensure that research and implementation of new technologies are adapted to patient care and evaluated in response to research results.

In our view, a platform of CCCs linked to basic research centres will provide the world-class infrastructure that Europe needs to perform state-of-the-art discovery-driven translational research.

We have therefore decided to work together towards the creation of a collaborative platform comprising leading CCCs and basic/preclinical research centres in Europe. Such a platform of centre's, we believe, is the only possible way to reach the critical mass and sustainability that is necessary to innovate and deliver in all areas of cancer research.

☆ This declaration is a public statement of commitment to the strategy and practice of a platform of comprehensive cancer centers (CCCs) and basic/preclinical cancer research centers. This initiative was launched on November 6th, 2007 in Stockholm, Sweden with 16 inaugural signatories.

Alliance Against Cancer, Italy (Angelo Paradiso).
Cancer Research UK Cambridge Research Institute, Cambridge, UK (Bruce Ponder).
Christie Hospital Manchester/Manchester Cancer Research Center, Manchester, UK (Chris Harrison).
~~Institute of Cancer Biology,~~ Danish Cancer Society, Copenhagen, Denmark (Julio E. Celis).
Erasmus University Medical Center, Rotterdam, The Netherlands (Alexander Eggermont).
European Institute of Oncology, Milan, Italy (Gordon McVie).
German Cancer Research Center (DKFZ), Heidelberg, Germany (Otmar D. Wiestler).
Institut Gustave-Roussy, Villejuif, France (Thomas Tursz).
Institut Jules Bordet, Brussels, Belgium (Dominique de Valeriola).
Institute Curie, Paris, France (Sergio Roman-Roman).
Karolinska Institutet, Stockholm, Sweden (Ulrik Ringborg).
The Netherlands Cancer Institute, Amsterdam, The Netherlands (Anton Berns).
Centro Nacional de Investigaciones Oncologicas (CNIO), Madrid, Spain (Mariano Barbacid).
The Norwegian Radium Hospital Comprehensive Cancer Centre, Oslo, Norway (Anne-Lise Börresen-Dale).
University of Oxford, Oxford, UK (David Kerr).
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (Marco Pierotti).

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THANK YOU

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