The Future of Personalised Medicine

- New organizations
- New networks
- New alliances

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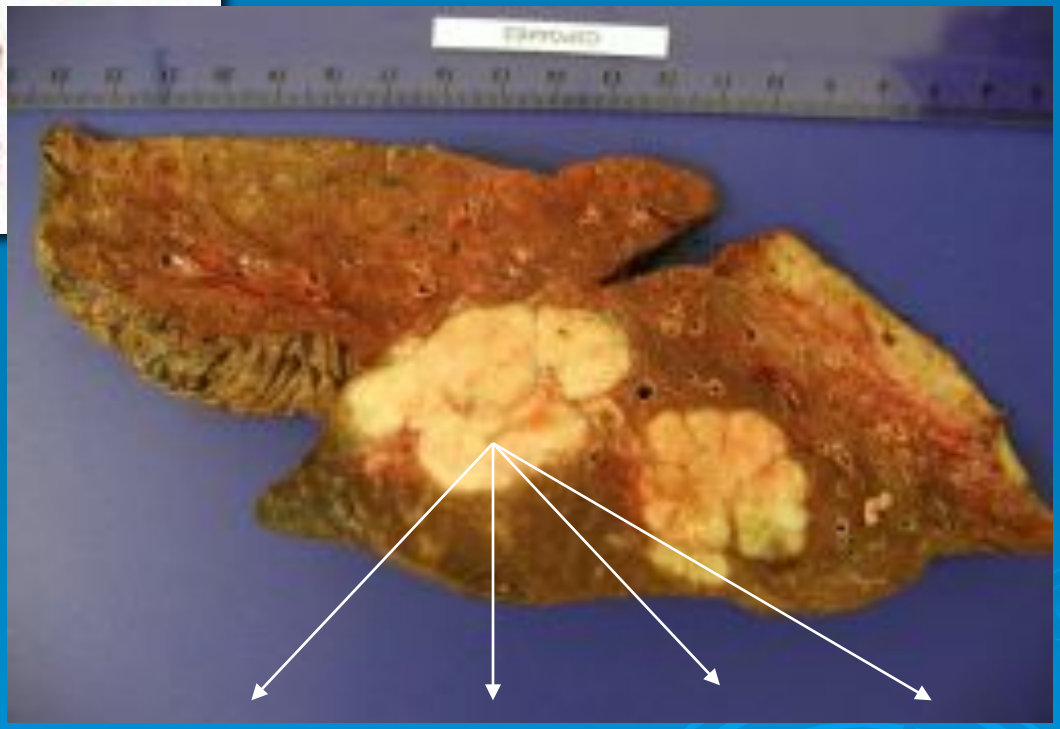
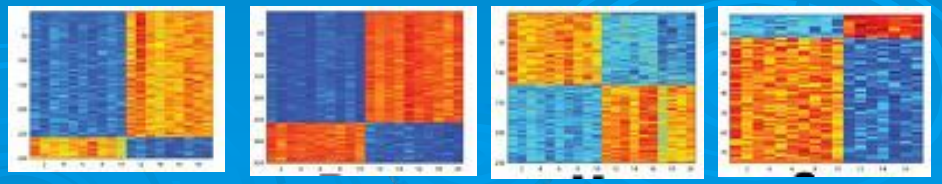
Villejuif - France

World Cancer Congress - UICC
August 25 - 29 2012
Montreal, Canada

Patient heterogeneity

Tumor molecular heterogeneity





RAS EGFR MYC MET


4

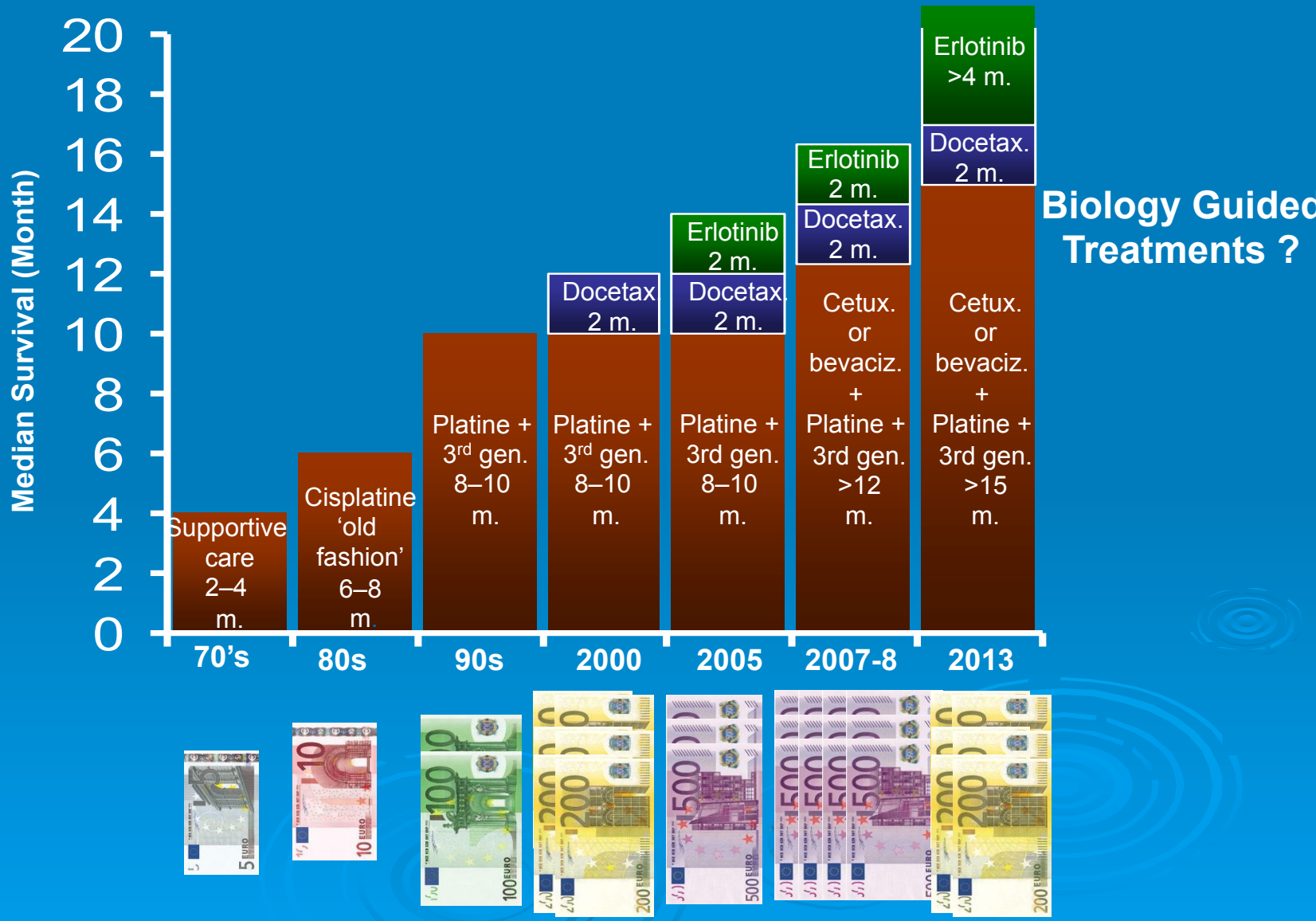
Oncology in Europe in 2012

- Basic Research and Healthcare are not developing at the same speed
- National health systems are rigid and fragmented
- Economical constraints as a ‘brake’ for innovation

Oncology in Europe in 2012
(and elsewhere… ,)

- Only 2-3 % of patients have access to one clinical trial
- Most of these clinical trials are designed for mere marketing objectives
- Major Pharmas are moving their R and D Divisions to the USA
- A number of large scale clinical Phase II and III trials are moving to Eastern Europe, China or India

Non Small Cell Lung Cancer Advanced and Metastatic



Economical Constraints

A wrong Question

‘How to treat cancer patients in 2020 like in 2010, but for less money ?’

A wrong Answer

‘Innovation is a costly fate which has to be limited or restricted’

Economical Constraints

A Good Question

- Could innovation lead to cure a small proportion of cancer patients, and thus decrease the overall costs ?

Good Answers

- Give the right treatment to the right patients but also
- Do not give the wrong treatment to the wrong patients

Academy and Industry relationships in Europe

- Personal and limited access to real deciders for R&D and global development
  - US based
  - US culture
  - Limited and fragmented vision of the European Institutes and the European Scientific potential.
- Tendancy to move basic research and R&D to the US (Sanofi Aventis)
- Intents to look for new and less expensive places for large Phase II and III studies (Eastern Europe, China and India)

The real risk …

Europe

=

Second zone continent

for clinical research

in oncology

Questions

Strategies and Methodology for Clinical Trials

1. Is the Current Drug Development Model through:

Pre clinical → Phase I → Phase II → Phase III studies really appropriate ?

2. How to study drug combinations early during development without waiting all the individual drugs entering the market?

Questions

Missions of Cancer Institutes

1. Are the roles and missions of all cancer Centers identical ?

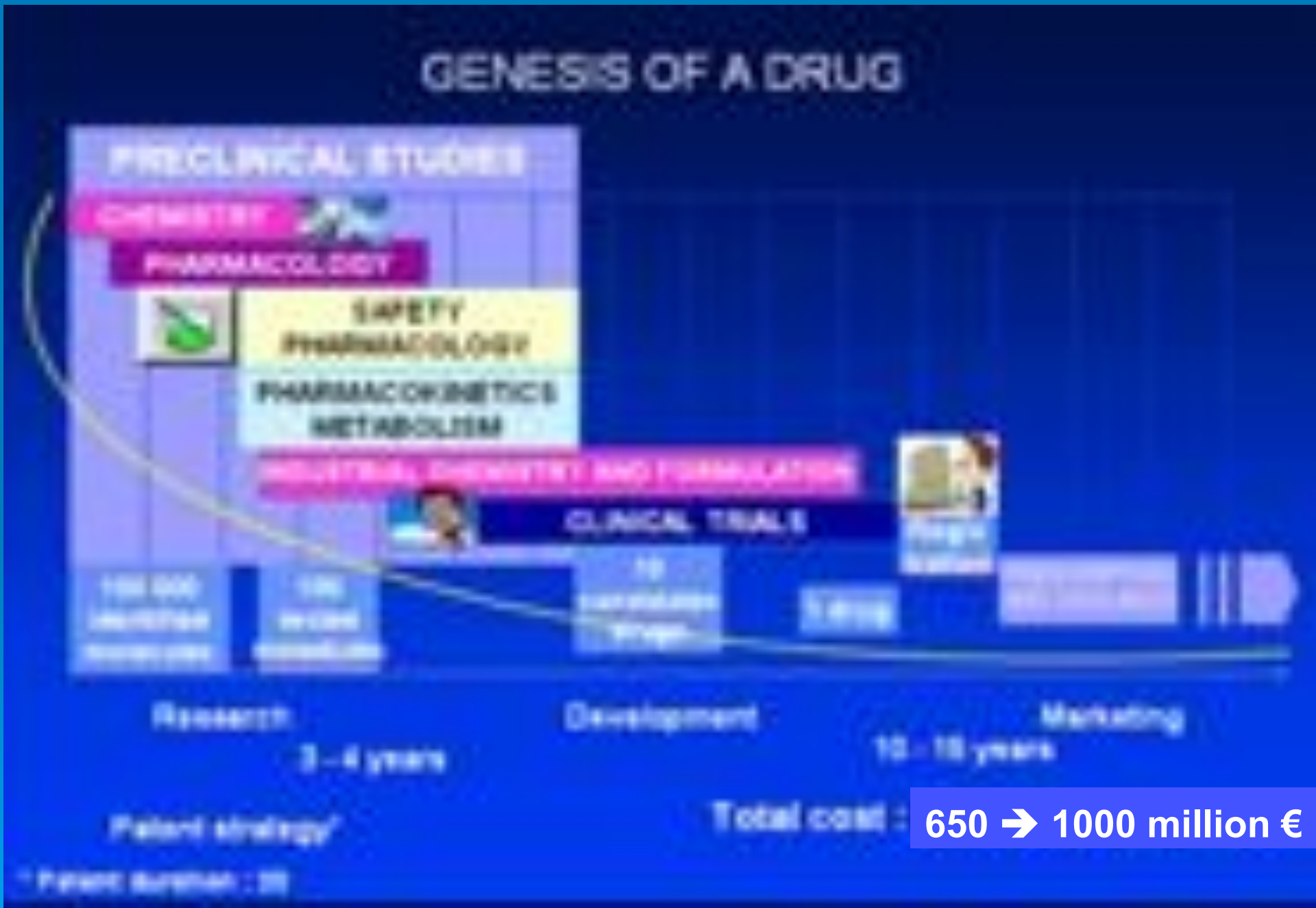
2. Can one individual Cancer Institute worldwide make the job alone ?

3. Importance of
   - Critical mass (patients-doctors-scientists)
   - Continuum from bench to bedside
   - Organization of translational research

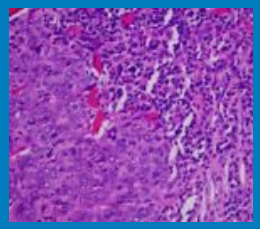
Questions

Strategies of Pharmaceutical Companies

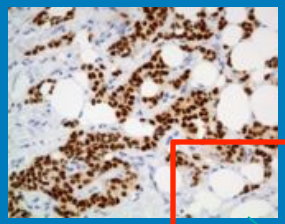
- Is the current fronteer between R-D and Marketing divisions accurate and functional ?
- Is the geographic organization of Pharmas appropriate for the needs of personalized medicine ?
- Need for a « translational development division » with global vision and specific partners ?


GENESIS OF A DRUG
PHARMACOLOGY
SAFETY
PHARMACOKINETICS
METABOLISM
CLINICAL TRIALS
Research
3 – 4 years
Development
Marketing
Total cost :
650 → 1000 million €

Breast Cancer Diagnosis in 2010

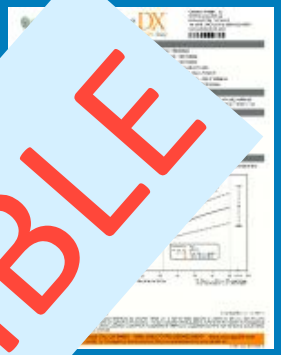


Histology



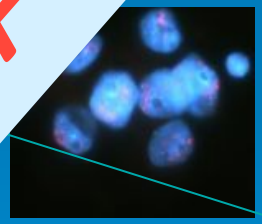
IHC
RE/Her2

Oncotyp

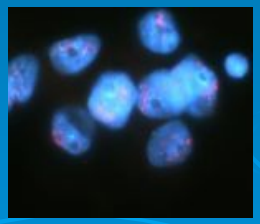


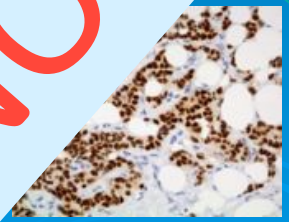
Mammaprint

CYP2D6



FGFR1





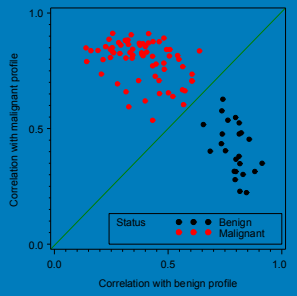
PI3K mutations

MDACC 30 gene
Génomic grade
SET index

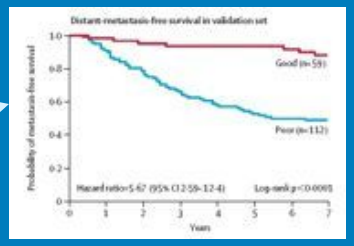
NOT FEASIBLE

Whole genome analysis

Pangenomic analysis
Expression
CGH
Sequencing

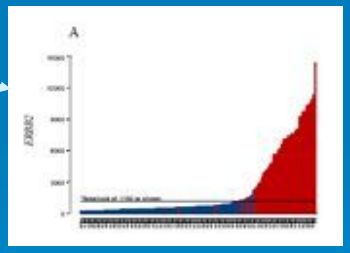


diagnosis

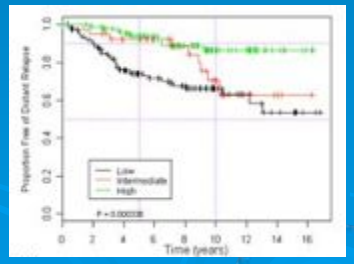


Pronostic / Grade

Cytopuncture
microbiopsies



RE / Her2



Prédictive signatures

pathology: Micro-path:
Stem cells?
Microenvironnement ?

