La médicine personnalisée en cancérologie: acquis et enjeux

Jean-Charles SORIA

SOCRATE
Stratified Oncology Cell dna Repair And Tumor immune Elimination
SIRIC

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

UNIVERSITÉ PARIS SUD

Instituts thématiques

Inserm
Institut national de la santé et de la recherche médicale

Plan

- Le contexte conceptuel
- Essais de 1ère génération et acquis
- Les essais de 2ème génération
- Enjeux et défis d’avenir

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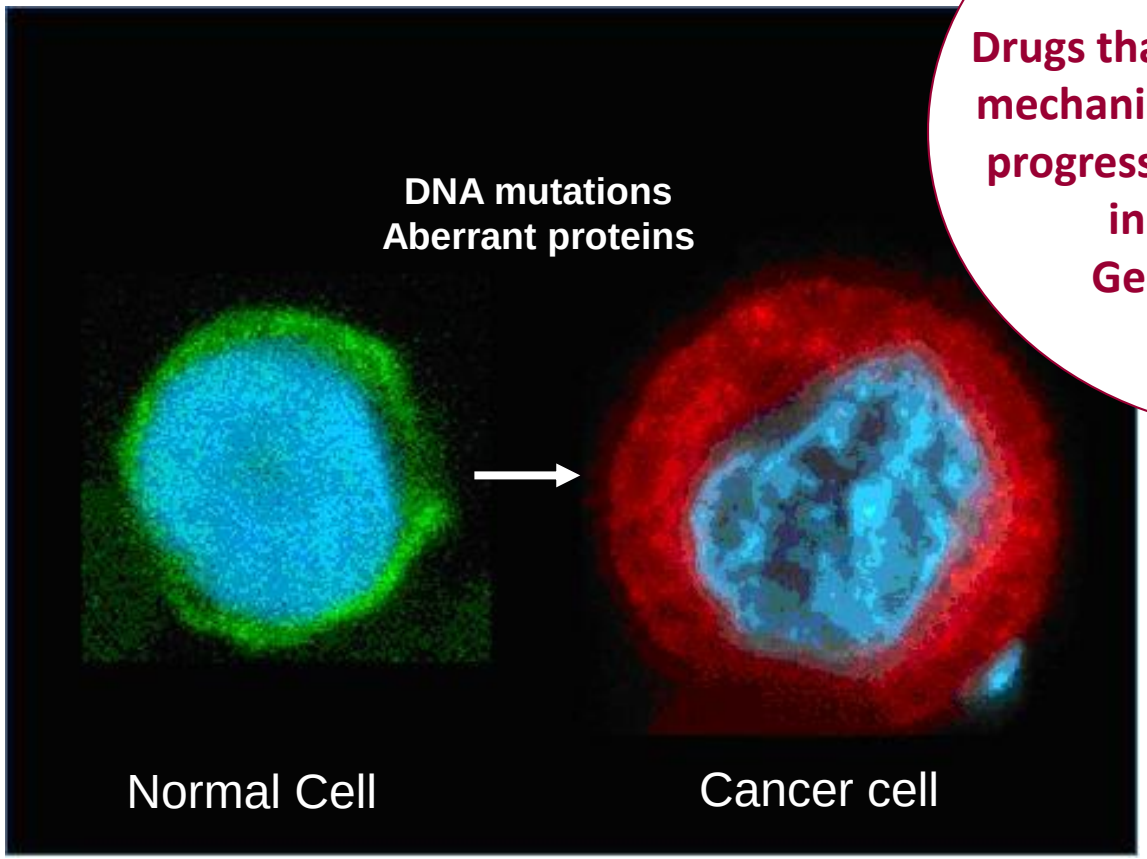
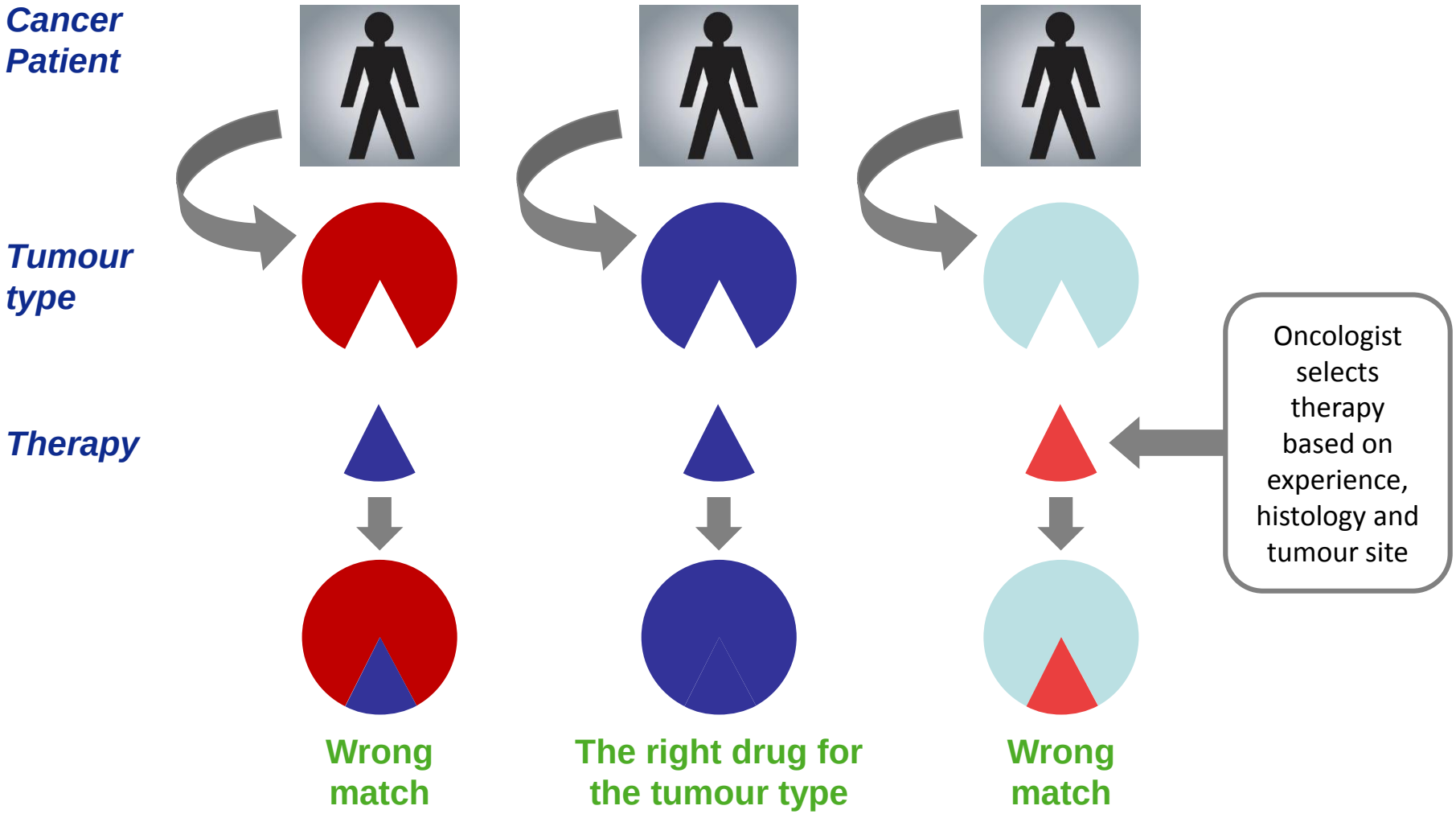
Working Hypothesis



Drugs that target the molecular mechanisms involved in cancer progression improve outcome in the absence of Genomic instability

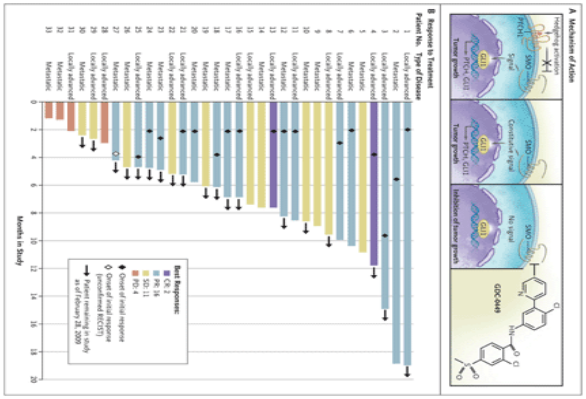
Selecting the right therapy



Adapted from D Weaver, On-Q-ity

Specific genetic traits can predict for the success of MTA

Tumor type with oncogenic addiction e.g. Hedgehog inhibitors in BCC (*PTCH* mutations), B-RAF inhibitors in melanoma (*B-RAF* mutations), ALK inhibitors in NSCLC (*ALK* translocation) – i.e. "superstars"!



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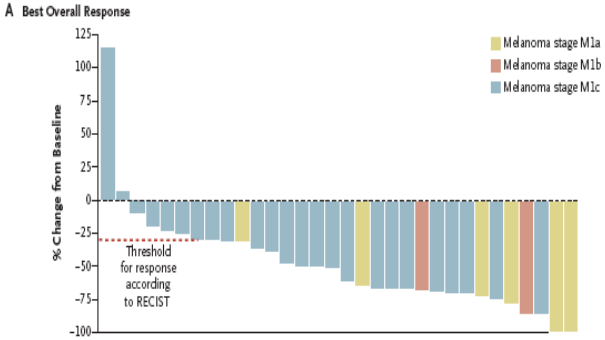
(*New Engl J. Med 2010*)



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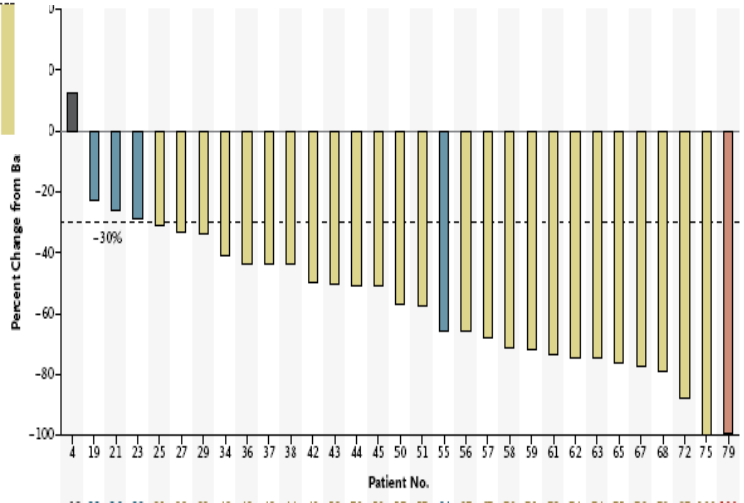