Microdissection

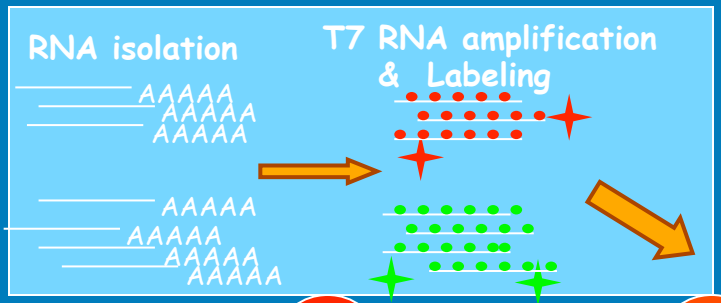
Available Equipments to date

- **Roche 454 FLX – first run in August**
  - Lease for 6 month
  - More improve approach
  - 12h long run
  - capacity : 500 Mb-1Gb

- **PGM-IonTorrent – first run plan in November**
  - Leasing 3 years
  - New technology (few experiences)
  - 2hr long runs
  - Capacity :10-100Mb (1Gb in 2012)

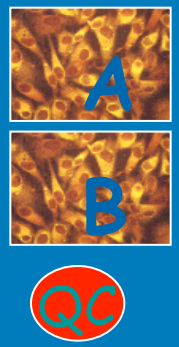
- **Evaluation of both approaches for targeted sequencing (ongoing)**
  - Evaluation of best approach for MP program analysis
  - Establishing SOPs for MP programm NGS analysis (including Bioinformatic)
- **Transfer of validated approach to LRT for production**

Genomics platform based on Agilent technology



Gene expression
microRNA

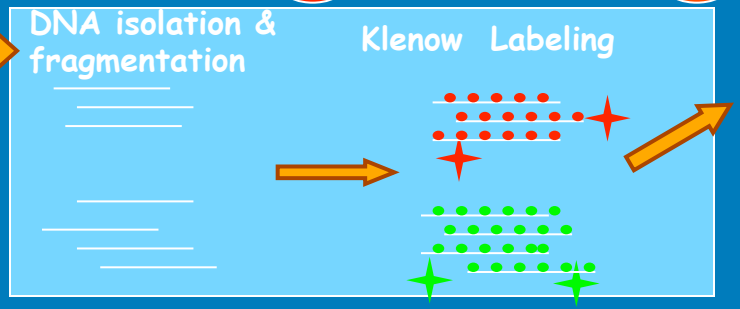
Sample



QC

QC

QC



Hybridization

Scanning

CGH
ChIP
methylation

Study design, Standard operating procedures, Quality control

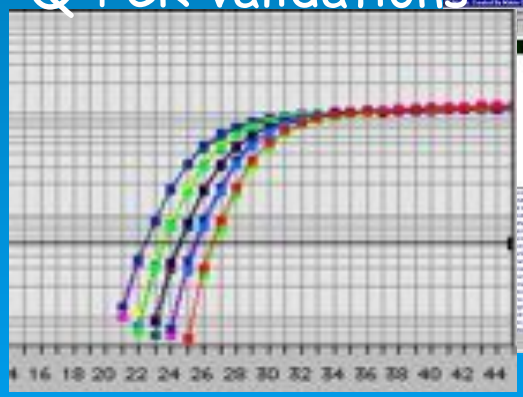
Bioinformatics, biological interpretation of data

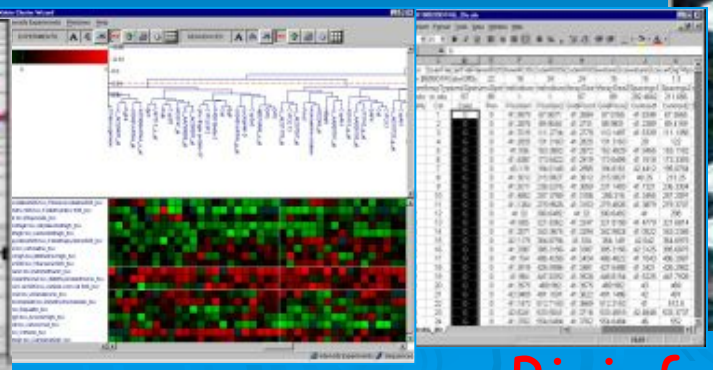
QC

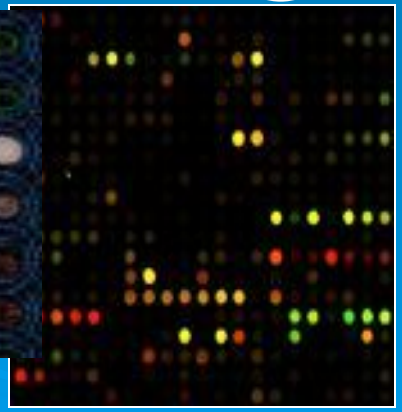
QC

Q-PCR validations

Resolver™

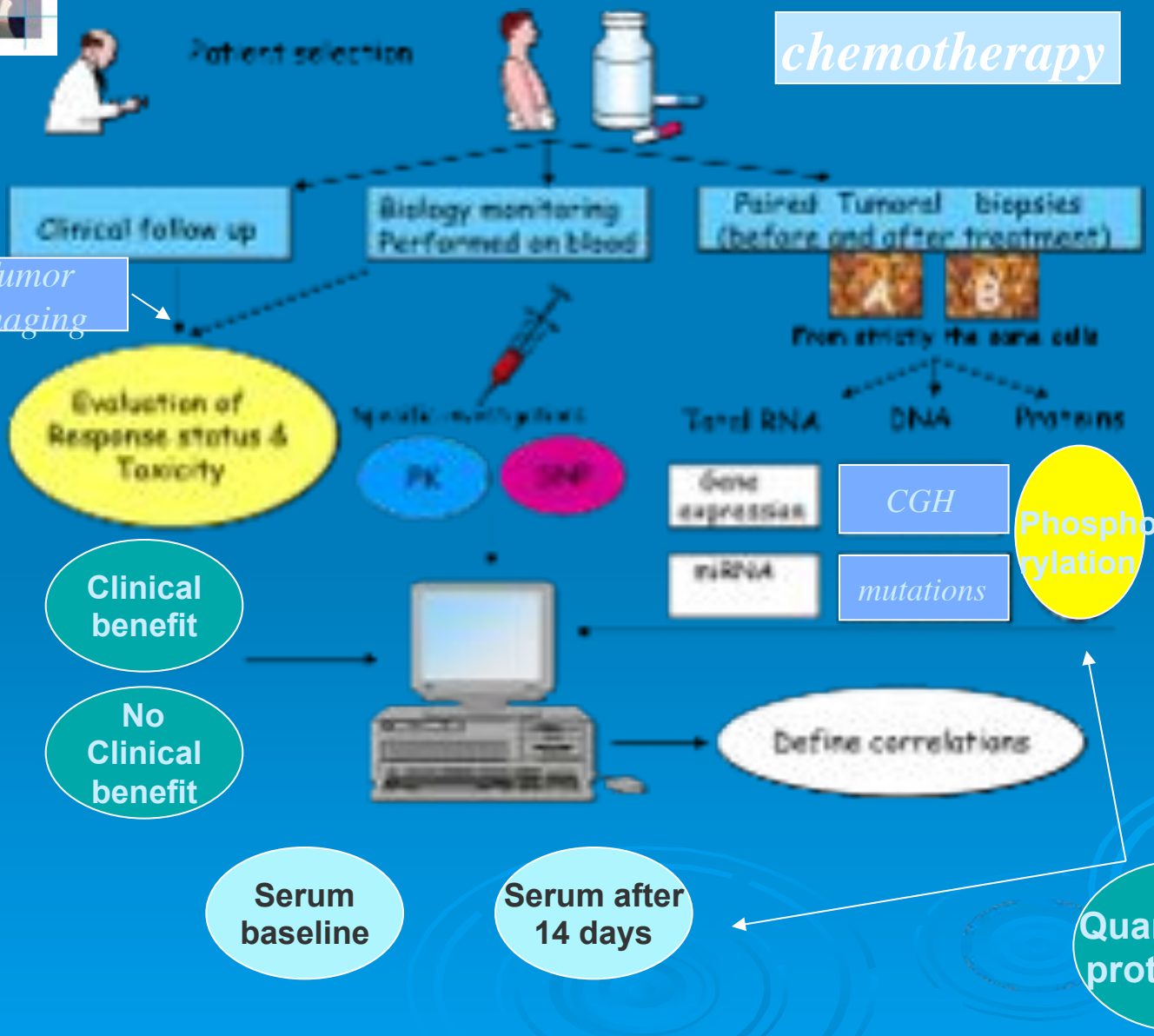






Bioinformatics

Integrated Biology Strategy

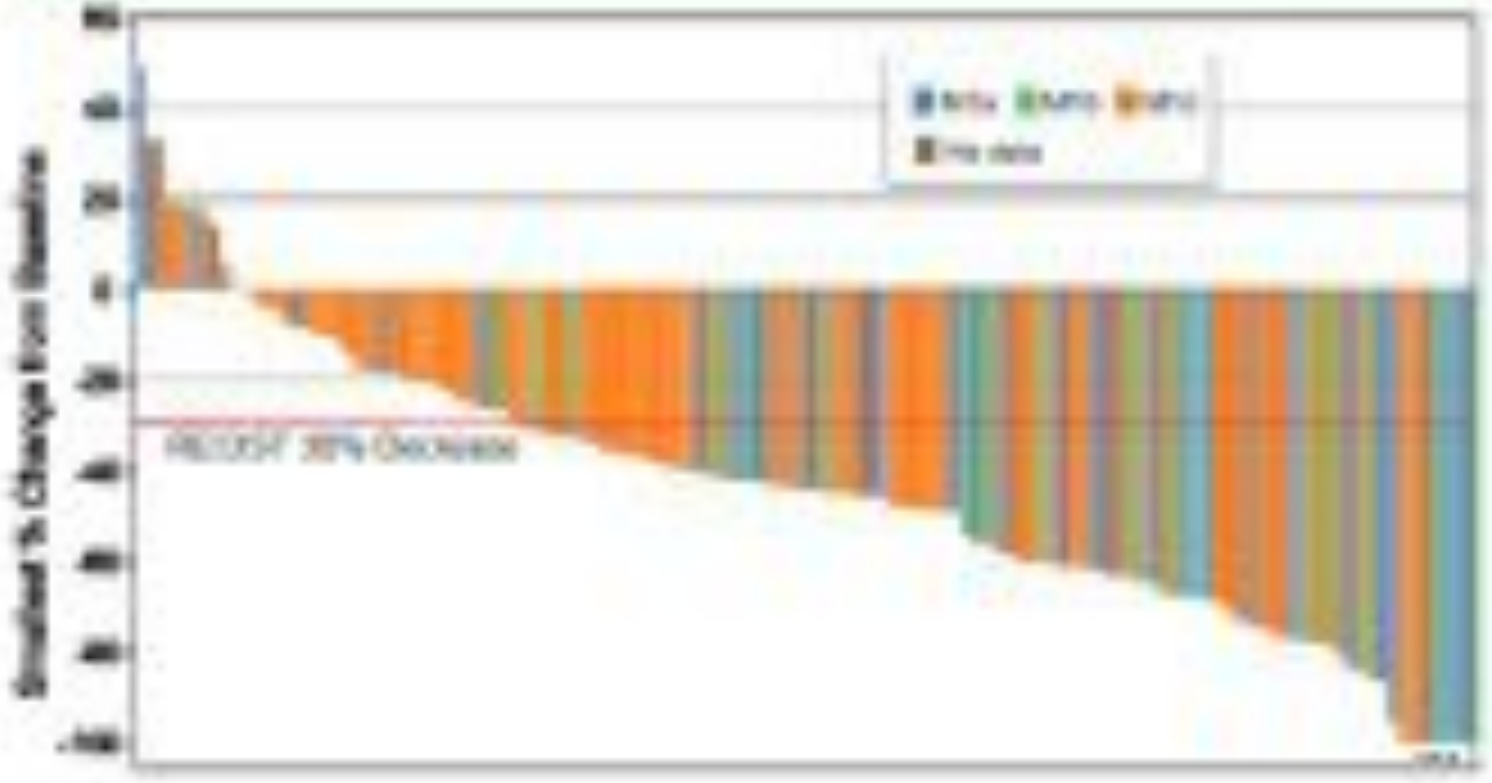


Correlation with benefit

What should we do for patients who are predicted NOT to be cured in 2011 ?

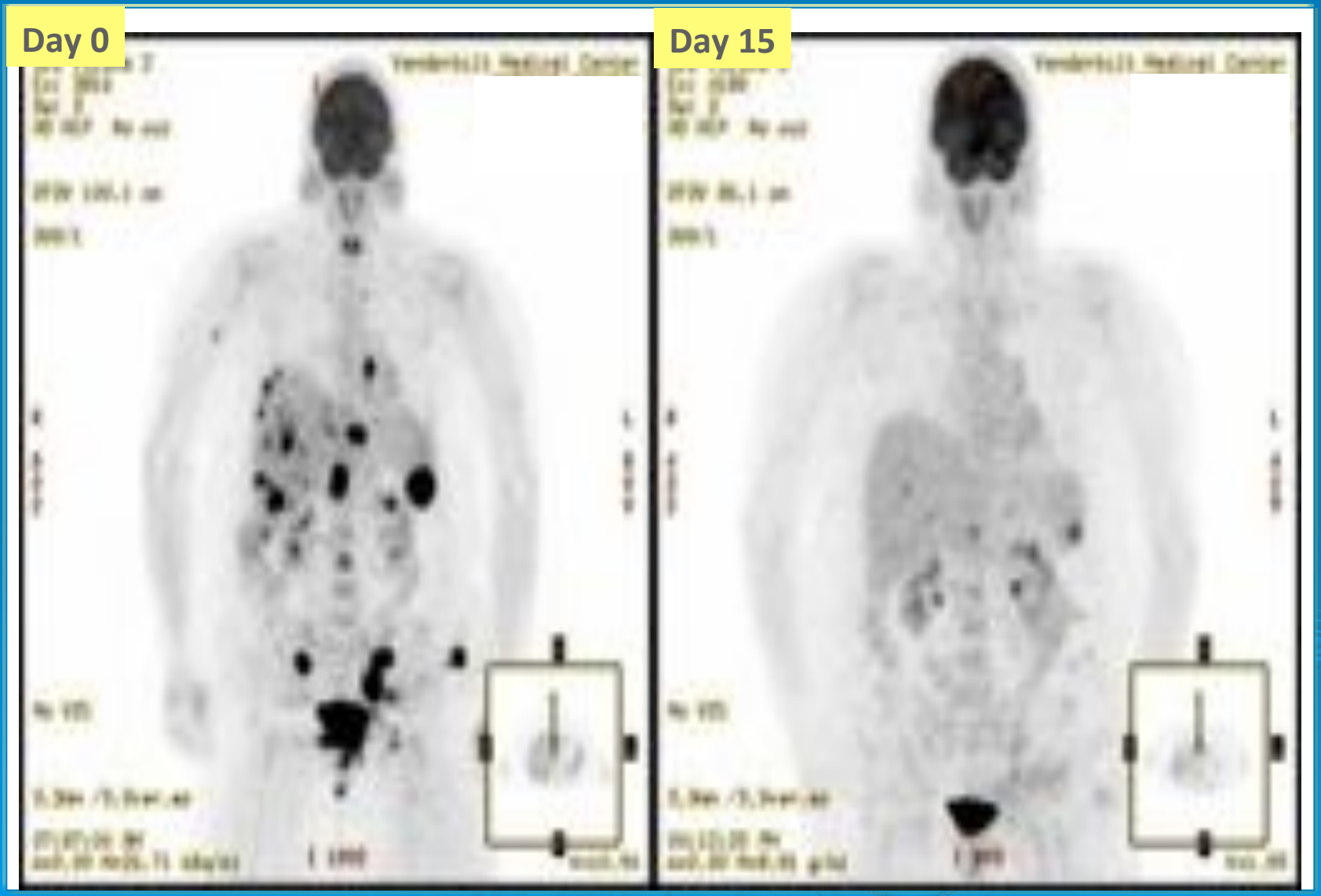
Phase II trials with molecular enrichment

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

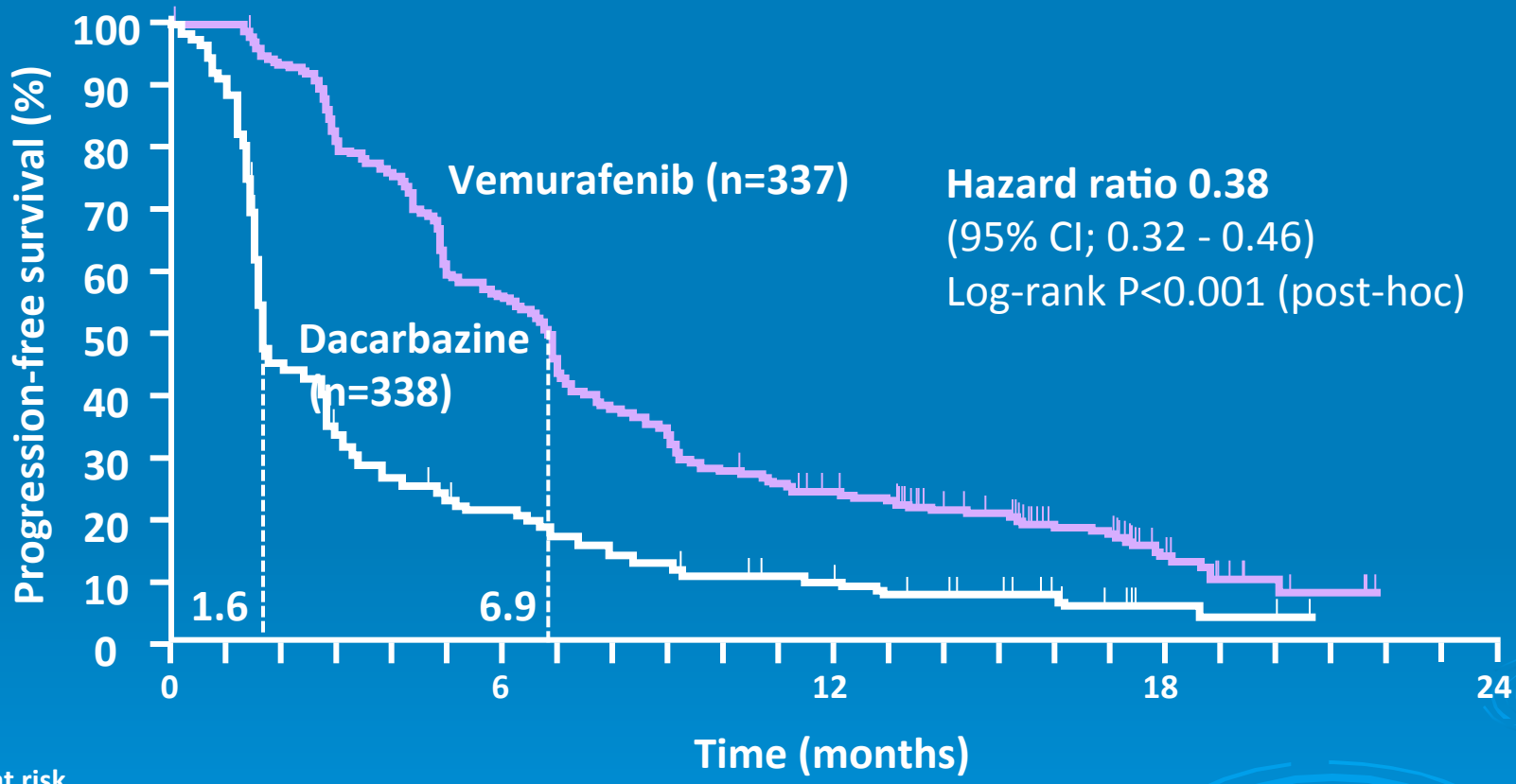


- 7 patients had ≥30% tumor shrinkage, **8 of which had confirmed CR**; 1 patient had unconfirmed CR and 3 patients had non-target lesions present
- 122 patients had baseline and ≥ 1 post-baseline scan with measurable disease