Examples of Registered MTA based on oncogene de-addiction

Trastuzumab

Pertuzumab

TDM1

Gefitinib

Erlotinib

Afatinib

Vemurafenib

Dabrafenib

Crizotinib

Cedirinib

Vismodegib

Imatinib

Plateformes hospitalières de génétique moléculaire des cancers

Arrivée des thérapies ciblées → Organisation pour fournir des tests moléculaires à l'échelle nationale

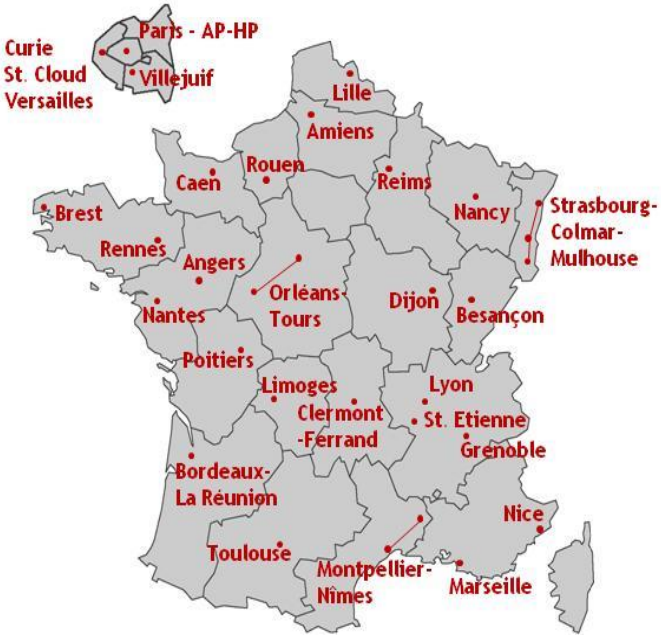
Le programme est piloté par l'INCa et le Ministère de la Santé depuis 2006

Objectifs

- Effectuer des tests moléculaires pour l'ensemble des patients;
- Pour tous les établissements (hôpitaux, cliniques…);
- Assurer un haut niveau de qualité;
- Hémopathies et tumeurs solides
- Tests gratuits pour les patients et les établissements locaux

28 plateformes de génétique moléculaire

- Partenariat entre plusieurs laboratoires répartis dans des CHU et des CLCC
- Organisation régionale
- Coopération entre pathologistes et biologistes

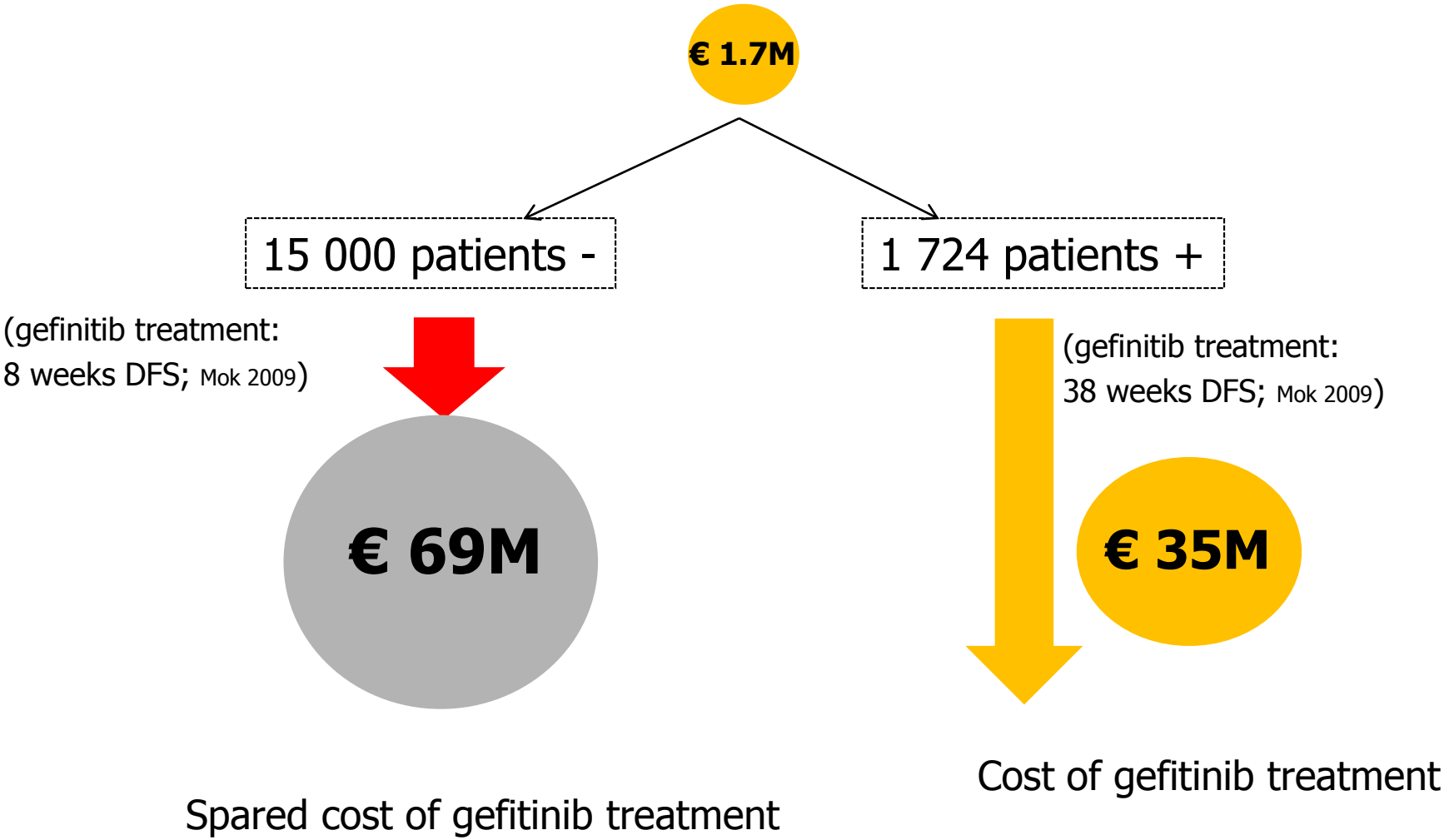


En 2013 → 75 000 patients testés ; 85 000 tests réalisés

A Buzyn

Example of gefitinib treatment : €69M spared cost for the health insurance

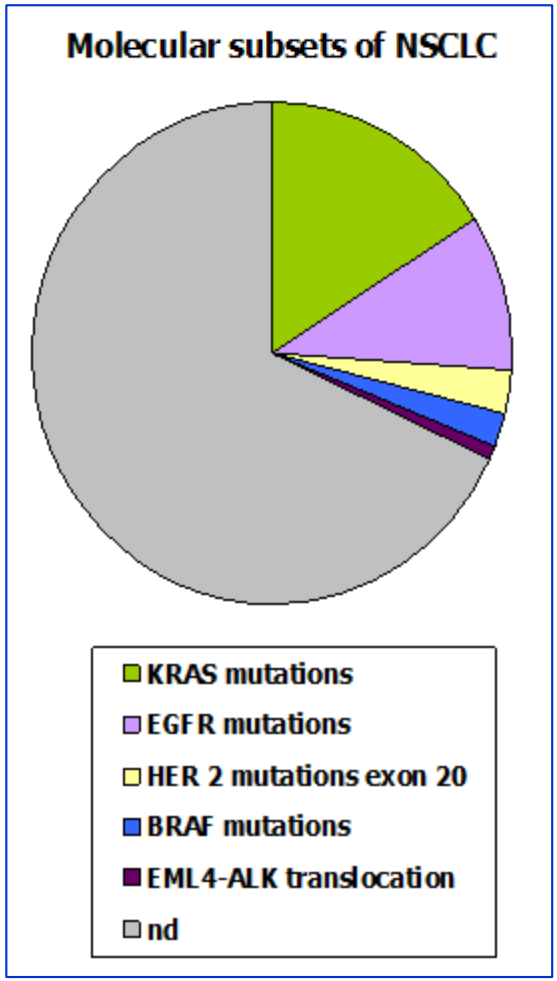
EGFR testing for lung cancer patients



INSTITUT NATIONAL DU CANCER

Nowak F, Soria JC, Calvo F. Nat Rev Clin Oncol 2012

Current biomarkers facilitating rapid access to targeted therapies



Biomarkers for targeted therapies currently evaluated in clinical trials (Phases I to III) tested within INCA platforms

Cancer	Molecular target
Lung	EGFR mutations
	KRAS mutations
	HER2 exon 20 mutations
	BRAF mutation
	PI3KCA mutations
	EML4-ALK translocation
Colon - rectum	KRAS mutations
	BRAF mutation
	microsatellite instability if < 60 years
Breast	HER2 amplification
	BRCA1/2 germinal mutations
	PI3KCA mutations
Melanoma	BRAF mutation
	cKIT mutation

Source: Inca ancer)

INSTITUT NATIONAL DU CANCER

FGFR & Patient selection: Challenges of single-gene prescreenig

Molecular screening in the BGJ398 trial

Breast

Samples tested	229
FGFR1 amplification	26
FGFR2 amplification	3

Bladder

Samples tested	95
FGFR3 mutation	7

Single gene pre-screening is a frustrating process

Samples tested	147
FGFR1 amplification	14

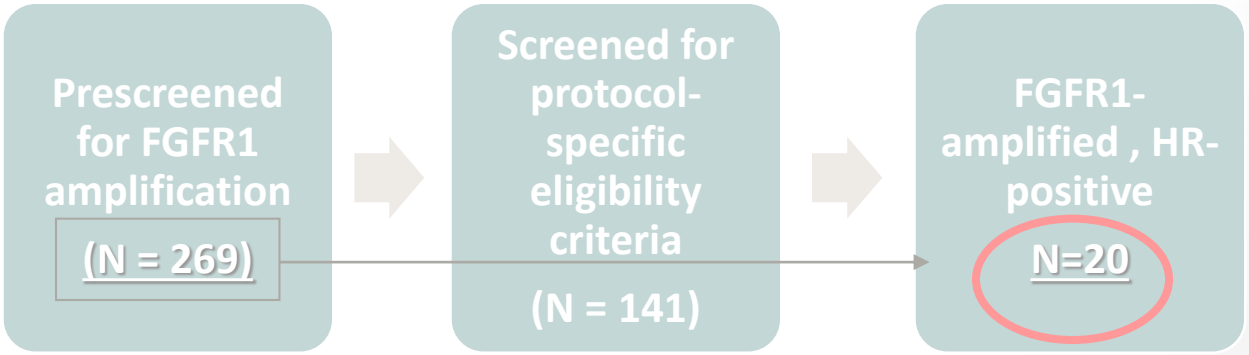
Samples tested	107
FGFR2 amplification	2

Samples tested	43
FGFR1 amplification	0
FGFR2 amplification	0

Lecia V. Sequist, American Association for Cancer Research 2014

Molecular screening in the TKI258 trial

56 centers, global trial
16 months recruitment



Andre F et al Clin Cancer Res 2013

Number Needed to Analyze: Biomarker-Driven Clinical Research

$$NNS = \frac{1}{(\text{fraction with biomarker X assay specificity X fraction trial-eligible X fraction giving informed consent})}$$

Example: HER2+ in BC= 1/(0.25 X 0.9 X 0.5 X 0.5) = 17.8 patients screened/patient entered into trial

Example: ALKtx in NSCLC = 1/(0.05 X 0.9 X 0.5 X 0.5) = 88 patients screened/patient entered into trial

Example: FGFRtx in GBM = 1/(**0.03** X 0.9 X 0.5 X 0.5) = 148 patients screened/ patient entered into trial

Courtesy J Rodon

Number Needed to Analyze: Biomarker-Driven Clinical Research

NNS = _____1_____

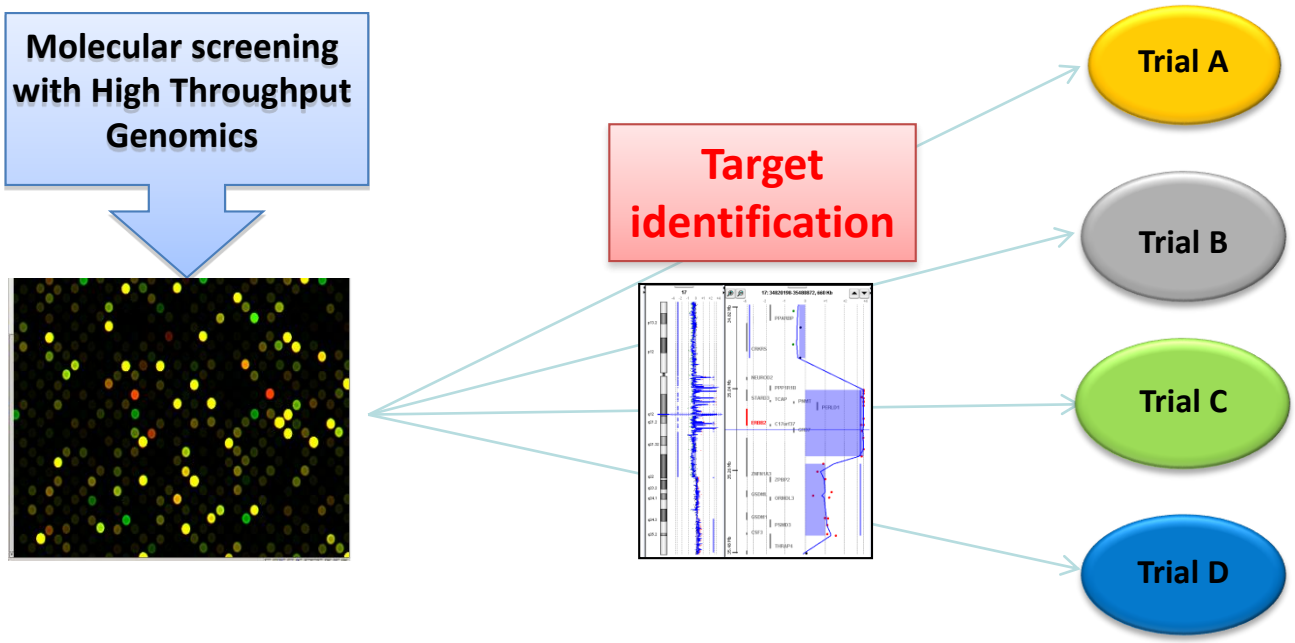
(fraction with biomarker X assay specificity

X fraction trial-eligible X fraction giving informed consent)

	Fraction with biomarker	Assay specificity	fraction trial-eligible	fraction accepting participation	Pt Needed to Analyze
HER2+ in Breast cancer	25%	90%	50%	50%	17,8
ALK fusion in NSCLC	5%	90%	50%	50%	88
FGFR fusion in GBM (freq 3-8%)	**3%**	90%	50%	50%	148
	8%	90%	70%	50%	39,7
	3-8%	70%	**60%**	50%	59,5-158,7

Courtesy J Rodon

Molecular screening programs: Concept



Short term Goal: to develop drugs in population defined by a biomarker

Andre, Delaloge, Soria, J Clin Oncol, 2011

Plan

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- Les essais de 2ème génération
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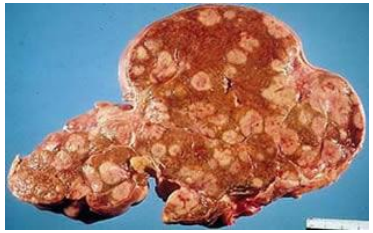
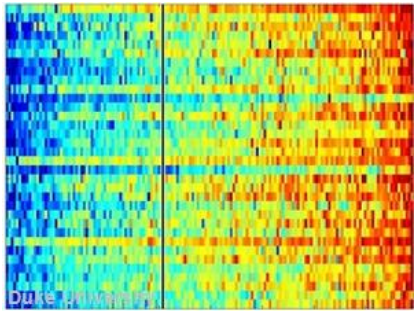
Precision Medicine: To identify and hit the target

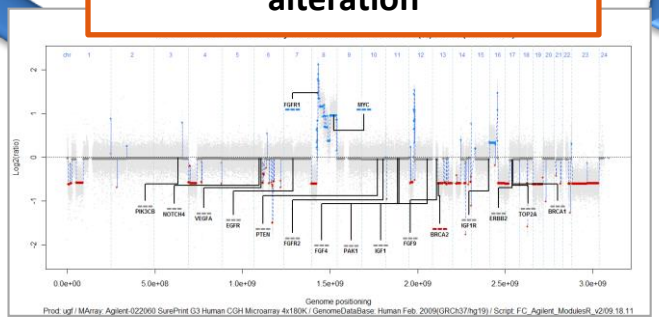


Tumor Specimen

Molecular profiling



Identification of the molecular alteration



Targeted therapy according to the molecular profile

Ongoing precision medicine programs in France

Sponsor	Pilot study	1st generation trials: No NGS	1st generation trials: NGS	Randomized trials
Unicancer		SAFIR01 (Andre TLO 2014)		SAFIR02 breast ,02 lung
Gustave Roussy / WIN	preSAFIR (Arnedos, EJC, 2012)	MOSCATO (Hollebecque, ASCO 2013)	WINTHER	
L Berard Lyon			Profiler	MOST
Curie Institute				SHIVA (Letourneau AACR 2013)

Unified Database: Pick-up the winner targets

2nd generation Algorithm for Personnalized medicine

Overall : >3 000 planned patients (all tumor types), >1000 already included

Breast Cancer: > 1 000 planned, >90 already treated (preSAFIR / SAFIR / MOSCATO)

Goal: To generate optimal algorithm for individualized therapy

SAFIR01: Study Flow

Biopsy metastases in patients PR/SD under treatment
2 Frozen samples
1 FFPE sample

Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER)

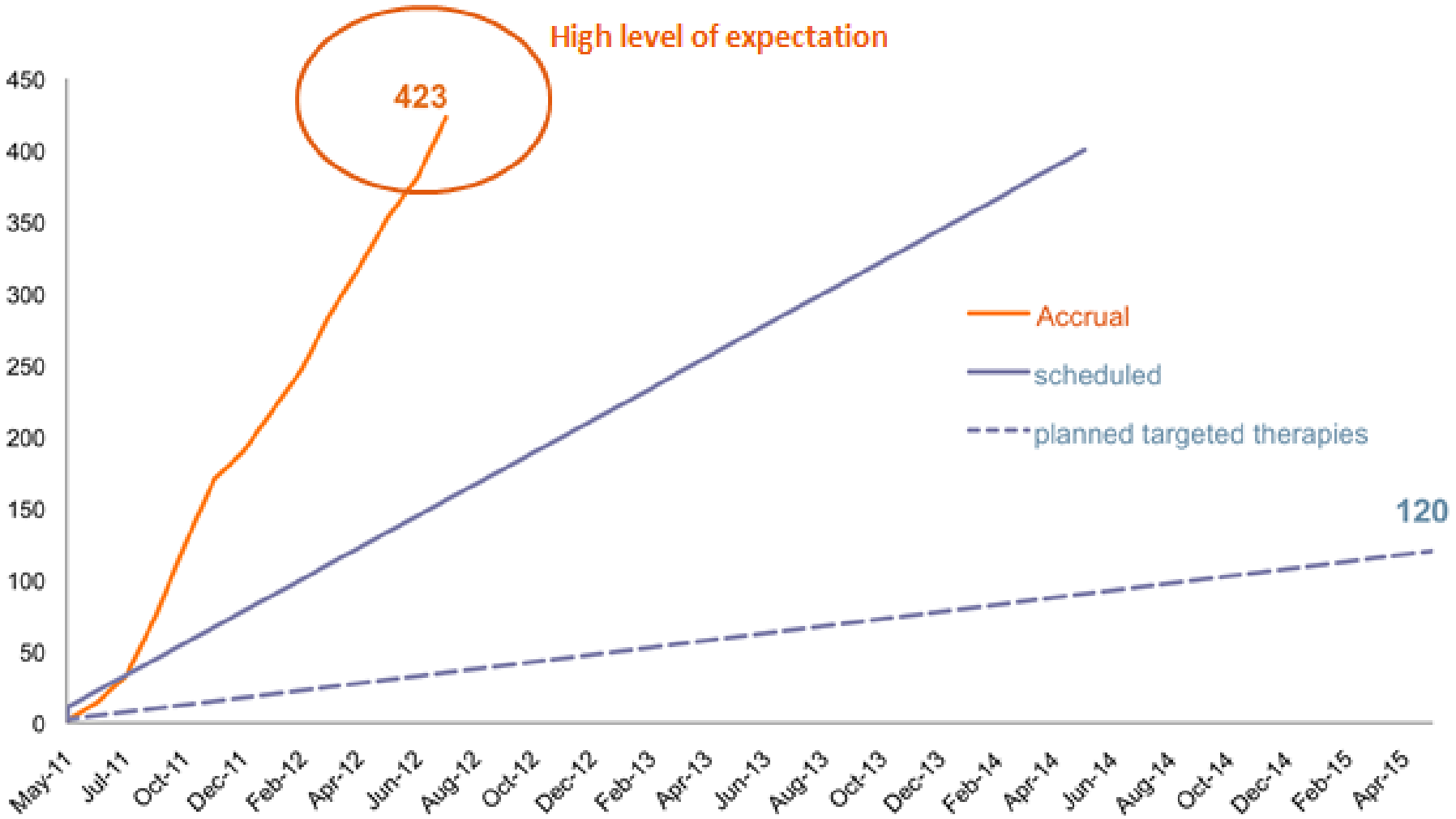
Fabrice André, Thomas Bachelot, Frederic Commo, Mario Campone, Monica Arnedos, Véronique Dieras, Magali Lacroix-Triki, Ludovic Lacroix, Pascale Cohen, David Gentien, Jose Adélaide, Florence Dalenc, Anthony Goncalves, Christelle Levy, Jean-Marc Ferrero, Jacques Bonneterre, Claudia Lefeuvre, Marta Jimenez, Thomas Filleron, Hervé Bonnefoi