$BRAF^{V600E}$ melanoma patient PET scan at baseline and day +15 after PLX4032 treatment at 720 mg BID



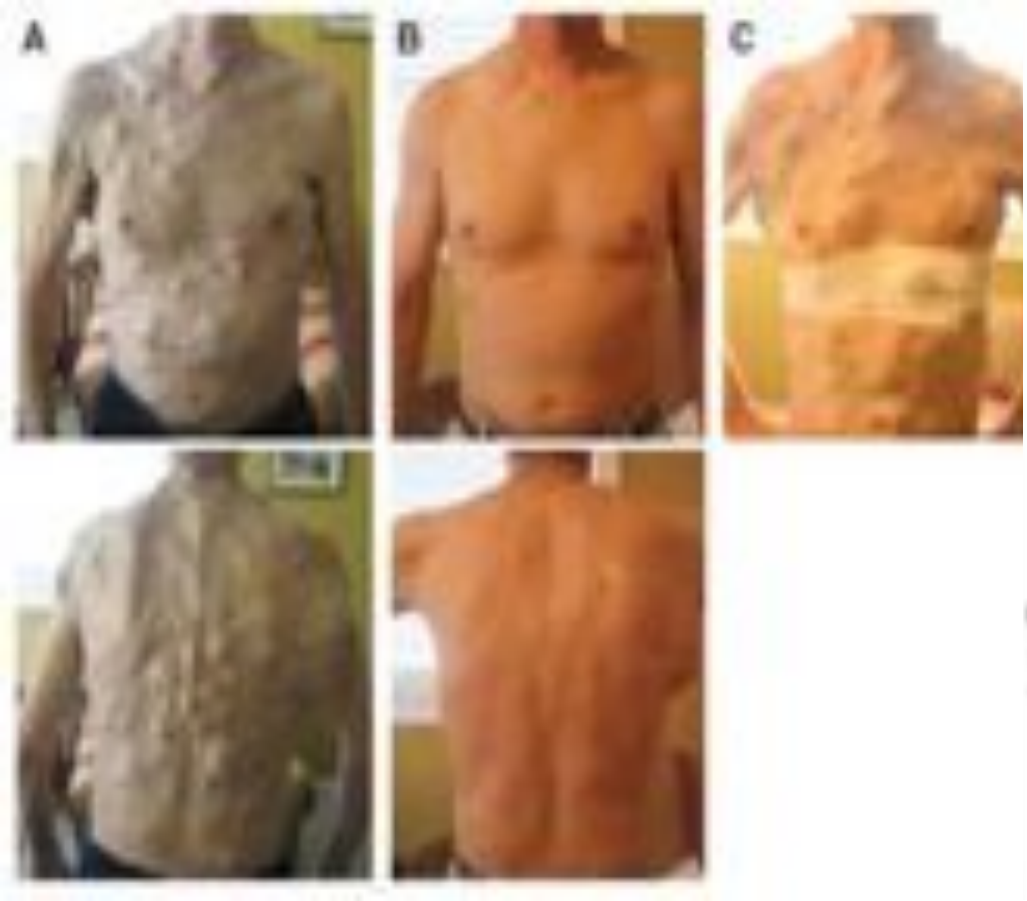
Progression-free survival (Feb 01, 2012 cutoff)
Censored at crossover

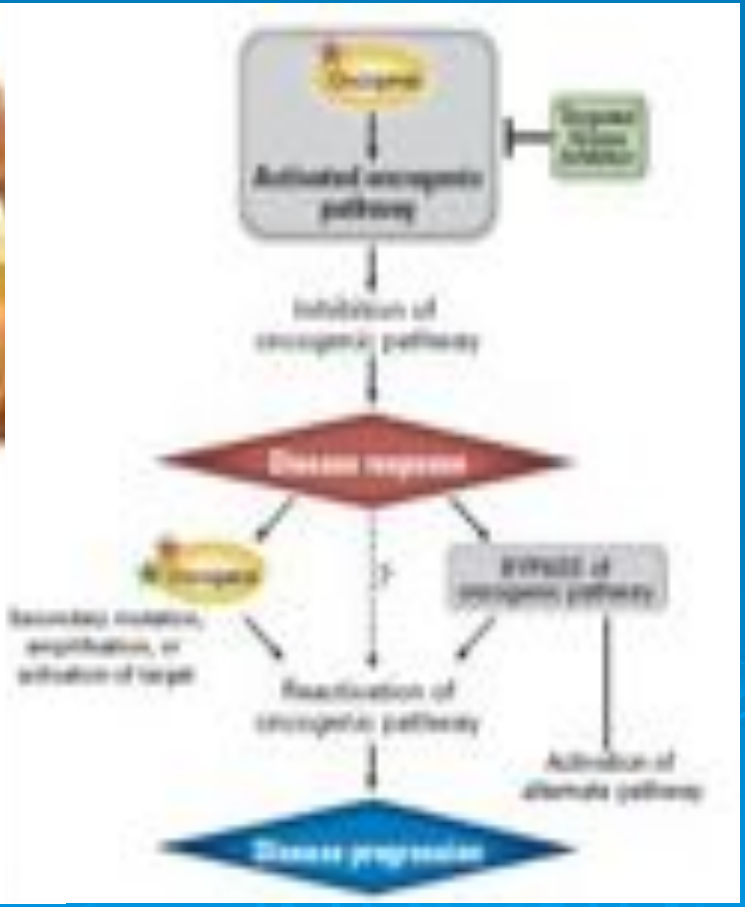


Hazard ratio 0.38
(95% CI; 0.32 - 0.46)
Log-rank P<0.001 (post-hoc)

No. at risk									
Dacarbazine	338	100	63	37	22	14	3	0	0
Vemurafenib	337	269	186	113	77	49	16	3	0

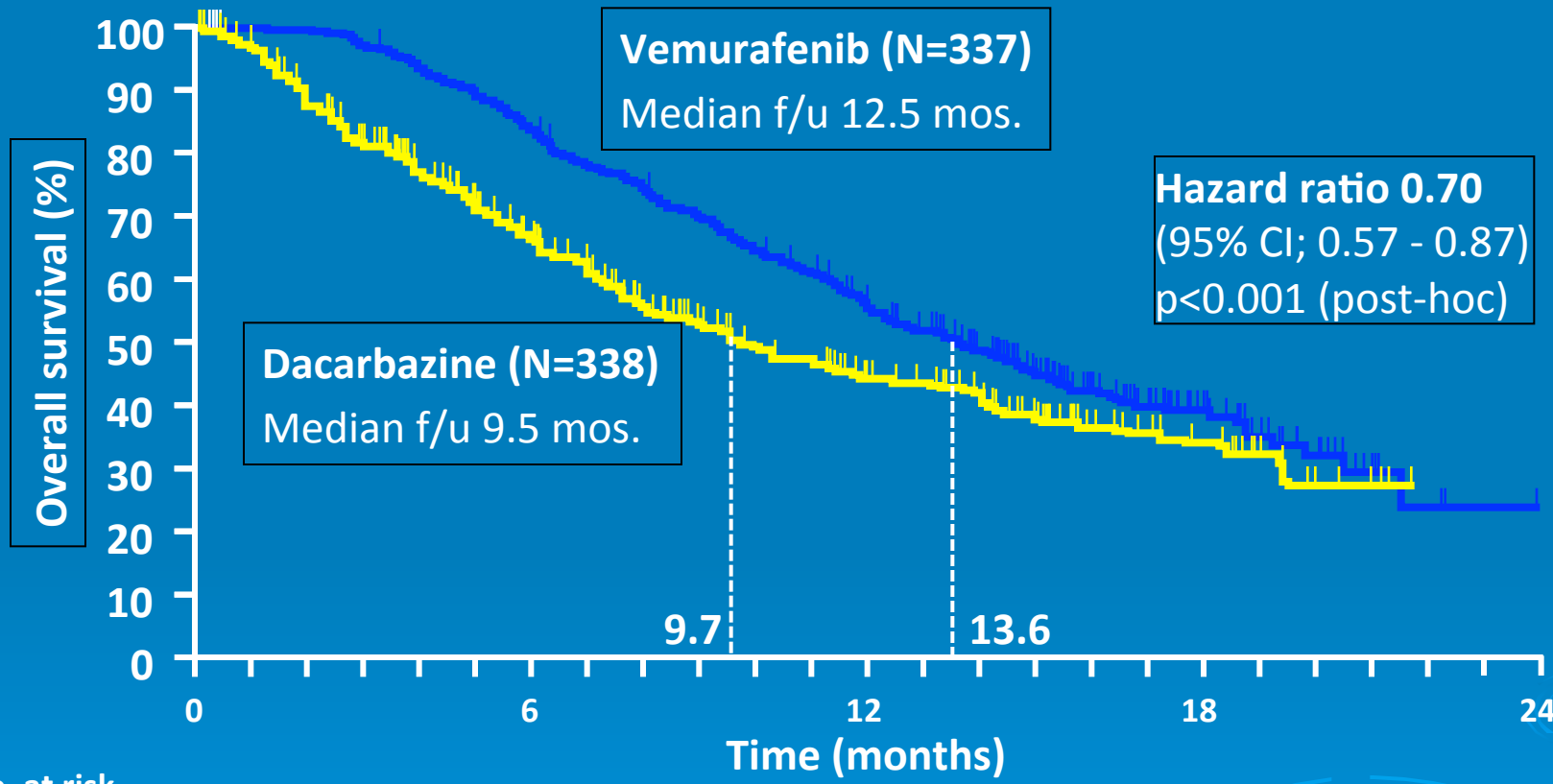
Main issue : secondary resistance to BRAF inhibitors





Solit & Rosen NEJM 2011; Nazarian et al Nature; Johannessen et al Nature; Wagle et al JCO

Overall survival (Feb 01, 2012 cutoff) Censored at crossover



No. at risk									
Dacarbazine	338	244	173	111	79	50	24	4	0
Vemurafenib	337	326	280	231	178	109	44	7	1

Selected adverse events (% of patients)

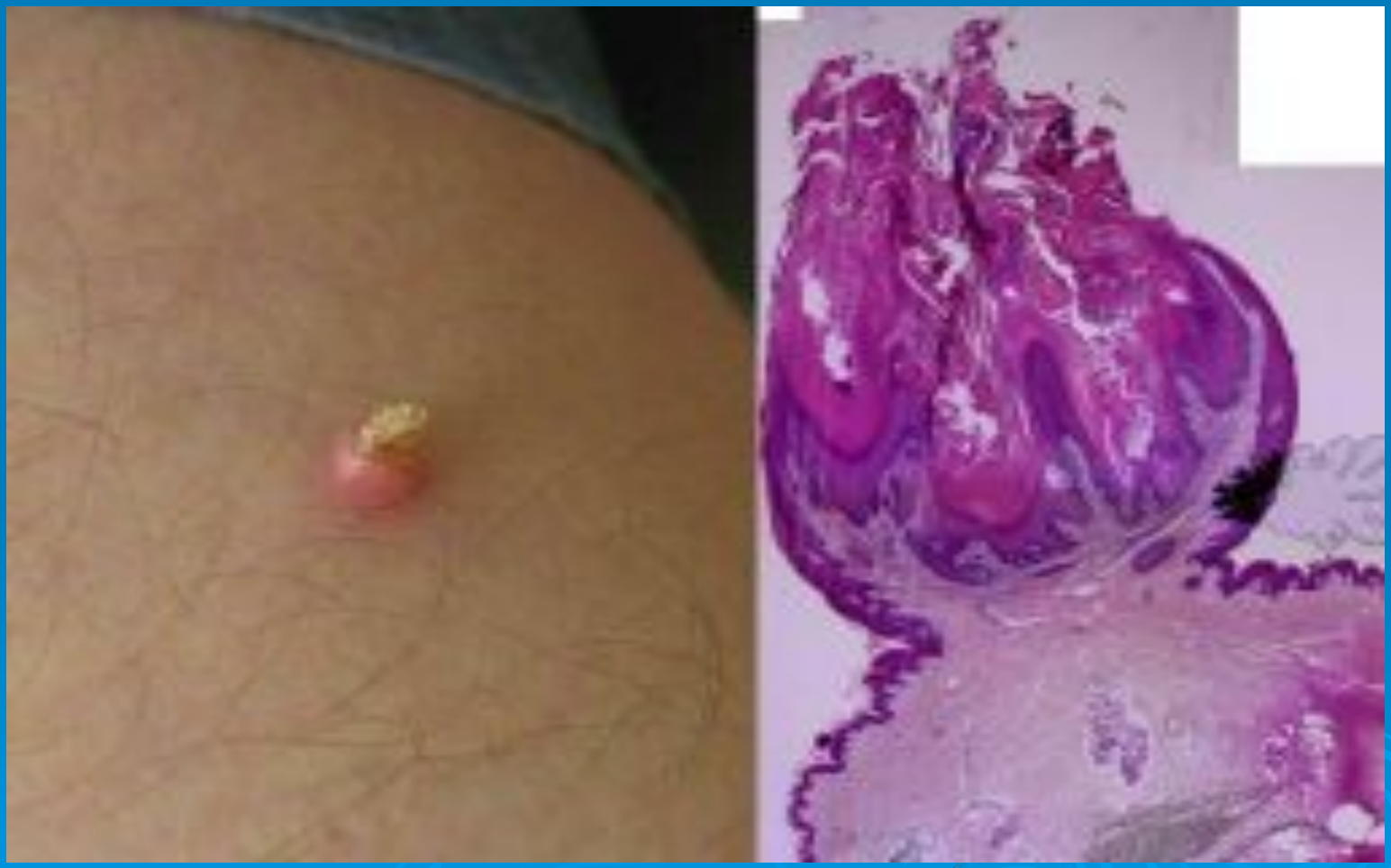
	Vemurafenib, n= 337			Dacarbazine, n= 287		
Adverse events	All	Grade 3	Grade≥ 4	All	Grade 3	Grade ≥4
Arthralgia	56	6	–	4	1	–
Rash	41	9	–	2	–	–
Fatigue	46	3	–	35	2	–
Photosensitivity	41	4	–	5	–	–
↑LFTs	26	10	1	6	2	–
Cutaneous SCC	19	19	–	<1	<1	–
Keratoacanthoma	11	10	–	<1	<1	–
Skin papilloma	28	<1	–	<1	<1	–
Nausea	38	2	–	45	2	–
Neutropenia	<1	–	<1	12	6	3

Discontinuations due to AE: 7% Vemurafenib; 2% Dacarbazine

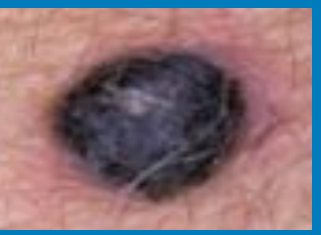
Data-cut: Feb 01, 2012

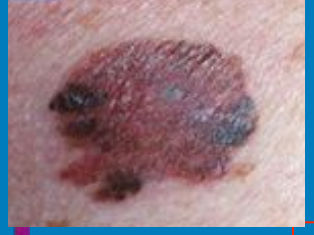
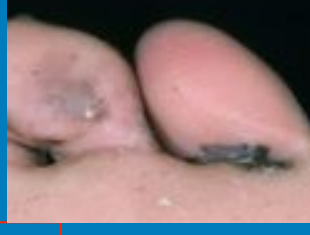
8 patients reported primary melanoma in the vemurafenib group.

Keratoacanthomas



Arnault et al, J Clin Oncol 2009



KIT

Imatinib, sunitinib, dasatinib

NRAS

Tipifarnib, lonafarnib, BMS-214662, nilotinib

Sorafenib
PLX-4032
RAF265
GDC-0879
XL-281

BRAF

RO-5126766

MEK

AZD-6244, PD-0325901, RO-4987655,
GSK-1120212

SCH-900353

ERK

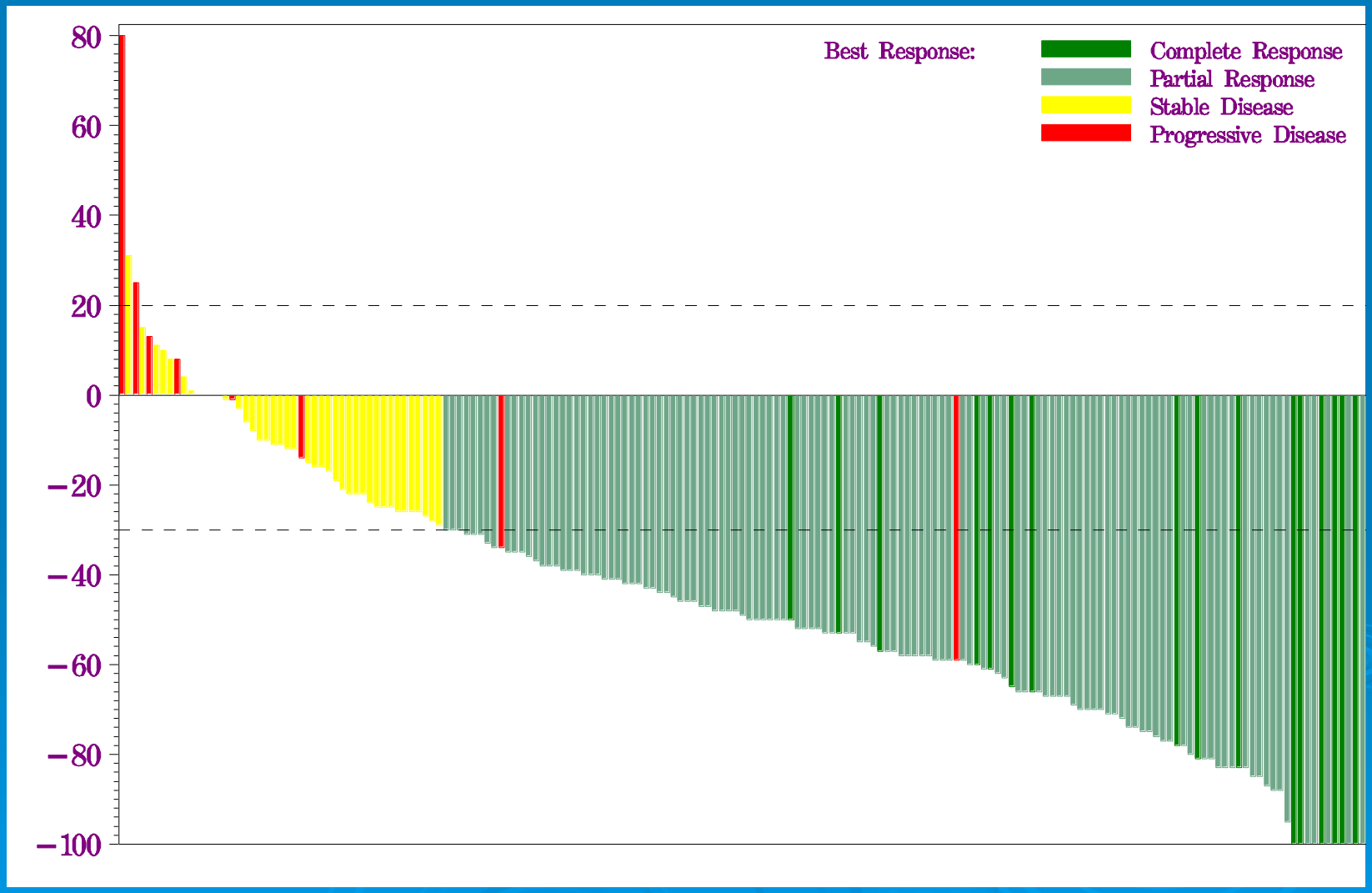
PD-0332991, P276-00

CCND1

CDK4/6

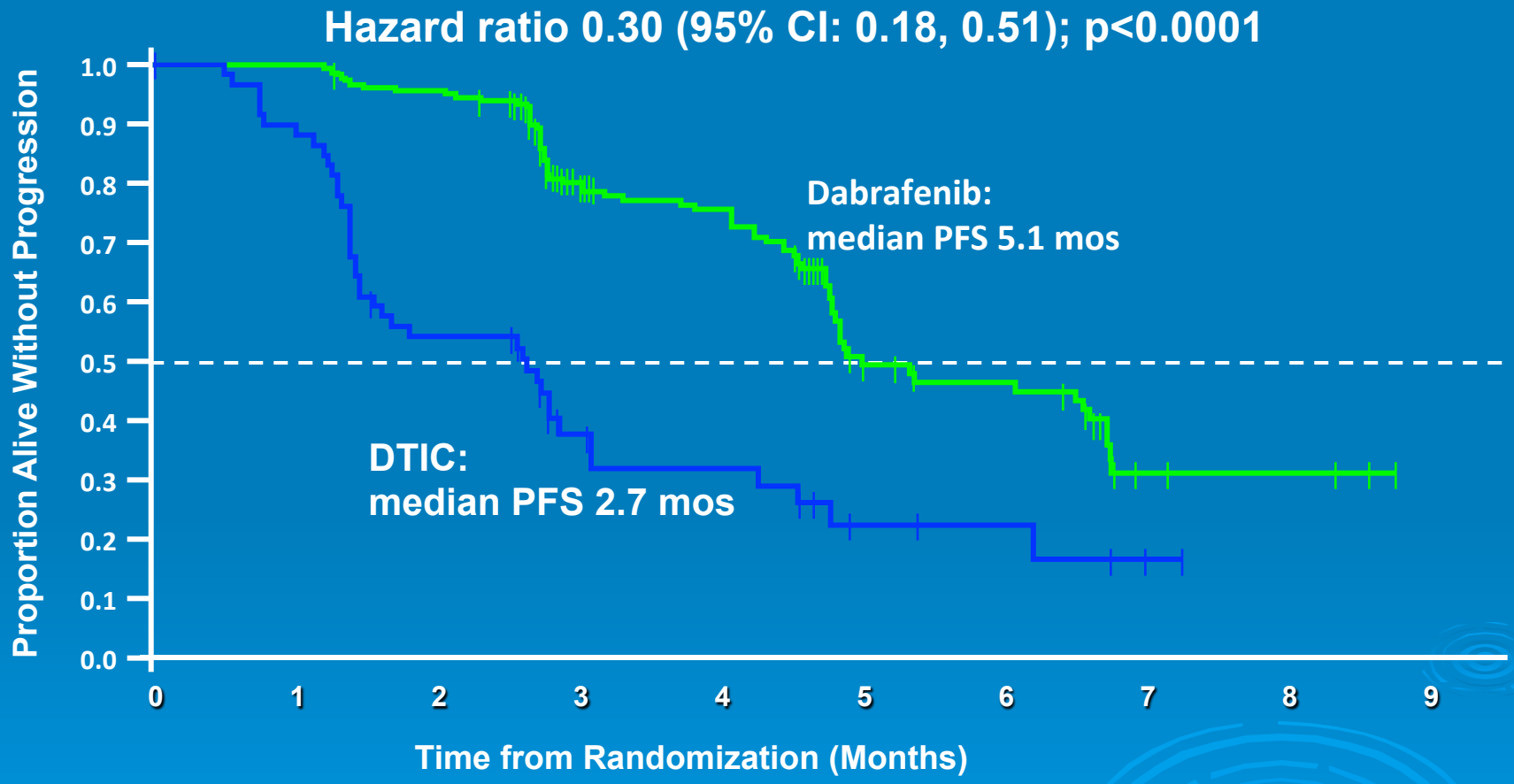
P16

Dabrafenib: Maximum Tumor Percent Change from Baseline Investigator-Assessed



Primary Endpoint: PFS

Investigator-Assessed (Cut-off: 19 December 2011)



Number at risk										
	187	184	173	113	100	41	31	5	3	0
	63	53	31	14	11	6	4	2	0	0

On randomized study treatment at cut-off: dabrafenib 57%, DTIC 27%
Median follow-up time: 4.9 months (dabrafenib 5.1 mos, DTIC 4.8 mos.)

Treatment-related AEs: ≥ 5% of Patients

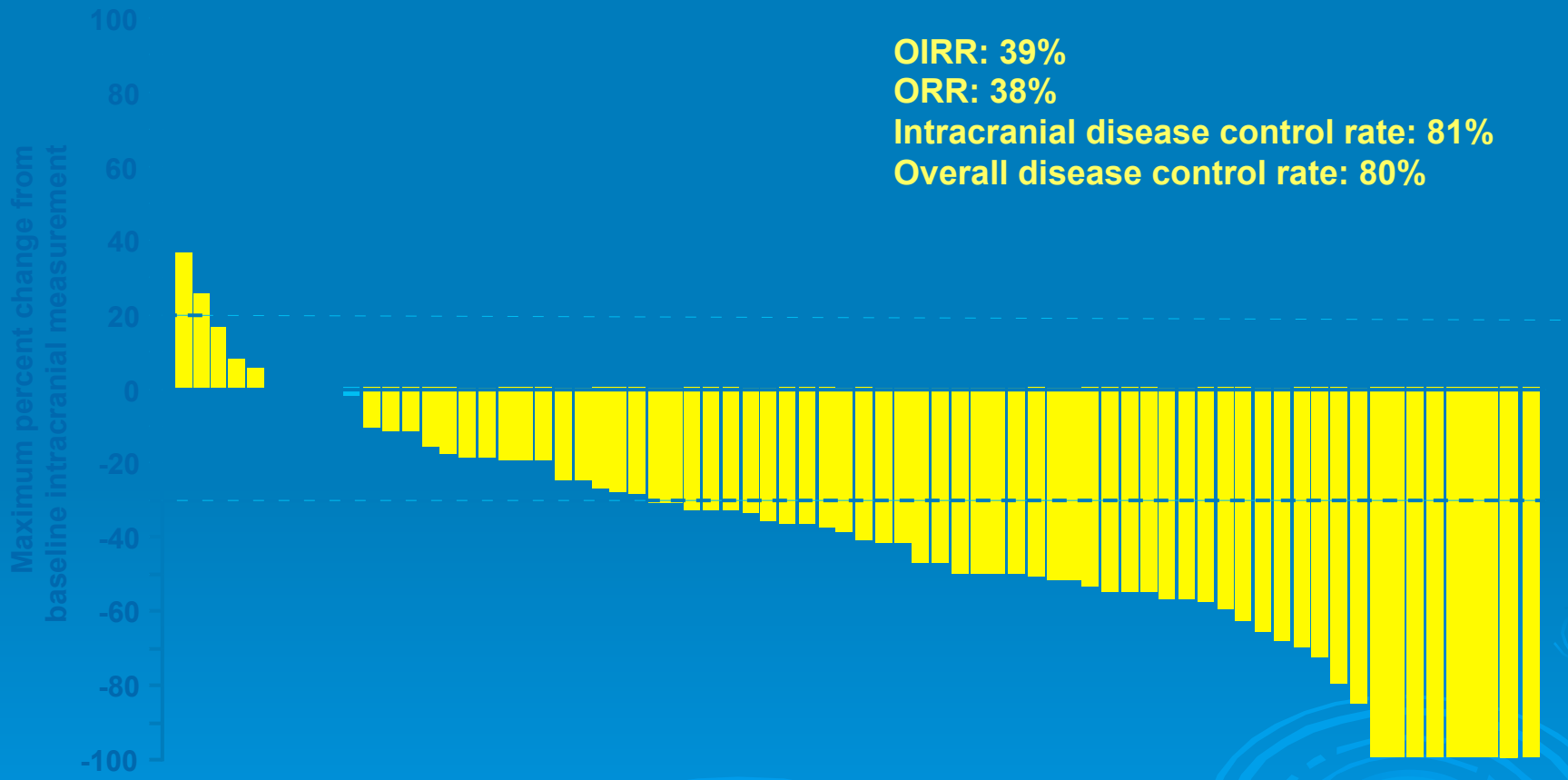
		Dabrafenib, n (%)			DTIC, n (%)		
	AE	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Skin	Hyperkeratosis	95 (51)	1 (<1)	1 (<1)	–	–	–
	Palmar-plantar hyperkeratosis	39 (21)	4 (2)	–	1 (2)	–	–
	SCC/KA	13 (7)	9 (5)	–	–	–	–
GI	Nausea	18 (10)	–	–	21 (36)	–	–
	Vomiting	8 (4)	–	–	12 (20)	–	–
Hematologic	Neutropenia	2 (1)	1 (<1)	–	9 (15)	3 (5)	4 (7)
	Thrombocytopenia	1 (<1)	1 (<1)	–	5 (8)	1 (2)	2 (3)
	Leukopenia	1 (<1)	–	–	3 (5)	1 (2)	–
Other	Arthralgia	30 (16)	1 (<1)	–	–	–	–
	Fatigue	32 (17)	2 (1)	–	13 (22)	–	–
	Headache	32 (17)	–	–	2 (3)	–	–
	Pyrexia	28 (15)	5 (3)	–	–	–	–
	Arthralgia	30 (16)	1 (<1)	–	–	–	–
	Asthenia	26 (14)	–	–	7 (12)	–	–

Overall Response Rate V600E

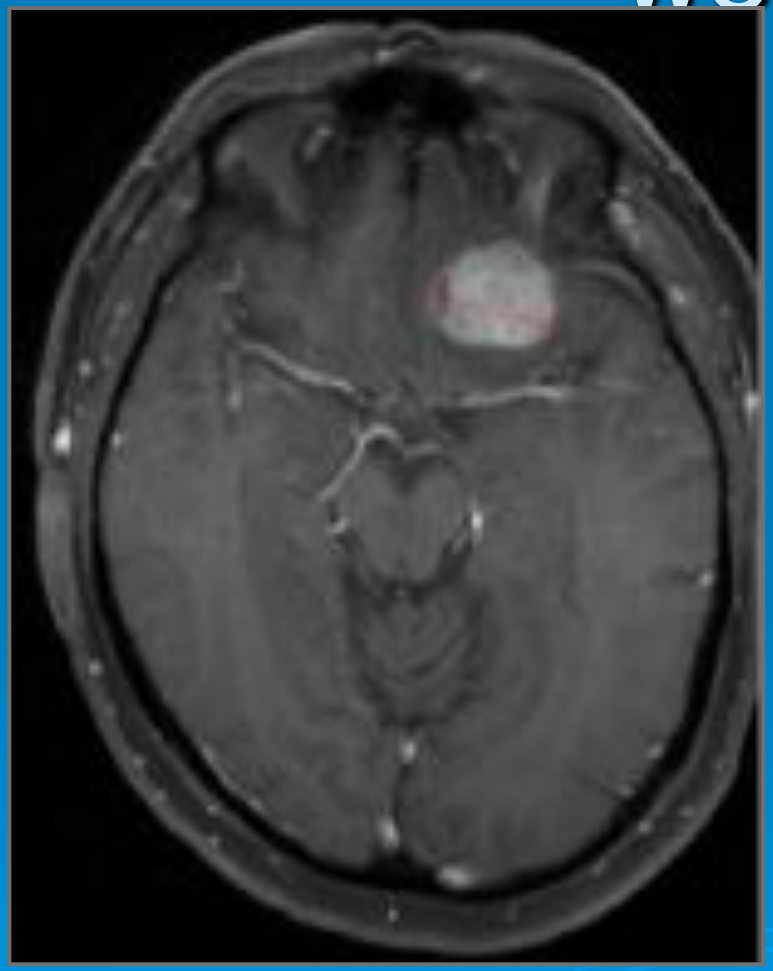
	Number of patients (%)	
	No prior brain treatment (n=74)	Prior brain treatment (n=65)
ORR (CR+PR)	28 (38)	20 (31)
Overall response		
CR	2 (3)	0
PR	27 (36)	20 (31)
SD	31 (42)	38 (58)
PD	9 (12)	5 (8)
Not evaluable	5 (7)	2 (3)
Overall disease control (CR+PR+SD)	59 (80)	54 (83)
Median duration of overall response (weeks)	27.6	20.1

CR, complete response; PR, partial response;
SD, stable disease; PD, progressive disease

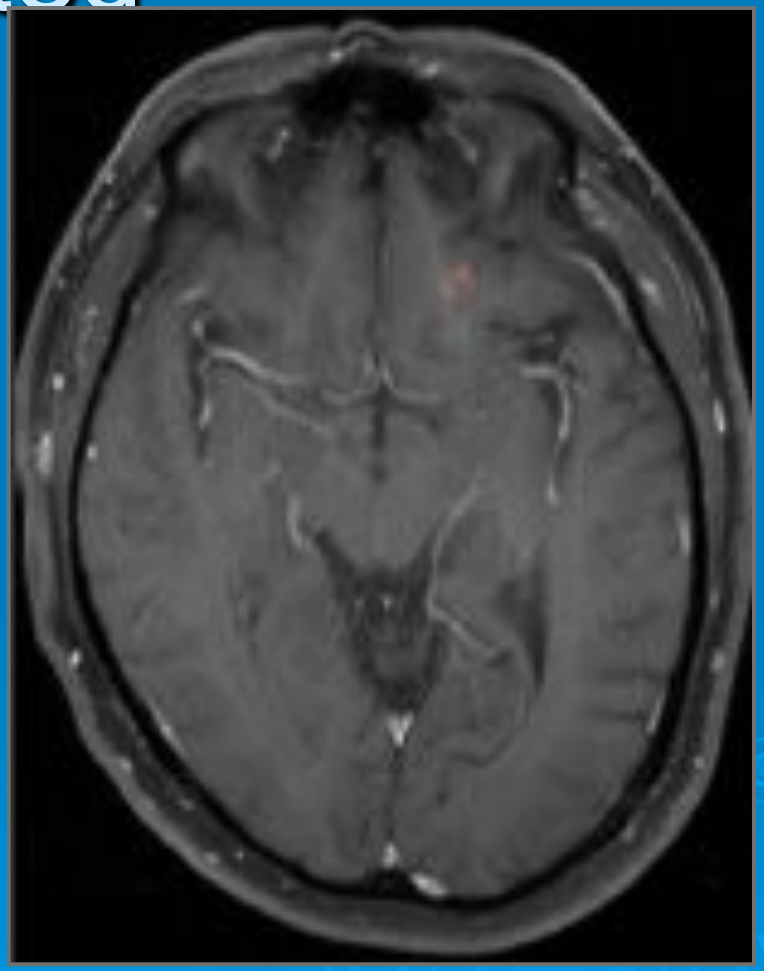
No prior brain treatment: Cohort A
$BRAF^{V600E}$ mutation-positive patients maximal intracranial target lesion reduction