Summary

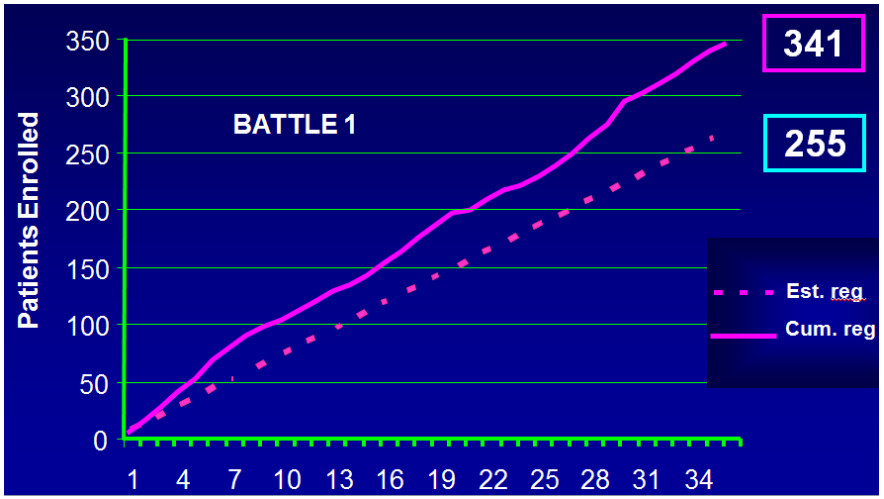
Background Breast cancer is characterised by genomic alterations. We did a multicentre molecular screening study to identify abnormalities in individual patients with the aim of providing targeted therapy matched to individuals' genomic alterations.

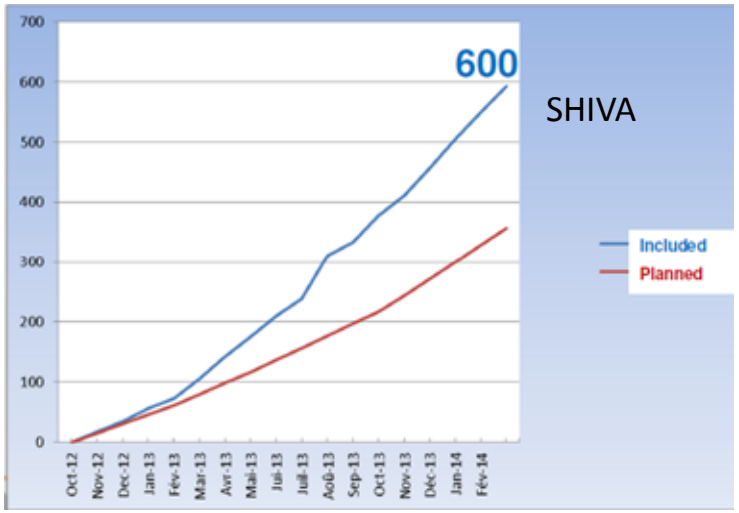
Lancet Oncol 2014
Published Online
February 7, 2014
http://dx.doi.org/10.1016/

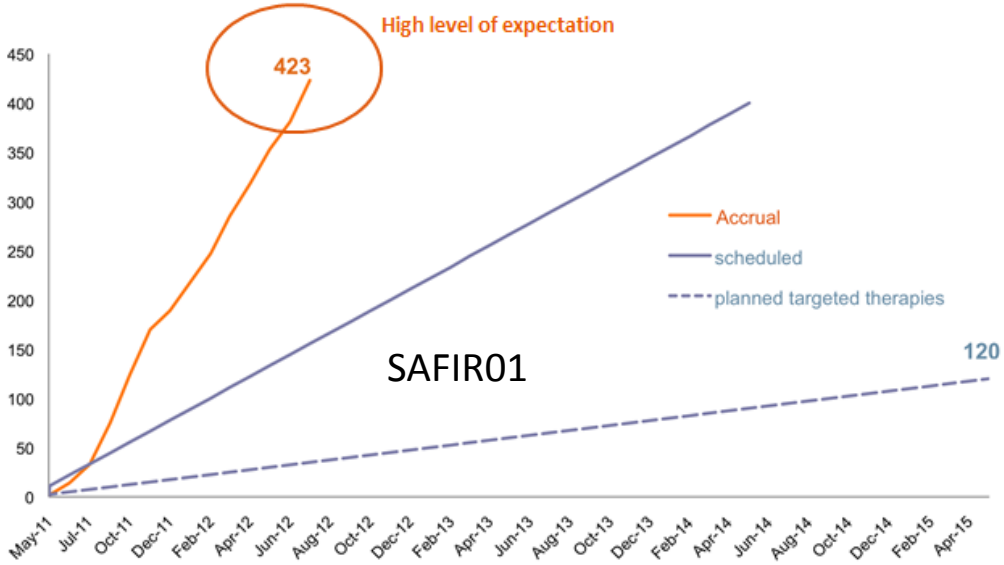
Clear enthusiasm of patients and physicians



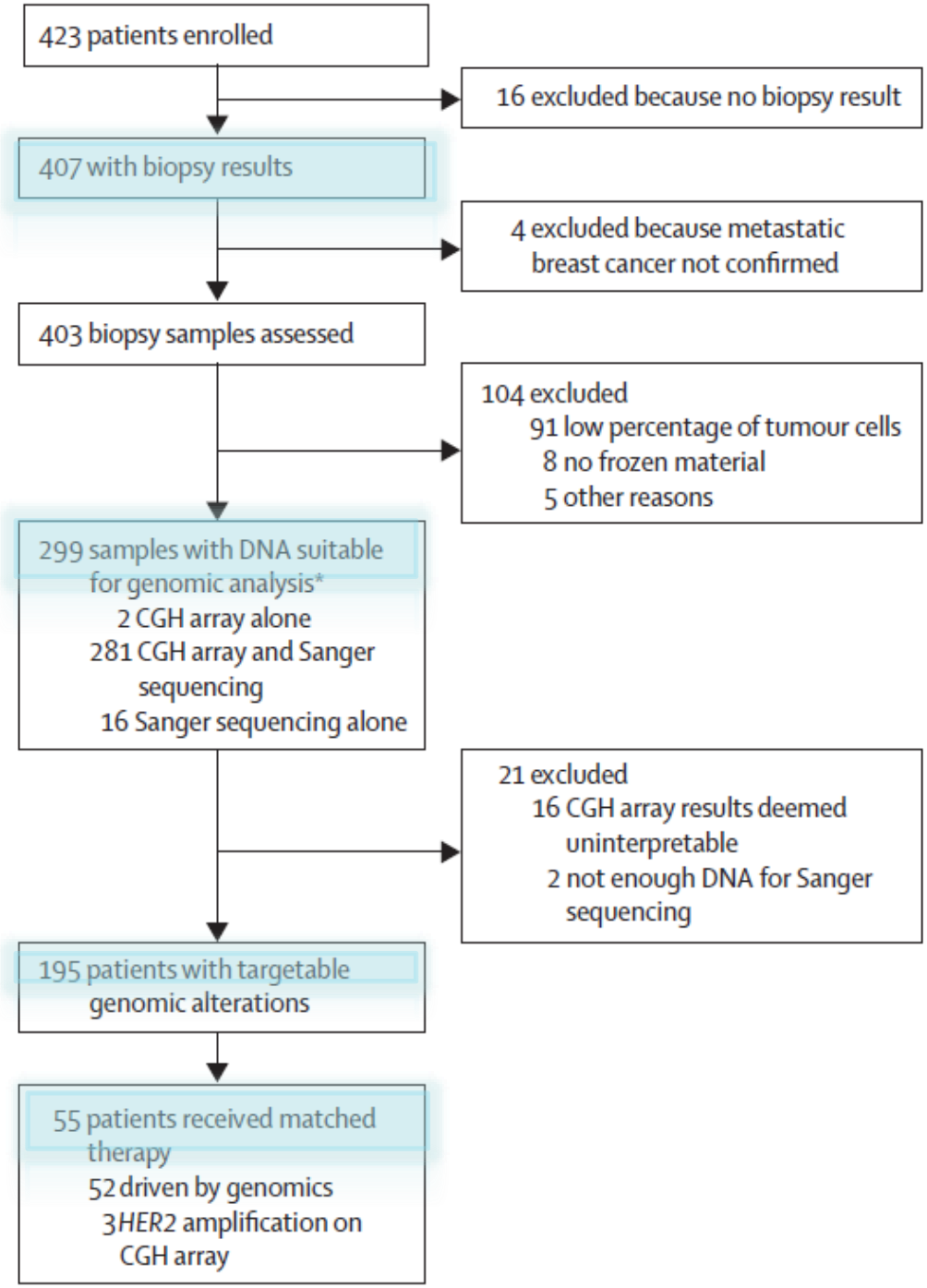
Clear enthusiasm of patients and physicians