Gadolinium-enhanced T1-weighted

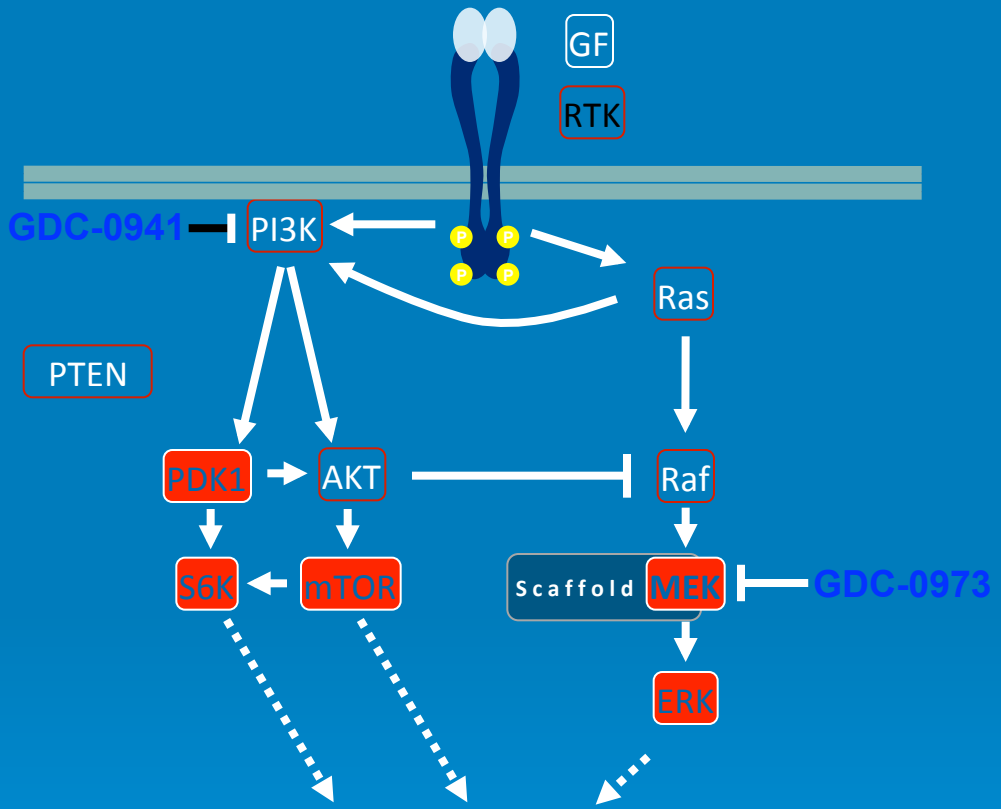


Baseline



Week 32

Targeting PI3K-AKT-mTOR and RAS-RAF-MEK Pathways

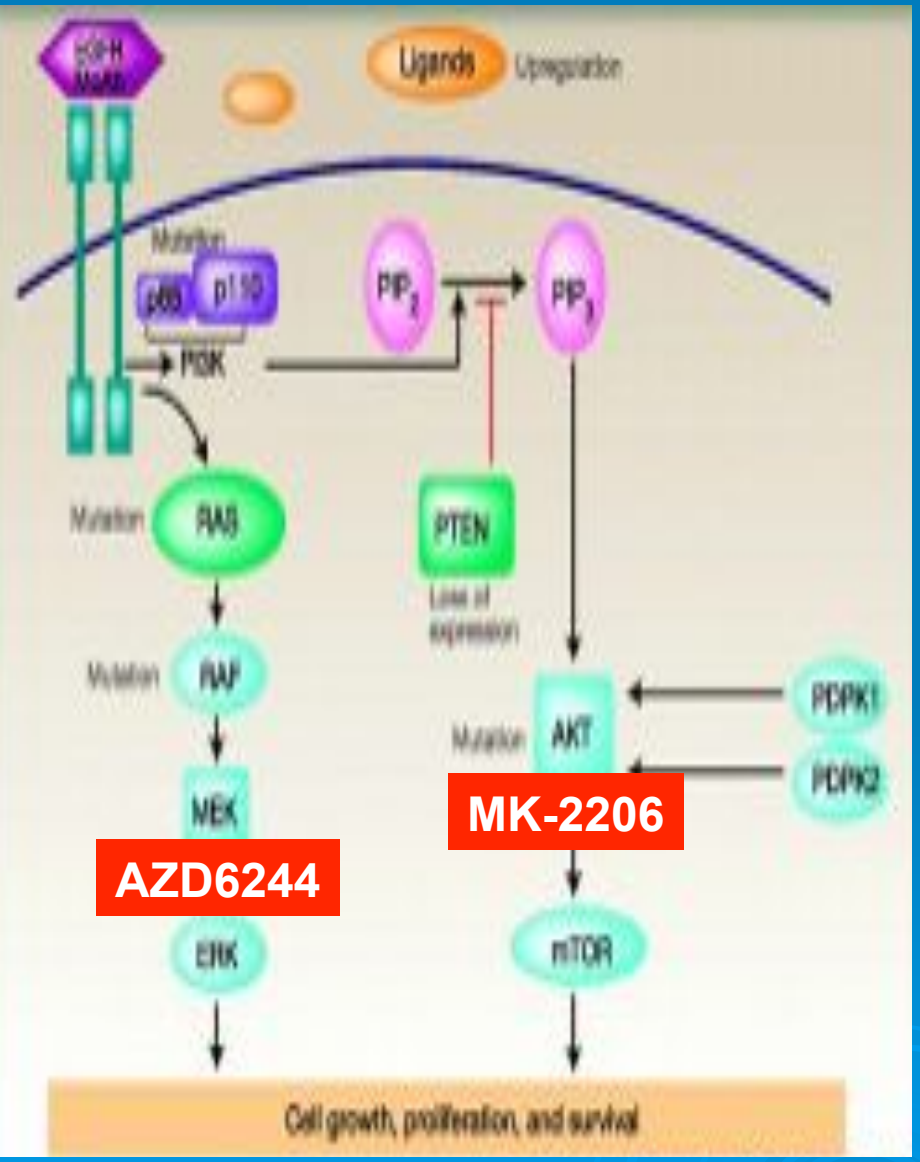


Scientific Rationale

- Pathways downstream of validated oncology drug targets (HER2, EGFR, KIT)
- Prominent mutational activation in multiple tumor types
- Extensive pathway cross-talk leading to primary or acquired resistance to single agent – single pathway therapy

Abstract #3005

Background



The RAS/RAF/MEK and PI3K/AKT/mTOR signaling pathways are frequently co-activated in malignancies

Preclinical antitumor activity by AKT inhibition was abrogated by activating Ras mutations

Similarly, activation of the PI3K & AKT decreases activity of inhibitors of the RAS/RAF/MEK pathway

Hypothesis that combined inhibition will enhance antitumor activity

Abs #77652

New disease classifications

2000

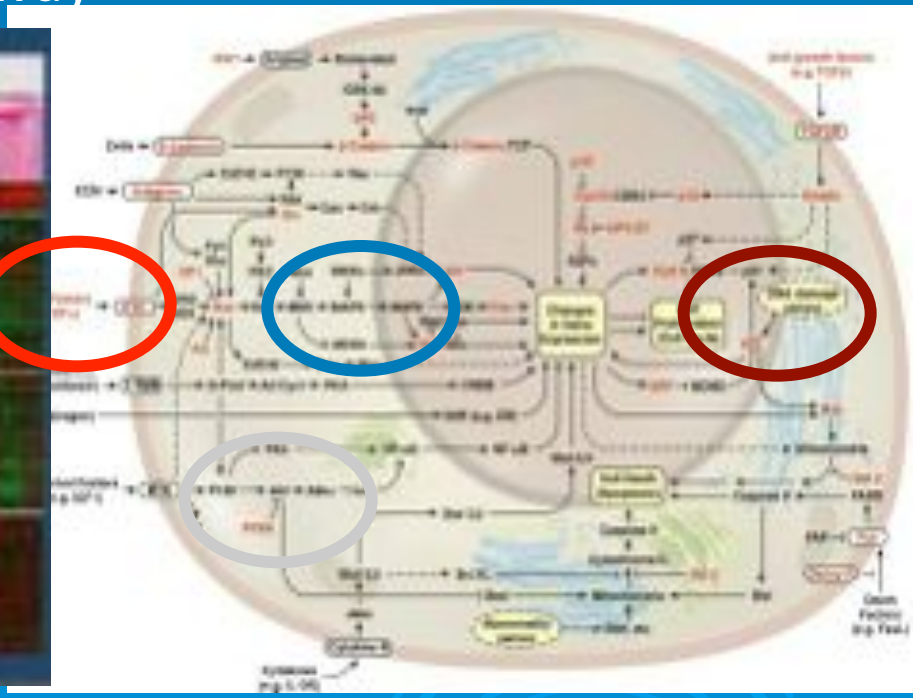
Breast cancer
= 1 disease

2000-2005:

Breast cancer:
4 diseases with dominant molecular pathway

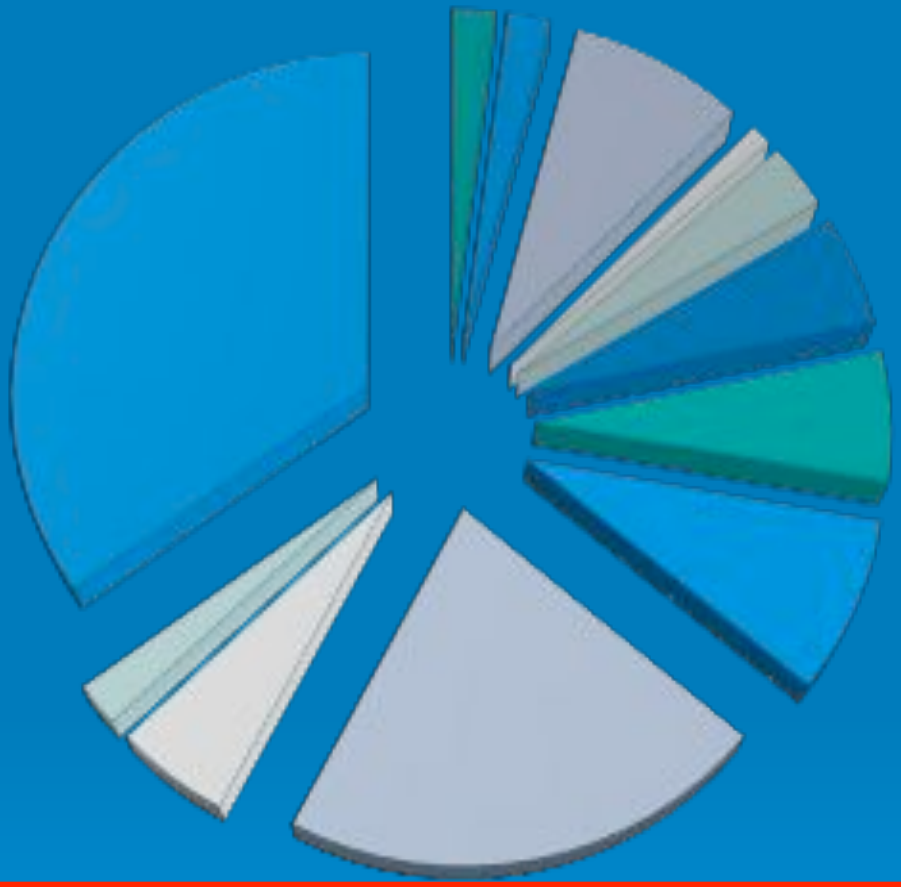
2005-2010:

Many molecular diseases



Moving from 1 frequent disease to a high number of orphan diseases:

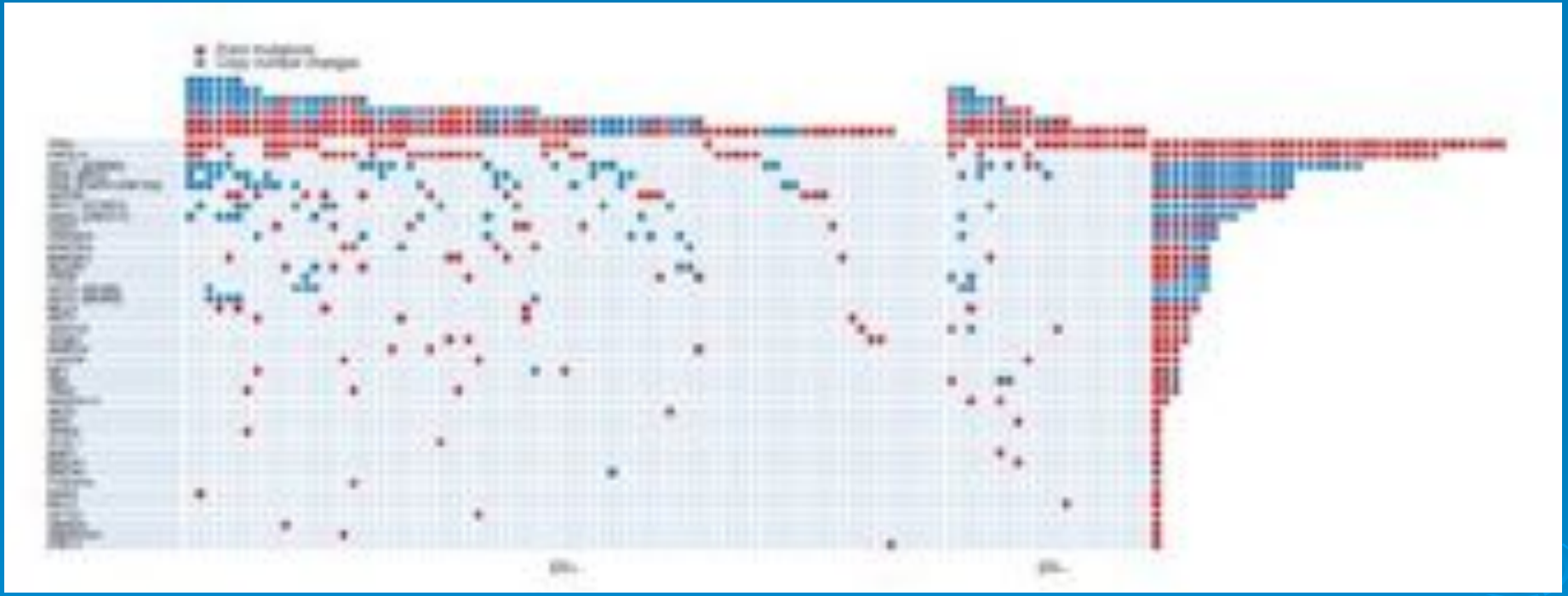
Molecular segmentation of breast cancers



Breast cancer includes **rare** molecular segments characterized by a specific molecular alteration That can be targeted by a new drug

Andre, Clin Cancer Res, 2009, Turner, Oncogene, 2010, Stemke-hale Cancer Res, 2008

Next generation sequencing to reclassify luminal breast cancers



Breast cancer (including LUMINAL) are being reclassified in
Rare genomic disease defined by oncogenic events
There is a need to enrich clinical trials testing new drugs in patients
Presenting « orphan » genomic alterations

Stephens, Nature, 2012

New model for cancer care in 2015

Cancer: Histologic definition

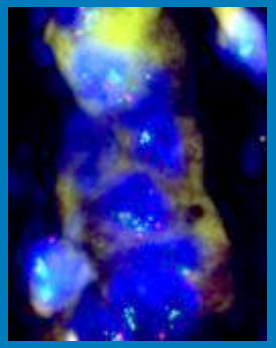
Molecular analyses
+ CTC detection

Orphan diseases = reference centers

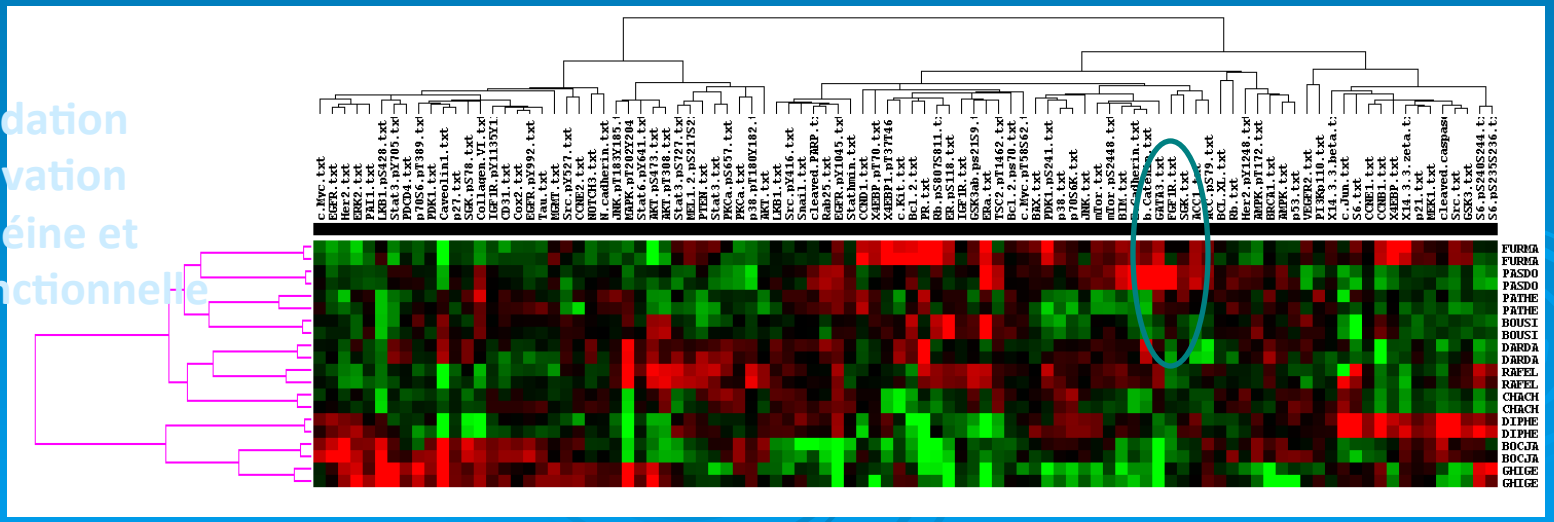
Illustration

Identification
Anomalie génomique

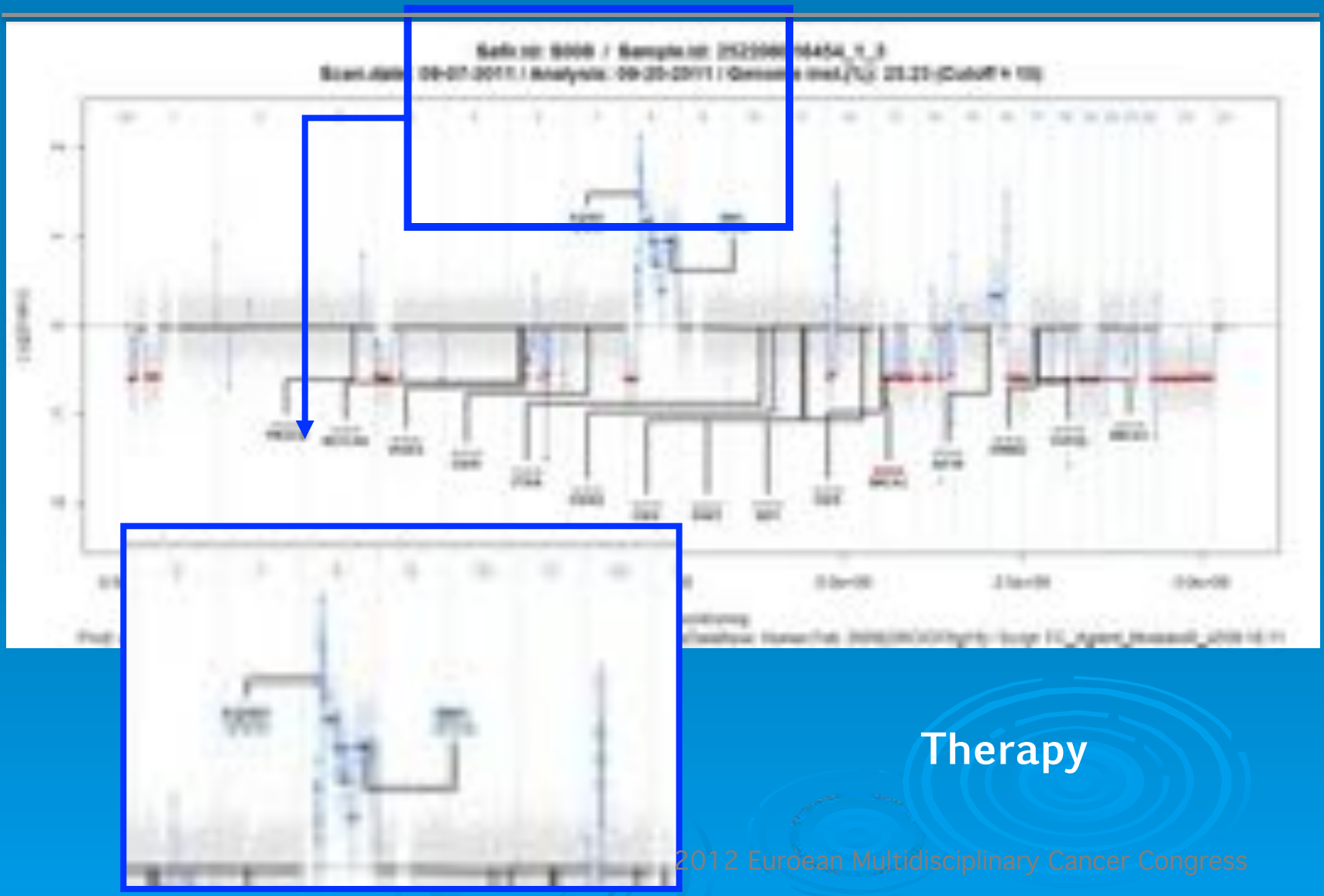
Validation
Anomalie
génomique



Validation
Activation
Protéine et
Voie fonctionnelle



SAFIR01



Therapy

Results (quality control)

QC	N (%)	Type of sample	Platform
Excellent quality (>98% valid probes)	82 (77%)	5 Paraffin 77 Frozen	72 in 4*44 K 7 in 244K 3 in 4*180 K
Good quality (95-98% valid probes)	14 (13%)	11 Paraffin 3 Frozen	4*44 K
Poor quality (<95% valid probes)	7 (6%)	6 Paraffin 1 Frozen	4*44 K
Non available	5 (4%)	2 Paraffin 3 Frozen	4 in 244K 1 in 4*44 K

Excellent quality	77 out of 84 (92%) of Frozen samples 5 out of 24 (21%) of Paraffin-embedded samples

Results (molecular alterations)

- 67 targetable molecular alterations in 53 (49%) patients:
- 11 PIK3CA mutations:
  - (p.Glu542Lys, p.His1047Leu, p.His1047Arg, p.Gly1049Arg)
- 7 Akt mutations:
  - (pGlu17Lys, pAsp46Glu, p.Leu52Phe)
- 15 amplifications in the FGF pathway
- Average number targetable alterations per patient 1.2 (range 1 to 4)

Personalised treatment

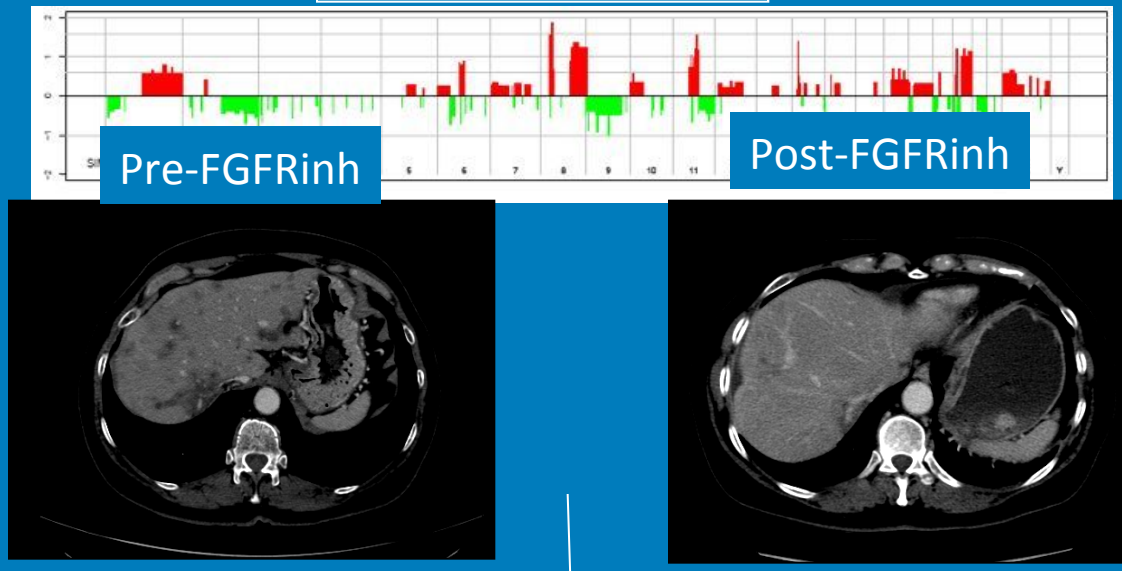
Targeted therapy	Molecular alterations	N patients	Average of previous lines (range)	Evidence of efficacy (PR or SD≥16 weeks)
FGFR inhibitor	FGFR1 ampl (2) FGF4 ampl (2) FRS2 ampl (1)	5	3 (1 to 5)	3/5 patients
mTOR inhibitor	PIK3CB ampl (2) PTEN loss (1) AKT1 mutation (1) PIK3CA mutation (2)	6	4 (1 to 7)	3/6 patients
VEGFA inhibitor	VEGFA ampl	2	1.5 (1 to 2)	1/2 patients
IGF1R inhibitor	IGF1R ampl	1	2	0/1 patient (SD 10 weeks)
HER2 inhibitor	Her2 ampl	1	1	1/1 patient
DNA alkylating agent	Genomic instability	2	2 (1 to 3)	0/2 patients
Metronomic cyclophos	BRCA2 loss	1	8	0/1

Evidence of antitumor activity in 8/18 patients

Personalised treatment

2008

Phase I FGFR1 inh



Phase II dovitinib FGFR1-amplified mBC
(Andre, Am Soc Clin Oncol, 2011)

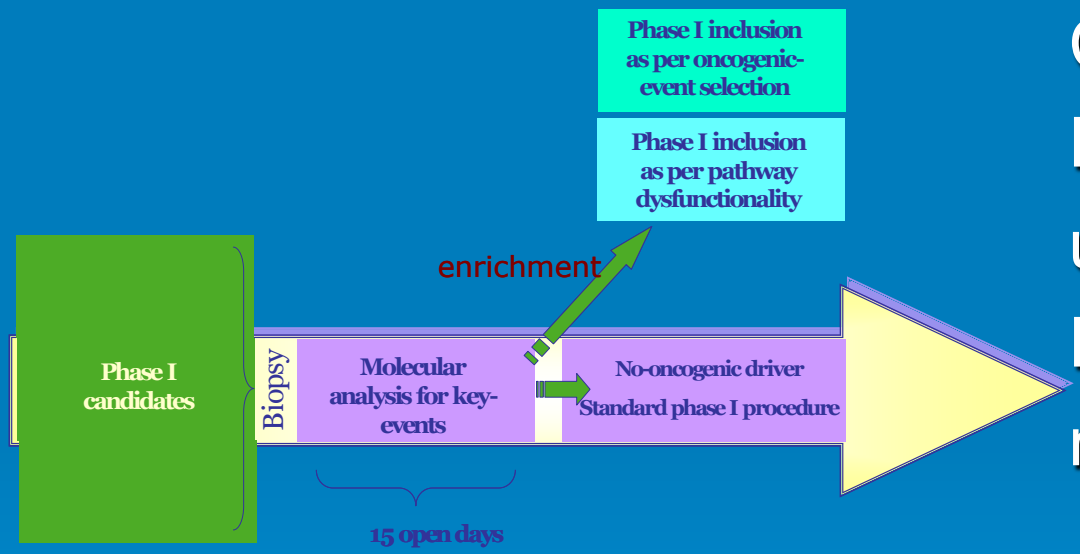
2011

Phase II randomized trial dovitinib FGFR1-amplified mBC

Molecular screening allowed finding a good indication early in the development

MOlecular Screening for CAncer Treatment Optimization

The MOSCATO trial – PI JC Soria



Portfolio 30 phase I open

CGHarray, SeqCan

Endpoint PFS2/PFS1 >1.3 under targeted therapy

H0 = 15% ; H1= 24%

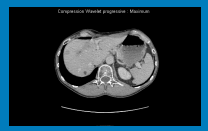
n=165

Study opening october 27th 2011

Switch to NGS in 2012

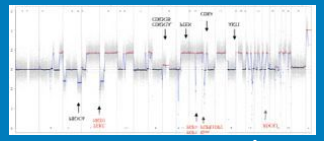
Amendment : pediatric cohort MOSKIDO – PI B Geoerger

MOSCATO



TUMOR BIOSPY

SEQCan



CGHarray Agilent

Early clinical trial unit

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PATIENT
Physicians select and identify patients, candidates for phase I-II trials

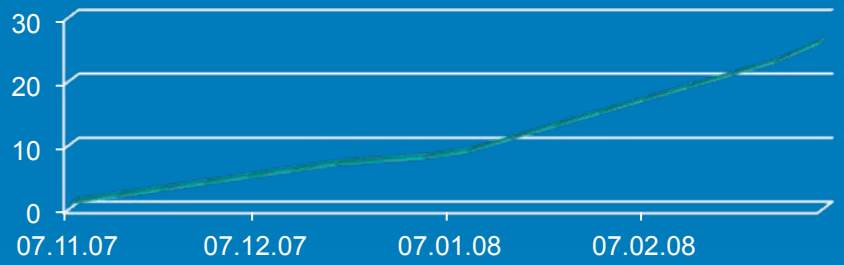
TISSUE (biopsy, blood)
Collect fresh tumor DNA/RNA
Collect blood samples (CTC, cDNA)
Collect normal tissue

MOLECULAR SCREENING
Mutation analysis-SEQCan
DNA analysis-CGHarray Agilent

CLINICAL DECISION
Physicians analyse report of genomic profile
Impact on treatment strategy

THERAPY
Enroll patients in phase I-II trials
Compassional program, FDA/EMEA approved drugs

26 pts enrolled in 17 weeks



Take home message

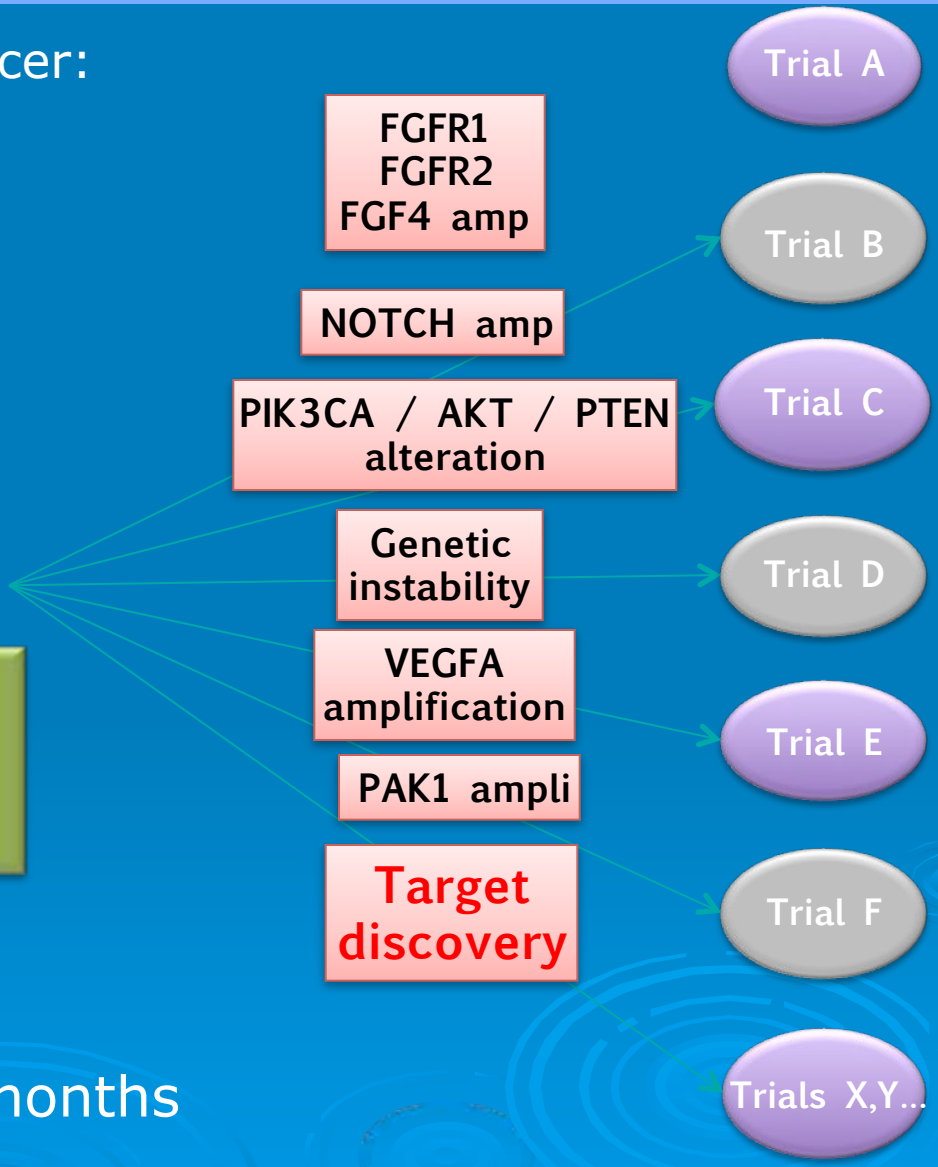
- National program in France that performs whole genome array in the context of daily practice, with the aim of identifying oncogenic genomic alteration in each patient
- This program should allow increasing the number of « informative » patients included in early trials
- Efforts are focusing on developing kinome (and DNA repair) functional tests to complement genomic analyses

SAFIR01 – PI Fabrice André
Multicentric Unicancer Sponsored study

Molecular screening in Breast cancer:
Which candidate target ?