Kim E et al, Cancer Discovery 2011
Andre F et al, Lancet Oncol 2014
Le Tourneau C et al, BJC 2014

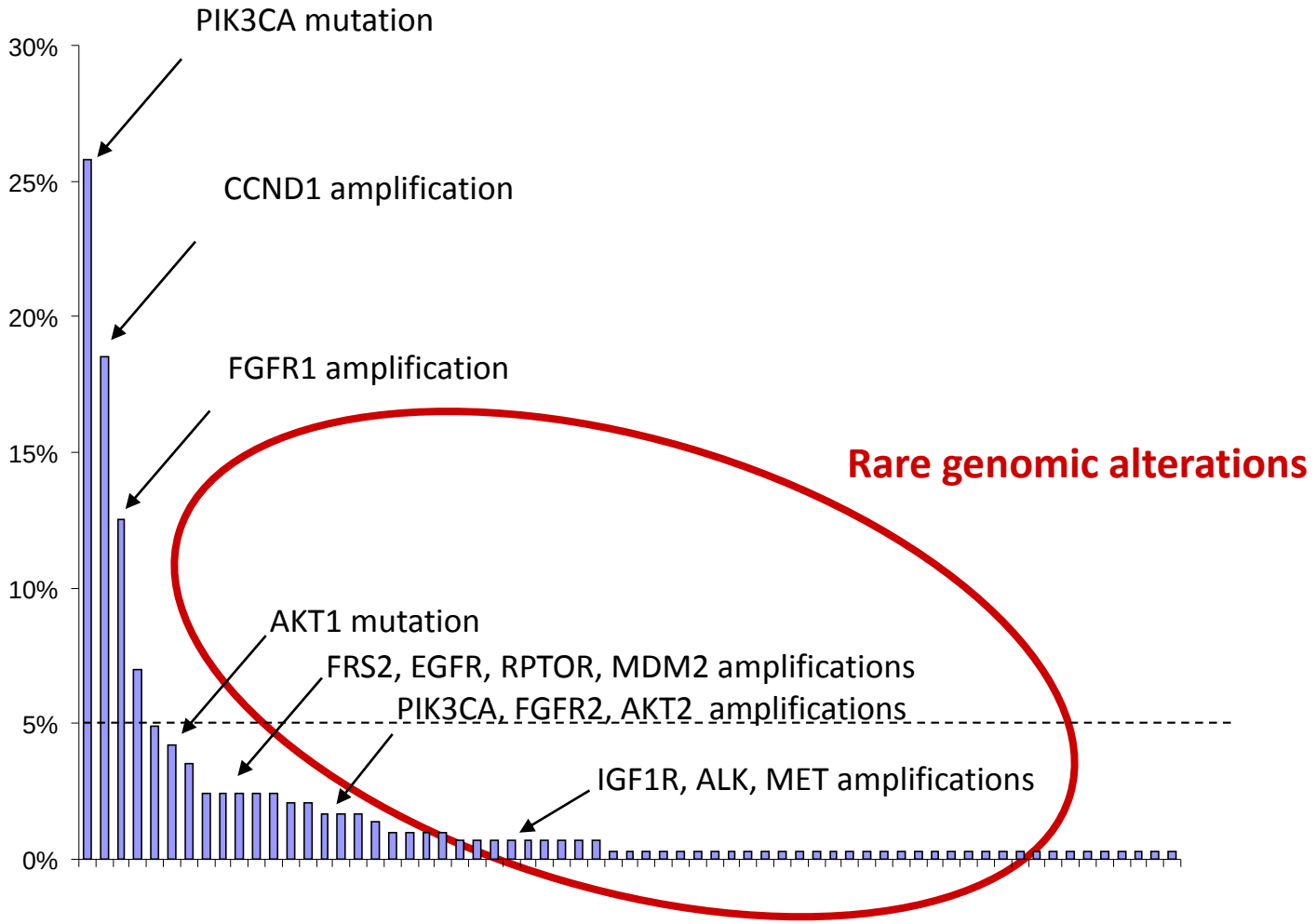


73% de succès

65% d'actionabilité

28% des actionables traités

Targetable alterations that led to treatment proposition



High frequency of rare targetable genomic alterations

Efficacy data on 48 patients treated with therapy matched to genomic analysis

Efficacy	n (%)
Objective response	4 (9%)
SD>16 weeks	8 (19%)
OR + SD>16 weeks	12 (28%)
Progression within 16 weeks	32 (72%)
Ongoing therapy SD <16 weeks	4
Erbb2 conversion (n=4)	1 OR 1 long term SD (10 months)

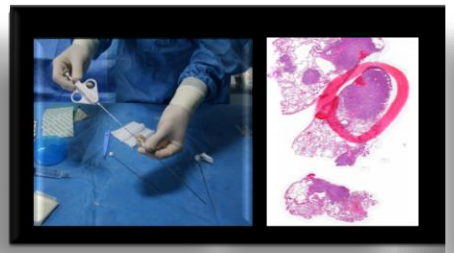
Targets picked-up:
EGFR amplification
AKT gene alteration
FGF-amplified BC
IGF1R amplification

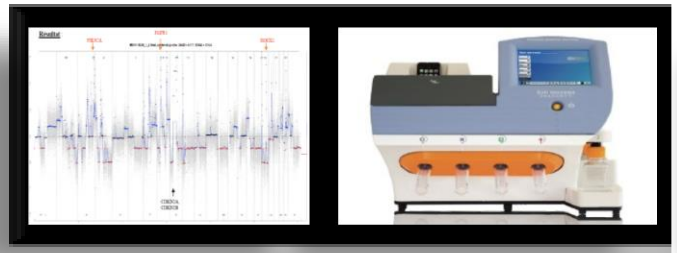
MOSCATO-01 prospective molecular screening program

- Monocentric (Gustave Roussy)

- Target Accrual = 900 patients

ON- PURPOSE FRESH TUMOR BIOSPSY & PATHOLOGY CONTROL → MOLECULAR PROFILING (CGH & NGS) → MOLECULAR TUMOR BOARD → TREATMENT





Median 14 days (95% CI: 7-35 days)

FRESH TUMOR

BIOPSY → PATHOLOGICAL CONTROL

→ **MOLECULAR SCREENING**

CGH Array & Sanger & NGS

→ **CLINICAL DECISION** → **TREATMENT**

- **Single site biopsy**
- **Metastatic site (+++) or primary site**
- **14 – 18 Gauge needle**
- **Ultrasound or CT guided biopsy, or surgical resection (HNSCC)**
- **Real time Pathologic Control to determine % of Tumor Cells**

Presented by: Antoine Hollebecque et al .ASCO 2013

FRESH TUMOR

BIOPSY → PATHOLOGICAL CONTROL

→ **MOLECULAR SCREENING**

CGH Array & Sanger & NGS

→ **CLINICAL DECISION**

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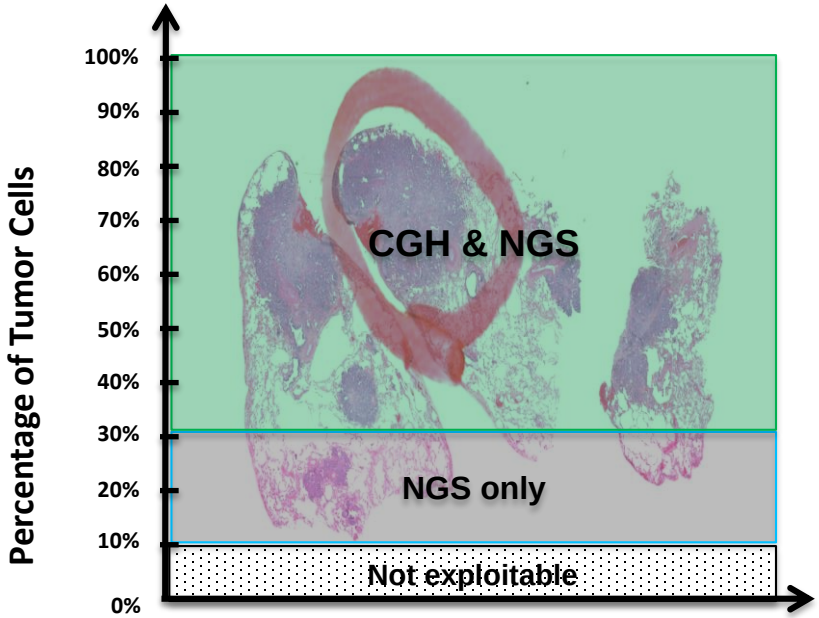
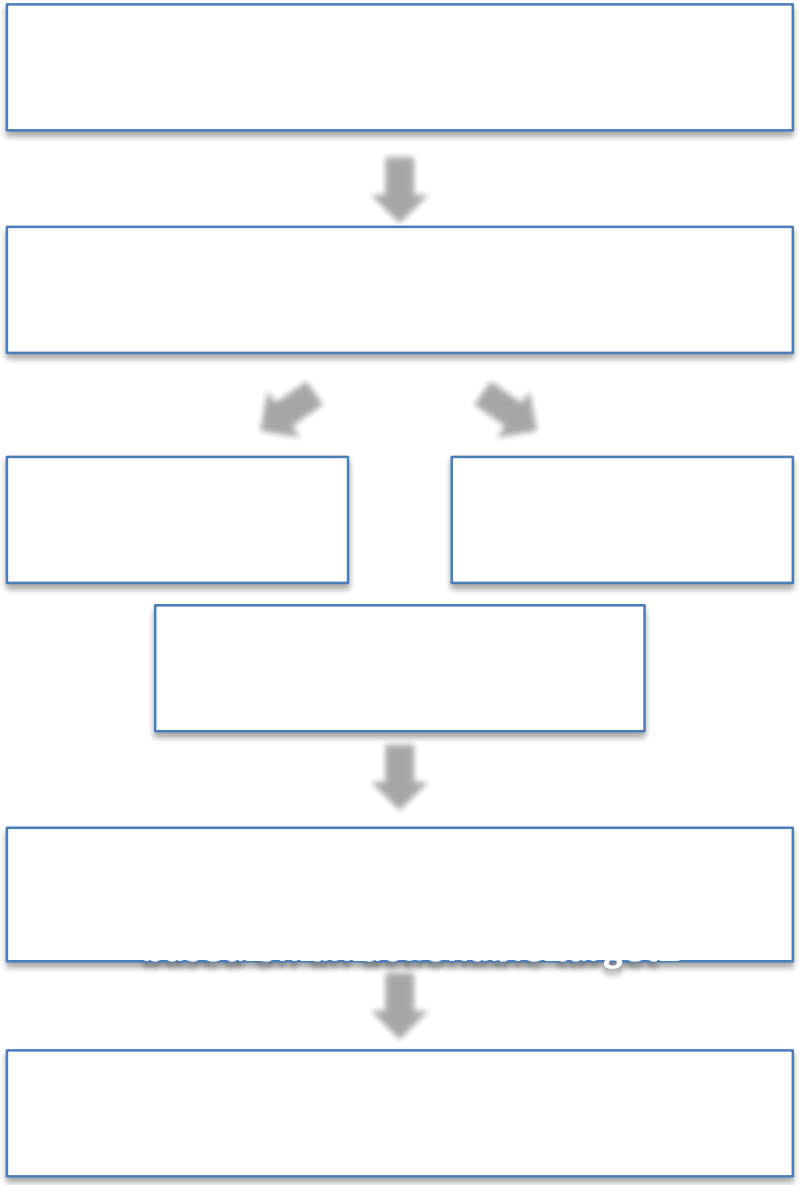