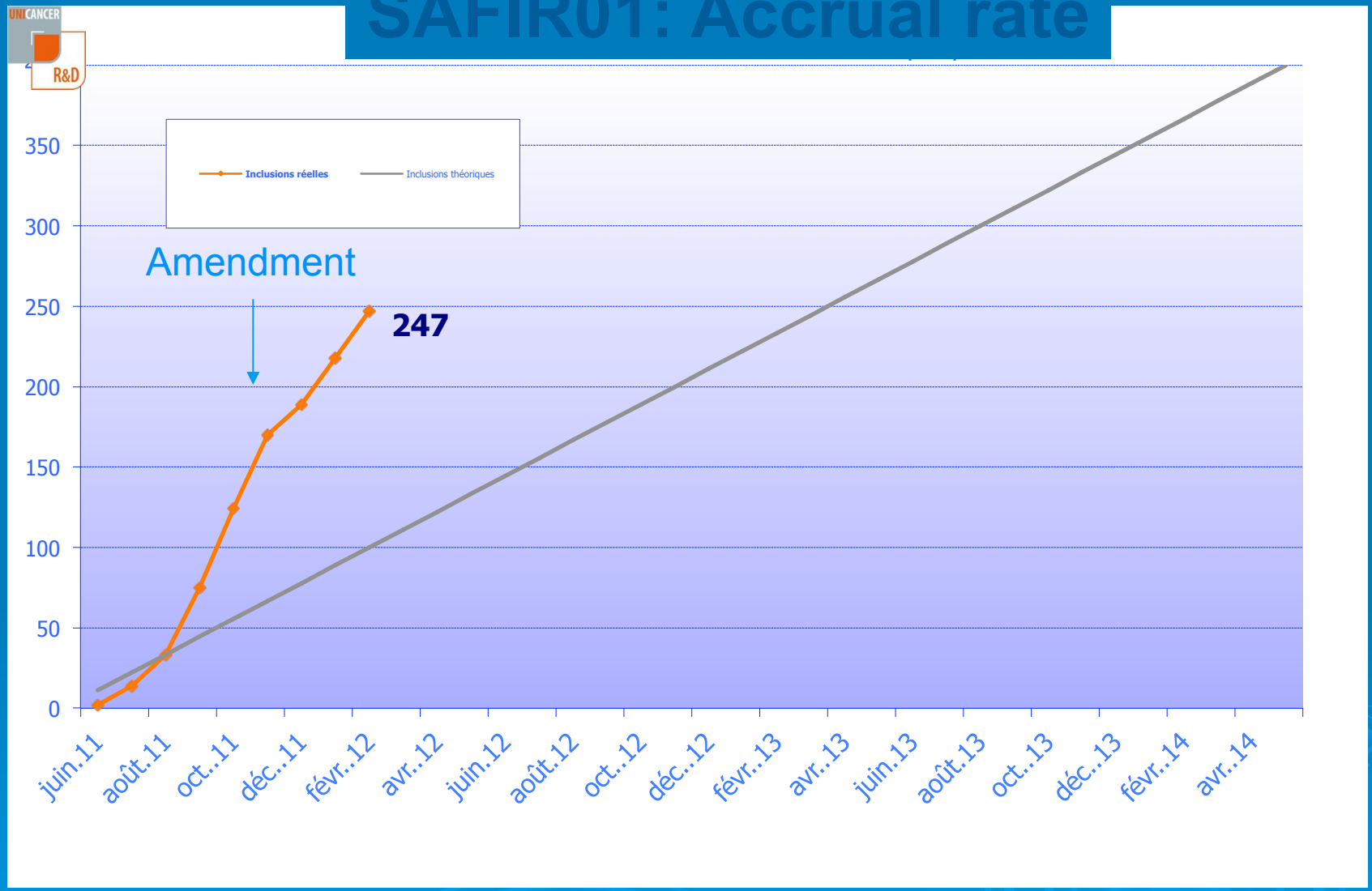
Biopsy of metastatic sites
Frozen sample
CGH/hot spot mutations
(PIK3CA/AKT)*
PS=0-1, eligible for phase I
SD / PR under treatment
N= 400

Primary endpoint:
% of patients included in phase I/II trial according to the profile



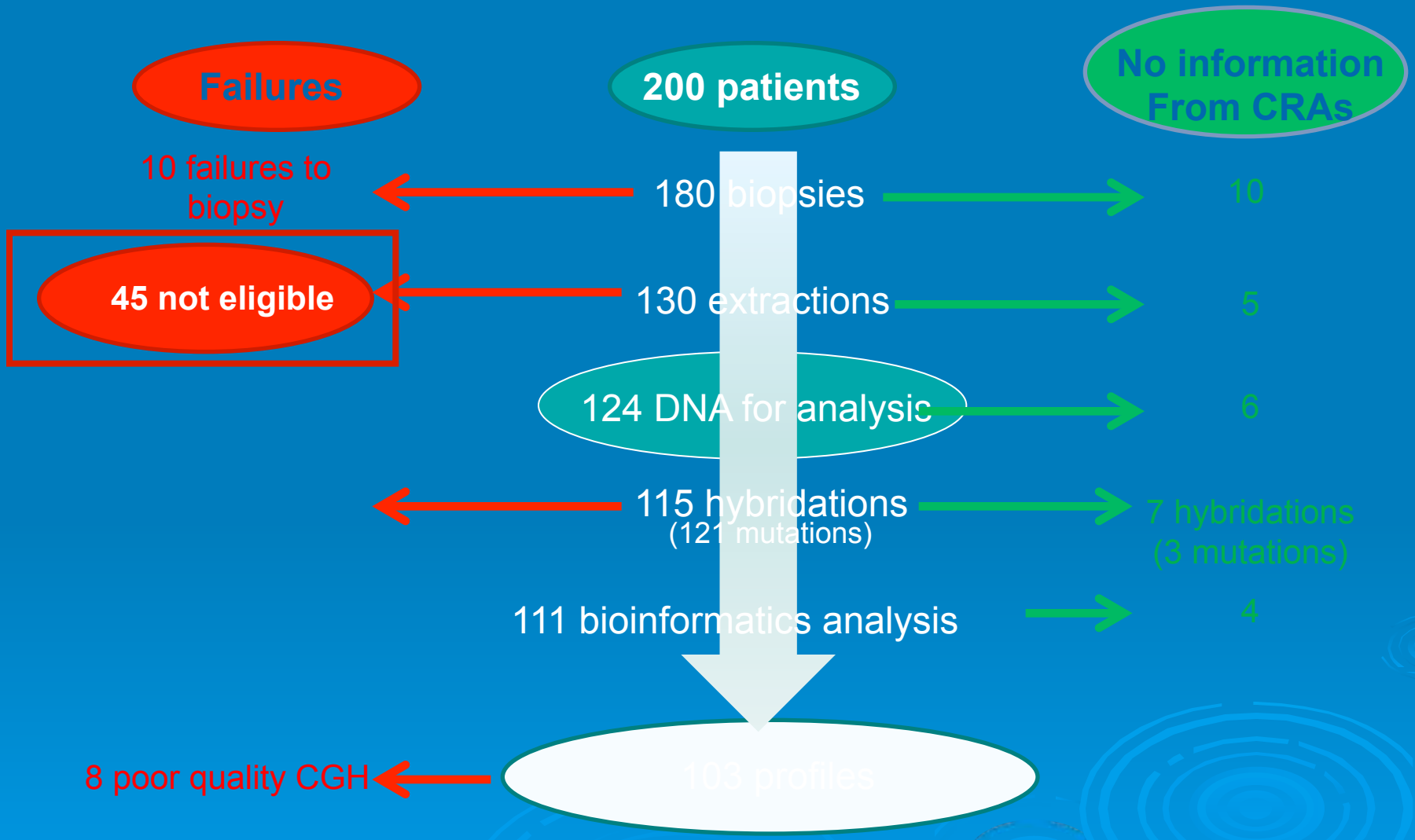
Funded by INCA/PHRC
4 platforms
FPI: 07/2011 ; 100 in 2.5 months
Next 30 genes, then NGS

SAFIR01: Accrual rate



Patients are highly motivated to be included in a trial that is proposing a biopsy from a metastatic site

Flow chart (first 200 pts)

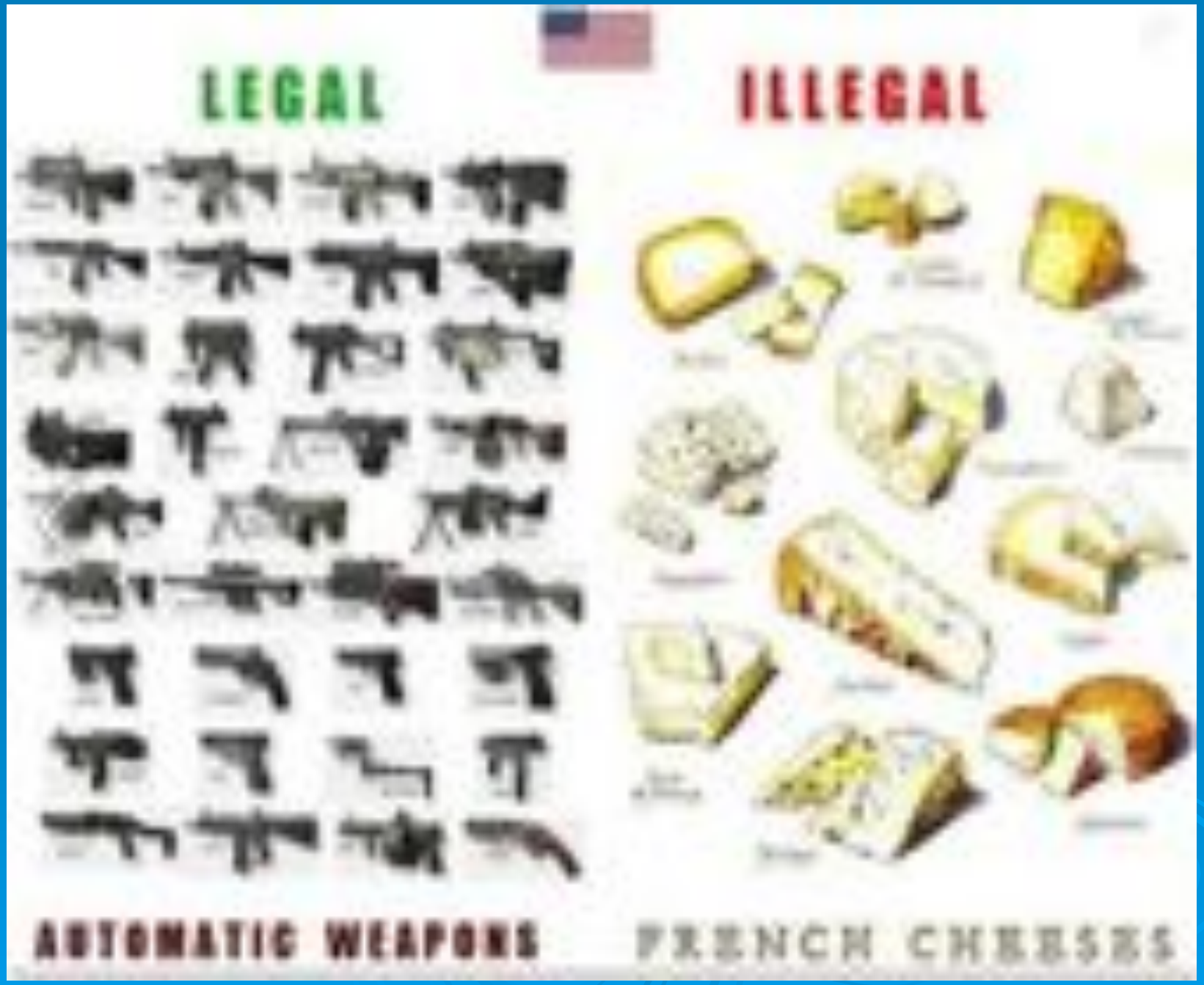


NEW ETHICAL AND LEGAL ISSUES

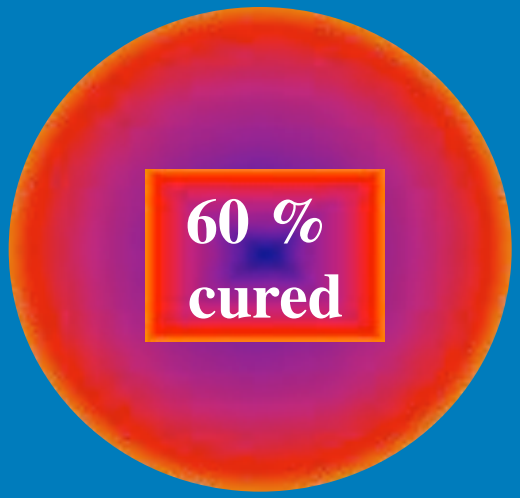
- Will freezing fresh tumor material of (all) early diagnosed cancer patients become mandatory?
- Freeze all relapses?
- Biopsy metastasis?

NEW ETHICAL AND LEGAL ISSUES

- Patients will soon realize that not to freeze their tumor materials or not to perform proper molecular analysis in due time clearly result in a loss of chances for their own survival.


LEGAL
ILLEGAL
AUTOMATIC WEAPONS
FRENCH CHEESES

Cancer Cures in Future ?



Early diagnosis

Guidelines

Phases III trials

Adjuvant treatment

National Cancer Plans

?

New strategies

A role for CCC ?

Network of CCC ?

The New Alliance

Acknowledgements

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UNICANCER
ASCO
Breast Cancer Research Foundation
Dassault System
Odyssea
Operation Parrain Chercheur

Academic Partners:
Curie Institute
Centre Léon Bérard
Institut Paoli Calmette
MD Anderson Cancer Center
Institut J Bordet

Conditions for a new partnership between European academy and Industry

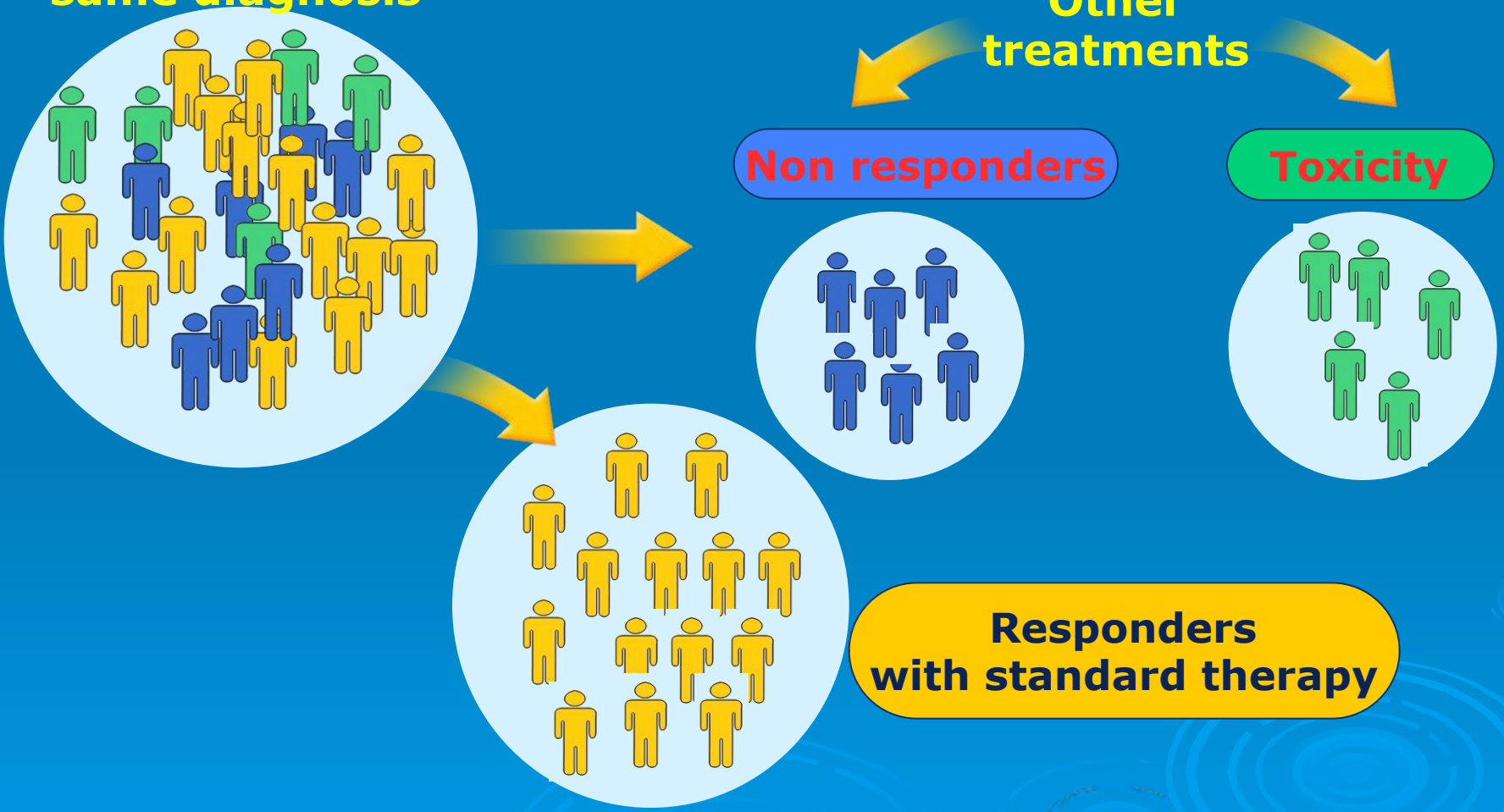
Upstream added-values

- New explanatory mechanisms for responses and/or toxicities
- New prognosis factors and predictive factors of responses
- New hypothesis driven drug development strategies

Downstream added-values

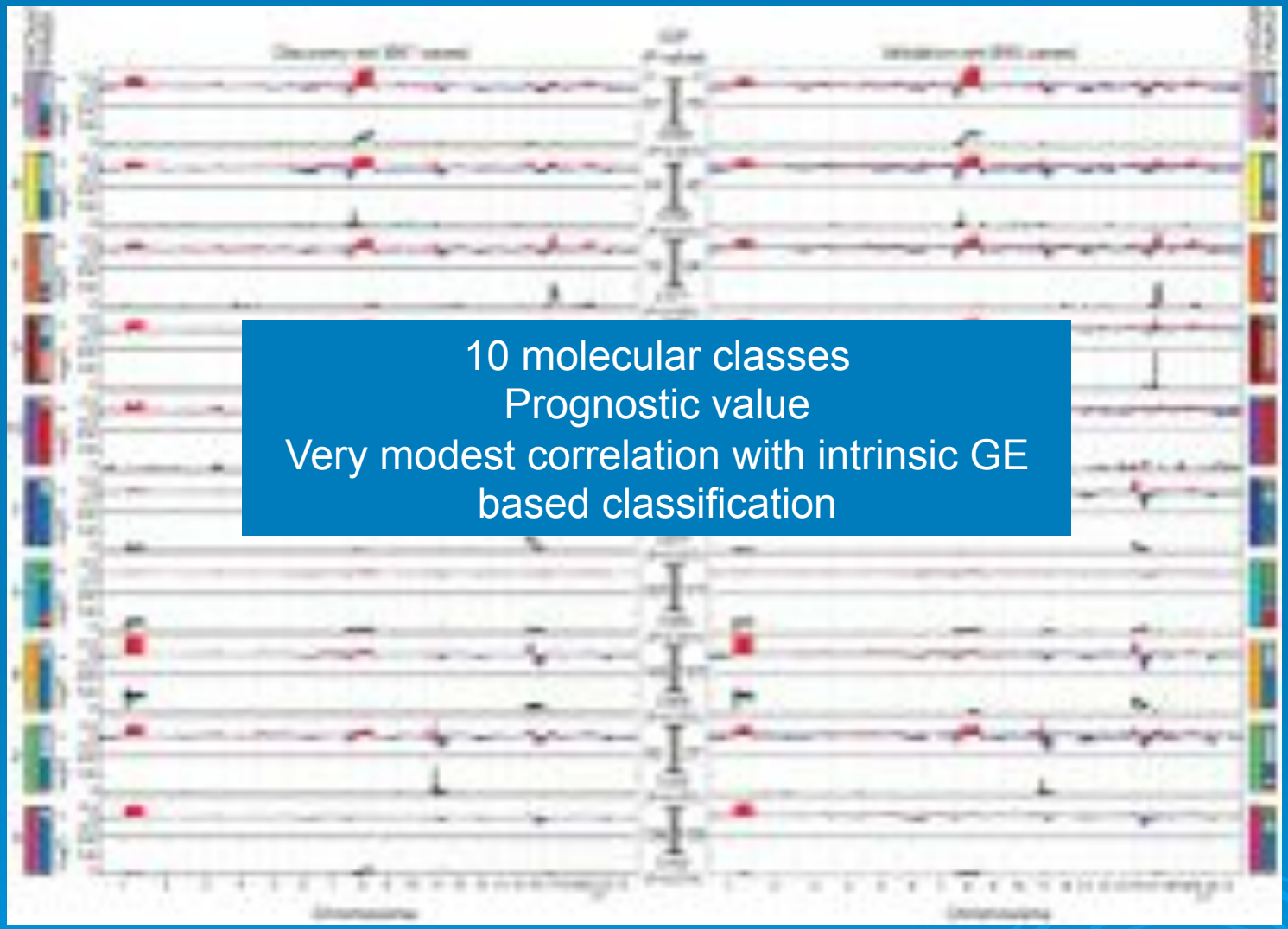
- New approaches for outcomes
- Quality of life questions
- Cost-effectiveness

Goals of tailoring therapy according to predictive markers



Gandara R, et al. J Clin Oncol, 2007: Abst 7500

New breast cancer classification based on gene copy number variations



10 molecular classes
Prognostic value
Very modest correlation with intrinsic GE based classification

How does it integrate with NGS data ?

Curtis et al, Nature, 2012

Short-term improvements

Implementing NGS (Ion Torrent technology)
250 genes before end of the year

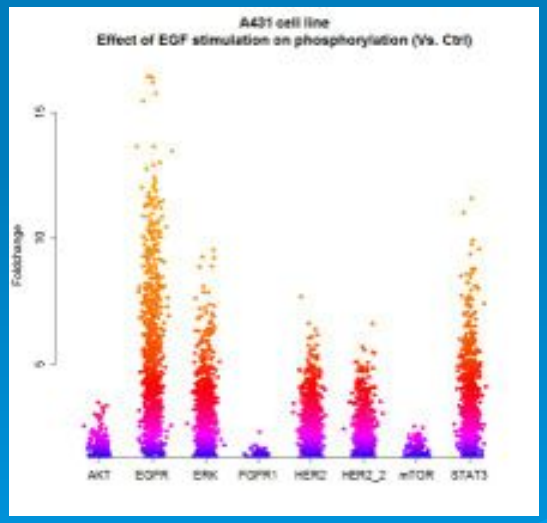
Feasibility study on 20 samples / 4 centers

↓

200 genes on 300 SAFIR samples
before end of the year

↓

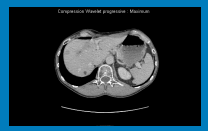
Prospective trial using Ion Torrent



Completing the genomic profile with
quantification of kinase activation (90 kinases)

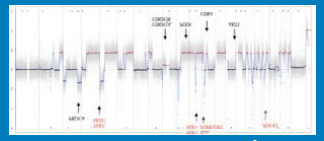
Expected « final product »:
200-300 genes by NGS and quantification of kinase activation

MOSCATO



TUMOR BIOSPY

SEQCan



CGHarray Agilent

Early clinical trial unit

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MOSCATO M01

45 years old patient

Metastatic melanoma

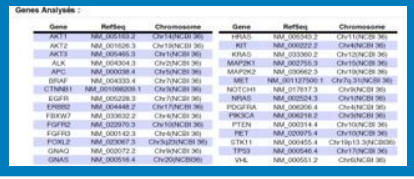
Hepatic, Cutaneous, lymph nodes mets

Previous CT: Abraxane, AKT inhibitor

10/2011: cutaneous progression

NECROSIS

SEQcan NA



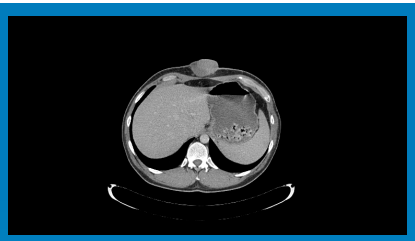
Genes Analysés :

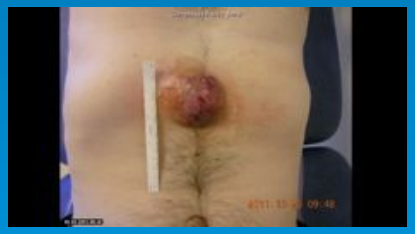
Gene	Refseq	Chromosome	Gene	Refseq	Chromosome
AKT1	NM_005163.2	Chr14(NCBI 36)	HRAS	NM_005343.2	Chr11(NCBI 36)
AKT2	NM_001626.3	Chr19(NCBI 36)	KIT	NM_000222.2	Chr4(NCBI 36)
AKT3	NM_005465.3	Chr1(NCBI 36)	KRAS	NM_033360.2	Chr12(NCBI 36)
ALK	NM_004304.3	Chr2(NCBI 36)	MAP2K1	NM_002755.3	Chr15(NCBI 36)
APC	NM_000038.4	Chr5(NCBI 36)	MAP2K2	NM_030662.3	Chr19(NCBI 36)
BRAF	NM_004333.4	Chr7(NCBI 36)	MET	NM_001127500.1	Chr7q.31(NCBI 36)
CTNNB1	NM_001098209.1	Chr3(NCBI 36)	NOTCH1	NM_017617.3	Chr9(NCBI 36)
EGFR	NM_005228.3	Chr7(NCBI 36)	NRAS	NM_002524.3	Chr1(NCBI 36)
ERBB2	NM_004448.2	Chr17(NCBI 36)	PDGFRA	NM_006206.4	Chr4(NCBI 36)
FBXW7	NM_033632.2	Chr4(NCBI 36)	PIK3CA	NM_006218.2	Chr3(NCBI 36)
FGFR2	NM_022970.3	Chr10(NCBI 36)	PTEN	NM_000314.4	Chr10(NCBI 36)
FGFR3	NM_000142.3	Chr4(NCBI 36)	RET	NM_020975.4	Chr10(NCBI 36)
FOXL2	NM_023067.3	Chr3q23(NCBI 36)	STK11	NM_000455.4	Chr19p13.3(NCBI36)
GNAQ	NM_002072.2	Chr9(NCBI 36)	TP53	NM_000546.4	Chr17(NCBI 36)
GNAS	NM_000516.4	Chr20(NCBI36)	VHL	NM_000551.2	Chr6(NCBI 36)

CGH NA

Thrombopenia

2 cycles DTIC: Response





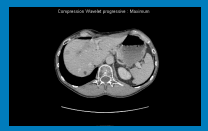
Failure

Metastatic melanoma with multiple metastases

Tumor biopsy: necrosis; 0% tumor cells

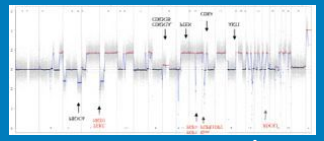
Proposition: standard chemotherapy (DTIC)

MOSCATO



TUMOR BIOSPY

SEQCan



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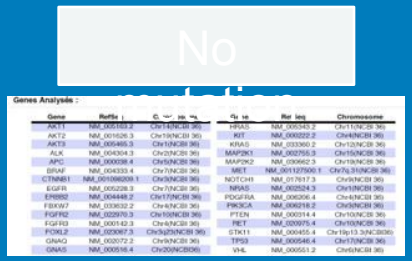
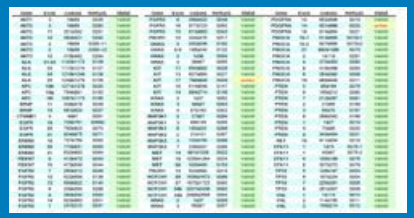
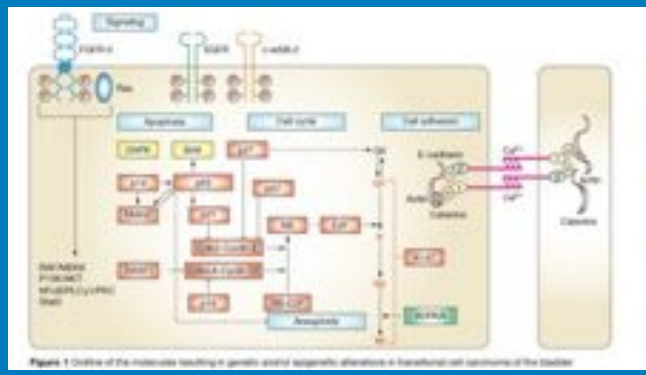
MOSCATO M08

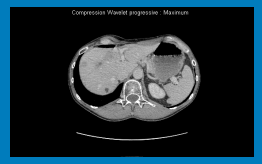
62 years old patient
With bladder cancer
Hepatic and lymph nodes mets
Previous CT: platin based chemotherapy
12/2011: hepatic progression



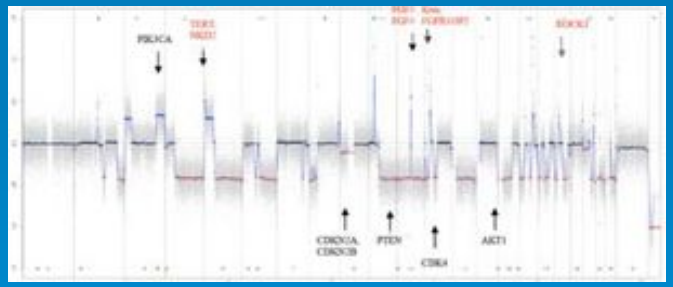




Bladder cancer biology



Amp: FGF4



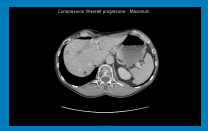
4 trials at IGR, SITEP

FGFR-FGF targeted therapies

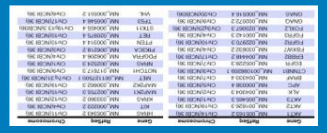
>50%

Bladder cancer with hepatic mets previsouly treated with platin-based chemotherapy
Amp FGF4, loss PTEN and AKT1
Proposition: FGFR inhibitor

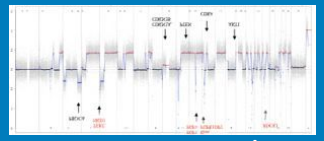
MOSCATO



TUMOR BIOSPY



SEQCan



CGHarray Agilent

Early clinical trial unit

SITEP

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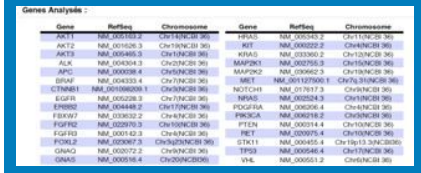
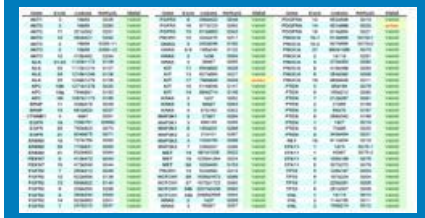
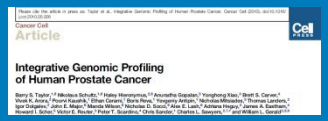
MOSCATO M15

62 years old patient
Castration resistant prostate cancer
Bone and lymph nodes mets
Previous Rx: agoniste LHRH, docetaxel, Inhibitor of androgen biosynthesis
01/2012: LN and bone progression

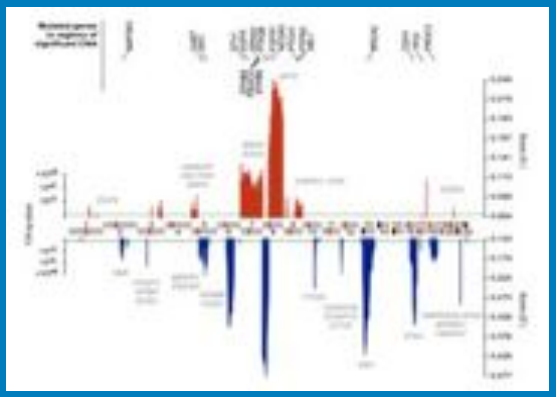
Mutation TP53



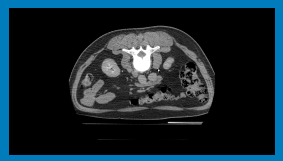


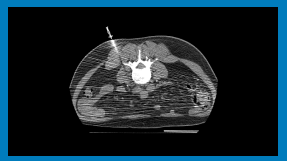


Integrative Genomic Profiling of Human Prostate Cancer

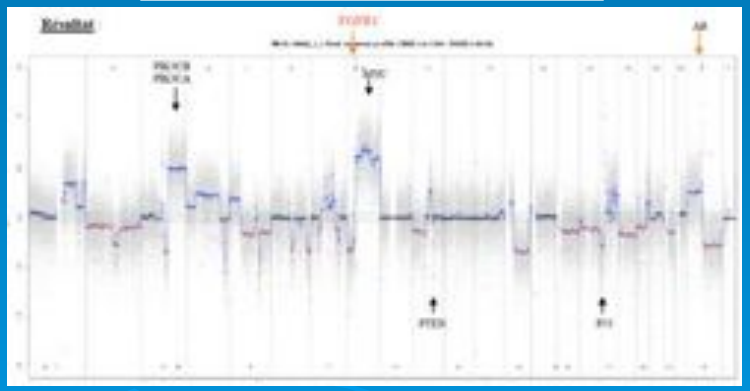


Prostate cancer biology





Amp FGFR1, MYC, AR and PTEN loss



>50%

4 trials at IGR, SITEP

CRPC pts with bone and lymhp nodes mets previsouly treated with docetaxel chemotherapy
Amp FGFR1, MYC, AR and PTEN loss
Proposition: PTEN loss oriented P1 trial … and then?

NATIONAL STRATIFIED MEDICINE PROGRAM

Molecular screening: Which candidate target ?

SAFIR 01
(UNICANCER)

Biopsy of metastatic sites
Frozen sample
CGH/hot spot mutations
(PIK3CA/AKT)
PS=0-1, eligible for phase I
SD / PR under treatment

n=400

Funding: French NCI

Primary endpoint:
% of patients included in phase I/II trial according to the profile

Target discovery and trial setting

SAFIR01 trial: logistics

18 centers

Patient inclusion
DNA extraction

Hybridization
Hot spot mutations

- Genomic unit Curie (Affy 6.0)
- Genomic unit Gustave Roussy (Agilent 4*44)
- Genomic unit Lyon (Affy 6.0)
- Genomic unit Marseille (Agilent)

Target identification
Quantification genetic instability

Bioinformatics

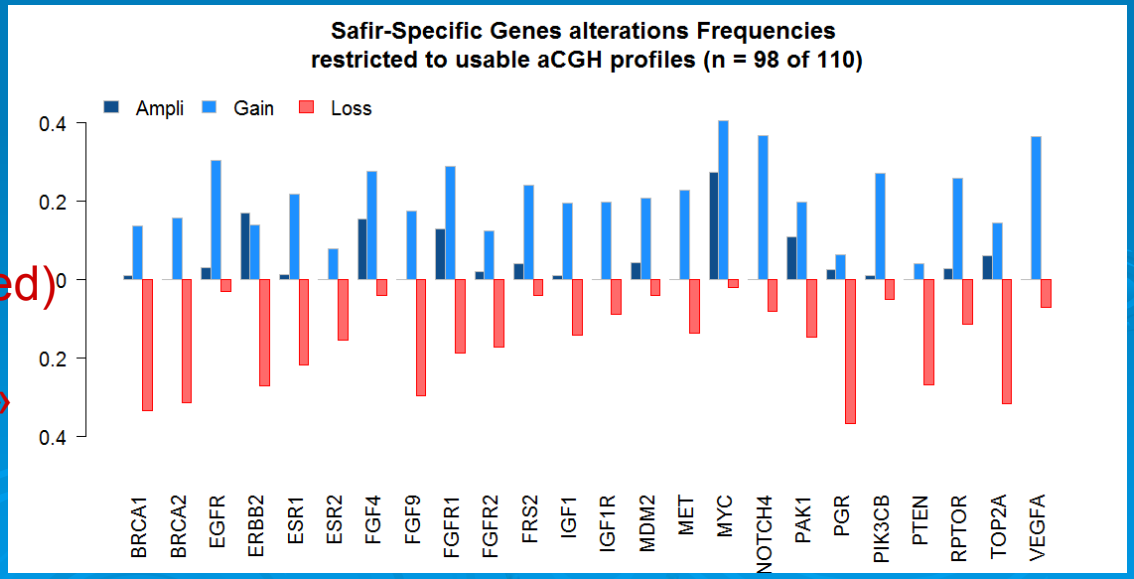
Bi-Monthly tumor board

Molecular alterations on previously defined targets

Mutations

PI3K / AKT / mTOR	
PIK3CA mutation	36 (30%)
exon 10	19
exon 21	17
AKT mutation	6

Copy number abnormalities



Actionable target identified in 58 patients (out of 98 analyzed)

Significant rate of « orphans » Genomic alterations