Presented by: Antoine Hollebecque et al .ASCO 2013

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

General flowchart

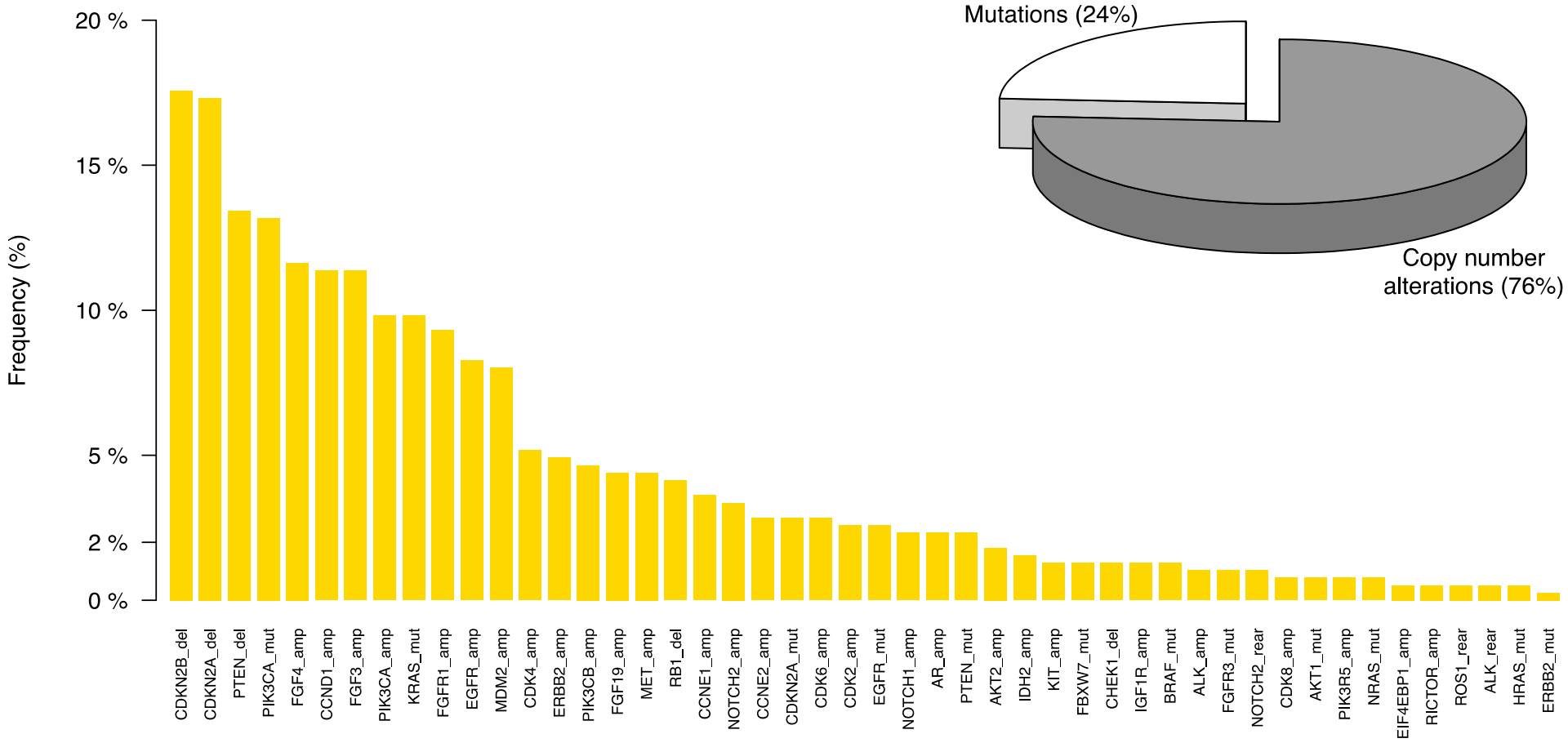


89 % de succès

44 % d'actionabilité

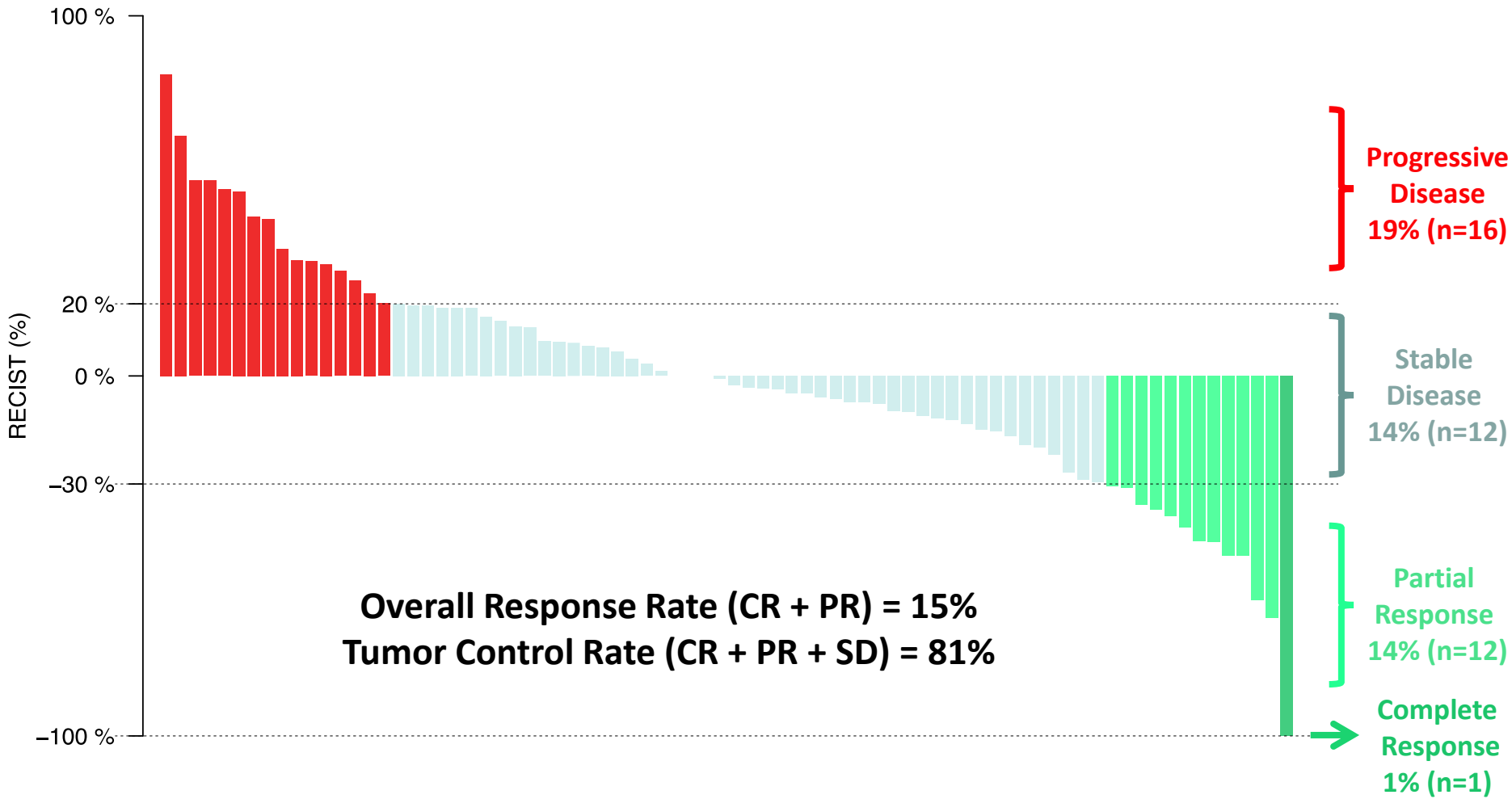
50% des actionables traités

Main actionable aberrations



Presented by: Charles Ferté et al .AACR 2014

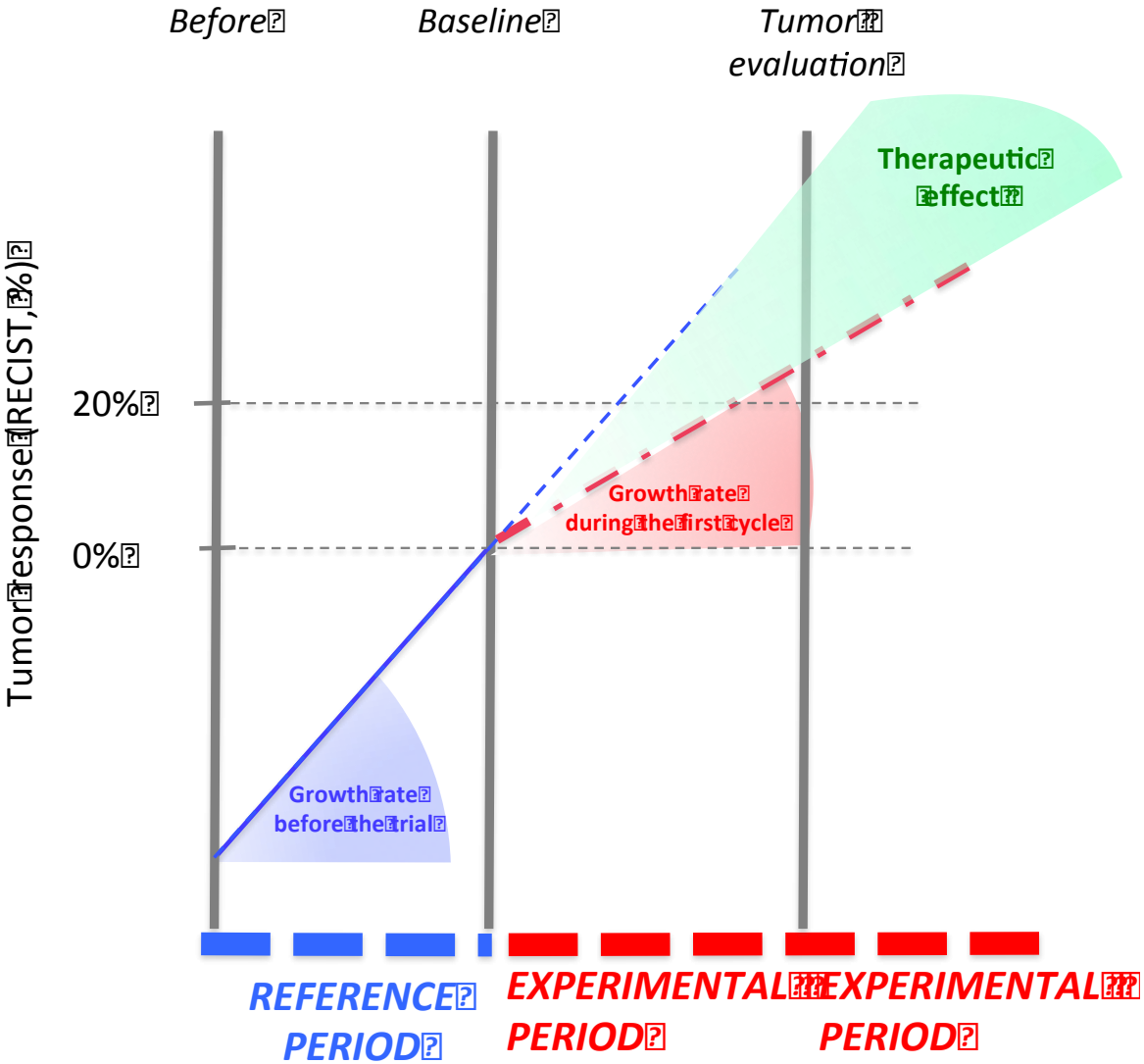
Best response rate (RECIST) in **oriented and treated** patients (n=85)*



** Excluding classical ALK, EGFR, BRAF, HER2, ER/PR alterations*

Presented by: Charles Ferté et al .AACR 2014

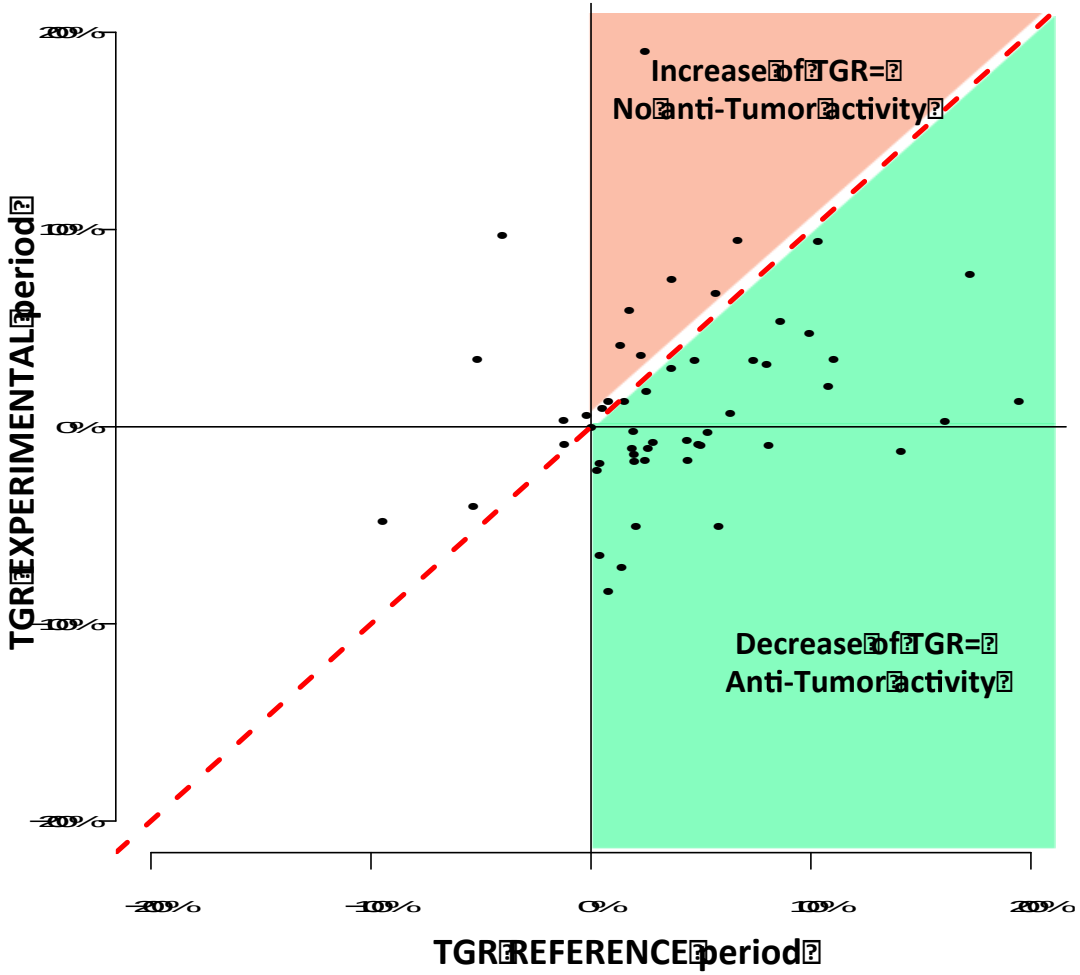
Tumor Growth Rates (TGR)



Opportunity to estimate the therapeutic effect independently from the course of the disease

Ferté et al, Clin Cancer Res 2013

Decrease of the tumor growth rate between the REFERENCE and the EXPERIMENTAL period



Comparison of the TGR distribution across the REFERENCE and the EXPERIMENTAL periods (each patient serves as his/her own control):

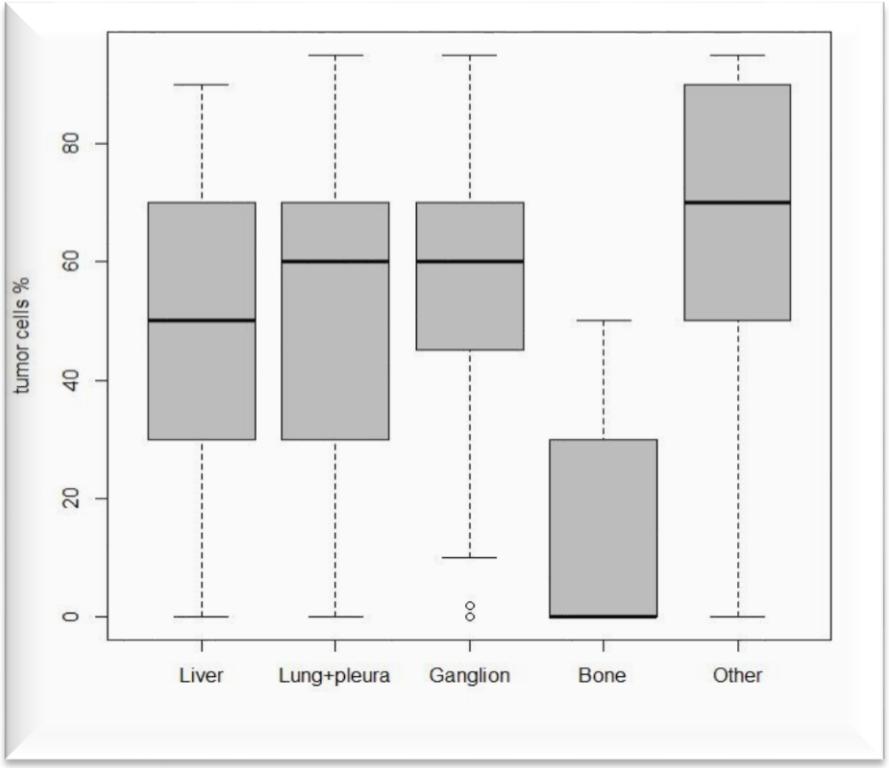
Wilcoxon paired test P = 5.3 e-05

Presented by: Charles Ferté et al .AACR 2014

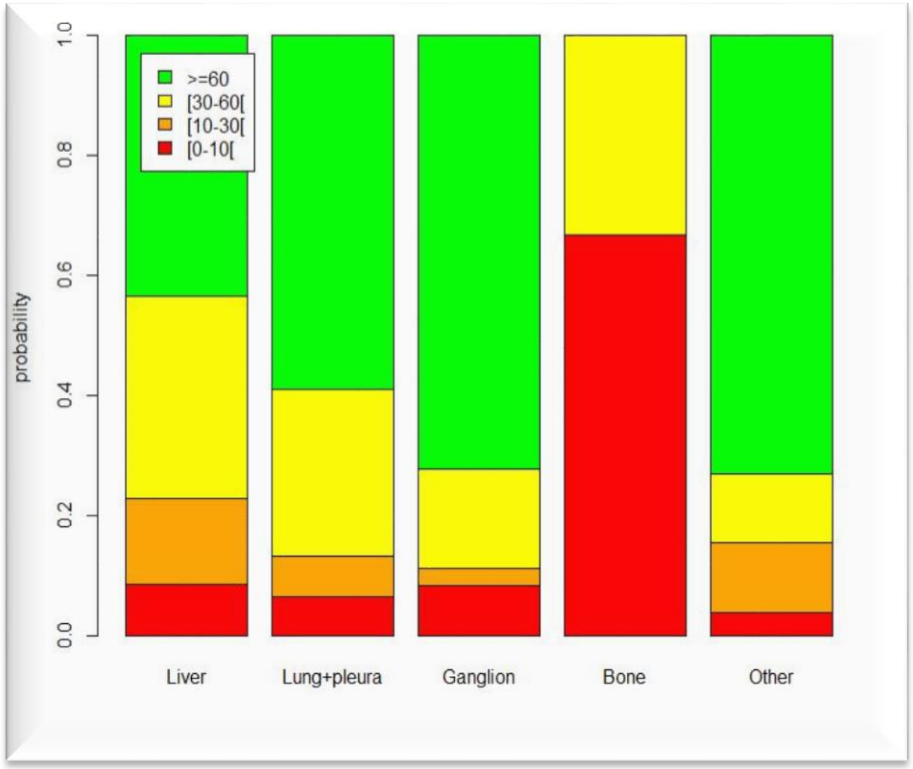
Biopsies characteristics

(based on 215 Needle biopsies)

Percentage of tumor cells according to the site of biopsy



Distribution of the Percentage of tumor cells according to the site of biopsy



No difference between Liver, Lung and Lymph nodes (p=0.07)

Bone biopsies are not appropriate for molecular analysis

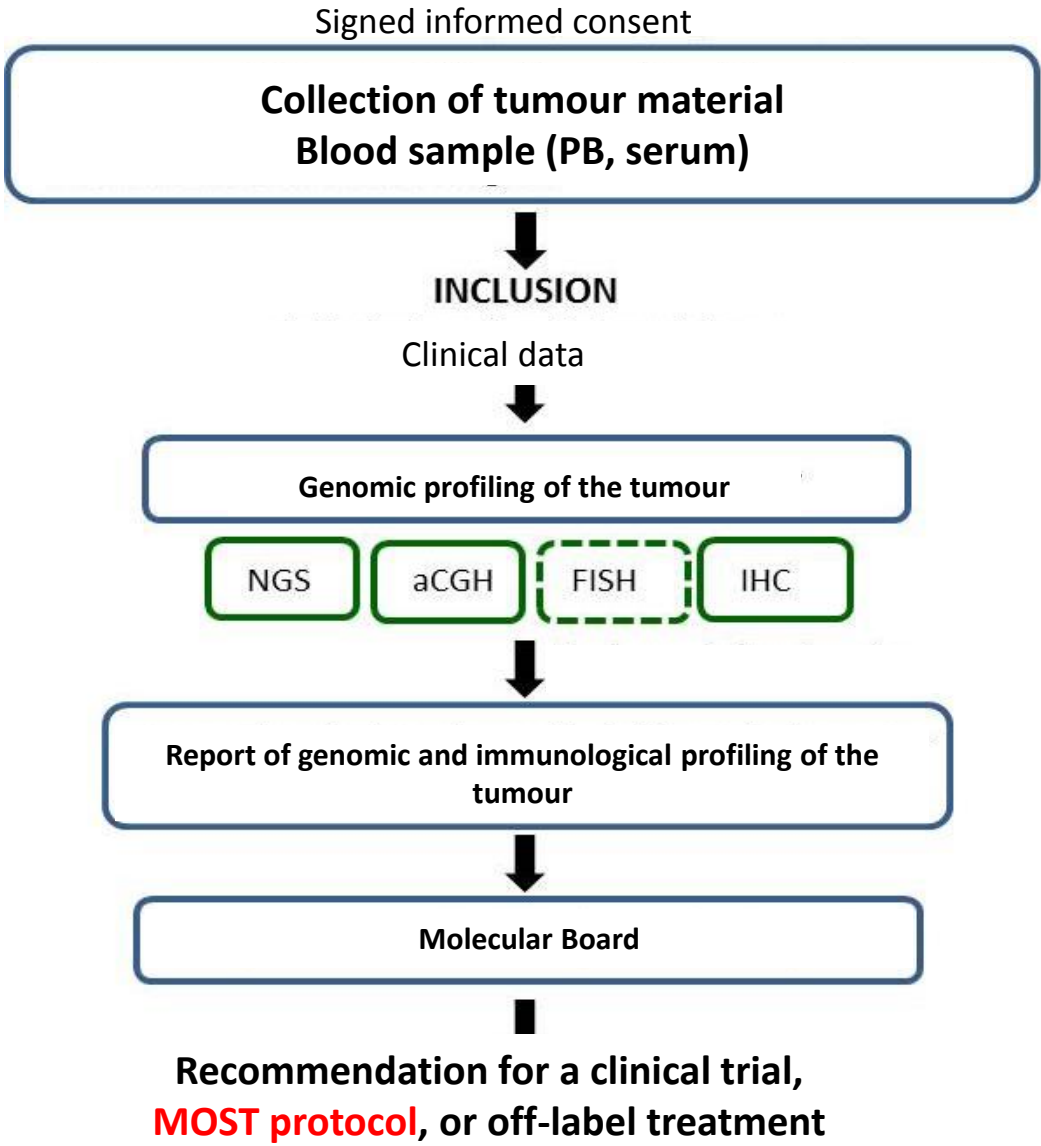
Biopsies characteristics

(based on 215 Needle biopsies)

	Cut-Off ≥ 30% Tumor cells		Cut-Off ≥ 60% Tumor cells	
Risk Factors	**OR (CI 95%)**	**p**	**OR (CI 95%)**	**p**
Diameter of the target lesion (> 30 mm vs ≤ 30 mm)	2.4 (1.1 - 5.1)	0.02	1.7 (0.97 - 3.0)	0.06
Number of biopsy samples (≥5 vs <5)	1.6 (0.8 - 3.2)	0.16	1.8 (1.1 - 3.1)	0.03
Diameter of the needle (<18G vs ≥18G)	1.1 (0.5 - 2.6)	0.8	1.1 (0.5 - 2.2)	0.8
Ongoing anti-tumor treatment (Yes vs No)	0.9 (0.4 - 1.7)	0.7	0.5 (0.3 - 0.9)	0.03
Method to guide biopsy (echo vs CT)	1.0 (0.5 - 2.1)	0.9	0.7 (0.4 - 1.3)	0.3
Senior vs junior radiologists	2.3 (1.1 - 4.7)	0.02	1.5 (0.9 - 2.6)	0.1
Training (≤ 6 months vs > 6 months experience in MOSCATO)	2.2 (1.0 - 5.0)	0.05	1.3 (0.76 - 2.3)	0.3
Central vs periphery of the target lesion	42±28% vs 45±30%	0.2		

Program to Establish the Genetic and Immunologic Profile of Patient's Tumour for All Types of Advanced Cancer (PROFILER)

- **Design:** non-randomised, multicentric, cohort study, combined with a biological sample collection, a retrospective clinical data collection and with a genetic and immunological biomarkers study
- **Start date: 28** February 2013
- **Enrolment single center:** n=414/2000 (June!)
- **Adapting tools and manpower** Reopening Oct 13



JY Blay, Centre Léon Bérard

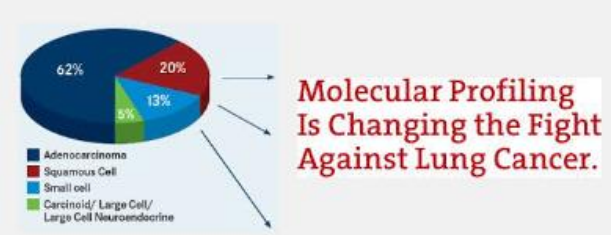
ClinicalTrials.gov identifier NCT01774409

Conclusion (I)

- 1st generation trials are feasable even at a natio-wide level
- Molecular screening programs allow enrichment of phase I/II trials in patients presenting genomic alteration
- Objective responses are observed with the strategy in patients with advanced stage disease across multiple tumor types, but activity is not disruptive
- Optimal programs include NGS in the context of broad availability of bioactive drugs

Molecular profiling a growing reality: academic and privately-driven

MY CANCER GENOME™
GENETICALLY INFORMED CANCER MEDICINE



SPECTA EORTC

INSTITUT NATIONAL DU CANCER

Ongoing precision medicine programs in France: 9 trials (high throughput genomics)

Sponsor	Pilot study	1st generation trials: No NGS	1st generation trials: NGS	Randomized trials
Unicancer		SAFIR01 (Andre, ASCO2013)		SAFIR02 breast; SAFIR02 lung
Gustave Roussy / WIN	preSAFIR (Arnedos, EJC, 2012)	MOSCATO (Hollebecque, ASCO 2013)	WINTHER	
L Berard Lyon			Profiler	MOST
Curie Institute				SHIVA (Letourneau TAT 2014)

Unified Database: Pick-up the winner targets → 2nd generation Algorithm for Personnalized medicine

Overall : >3 000 planned patients (all tumor types), >1 000 already included

FOUNDATION MEDICINE

CARIS LIFE SCIENCES

new oncology

Conclusion (II)

- Molecular profiling is increasingly part of patient's care
  - Either by analysis of their diagnostic sample
  - or by their participation into prospective molecular triage trials

- Clear enthusiasm of patients (recruitment curves)

- Great heterogeneity of practices accross the world
  - different models in different countries
  - different funding possibilities

- Multiple challenges remain

  - optimal setting
  - optimal technology
  - patient selection
  - access to therapies (+++)

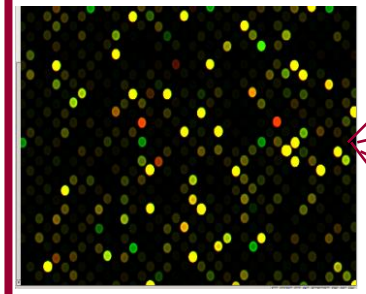
Plan

- Le contexte conceptuel
- Essais de 1ère génération et acquis
- Les essais de 2ème génération
- Enjeux et défis d'avenir

Precision Medicine:
From Molecular screening to personalized medicine trials

Molecular screening → **Personalized medicine**

High throughput Genomics



Test drug in a Biomarker-defined population

- **Treat A**
- **Treat B**
- **Treat C**
- **Tt d, e…**

Andre, J Clin Oncol, 2011

Stratified medicine:
Evaluation of drugs in populations defined by a biomarker

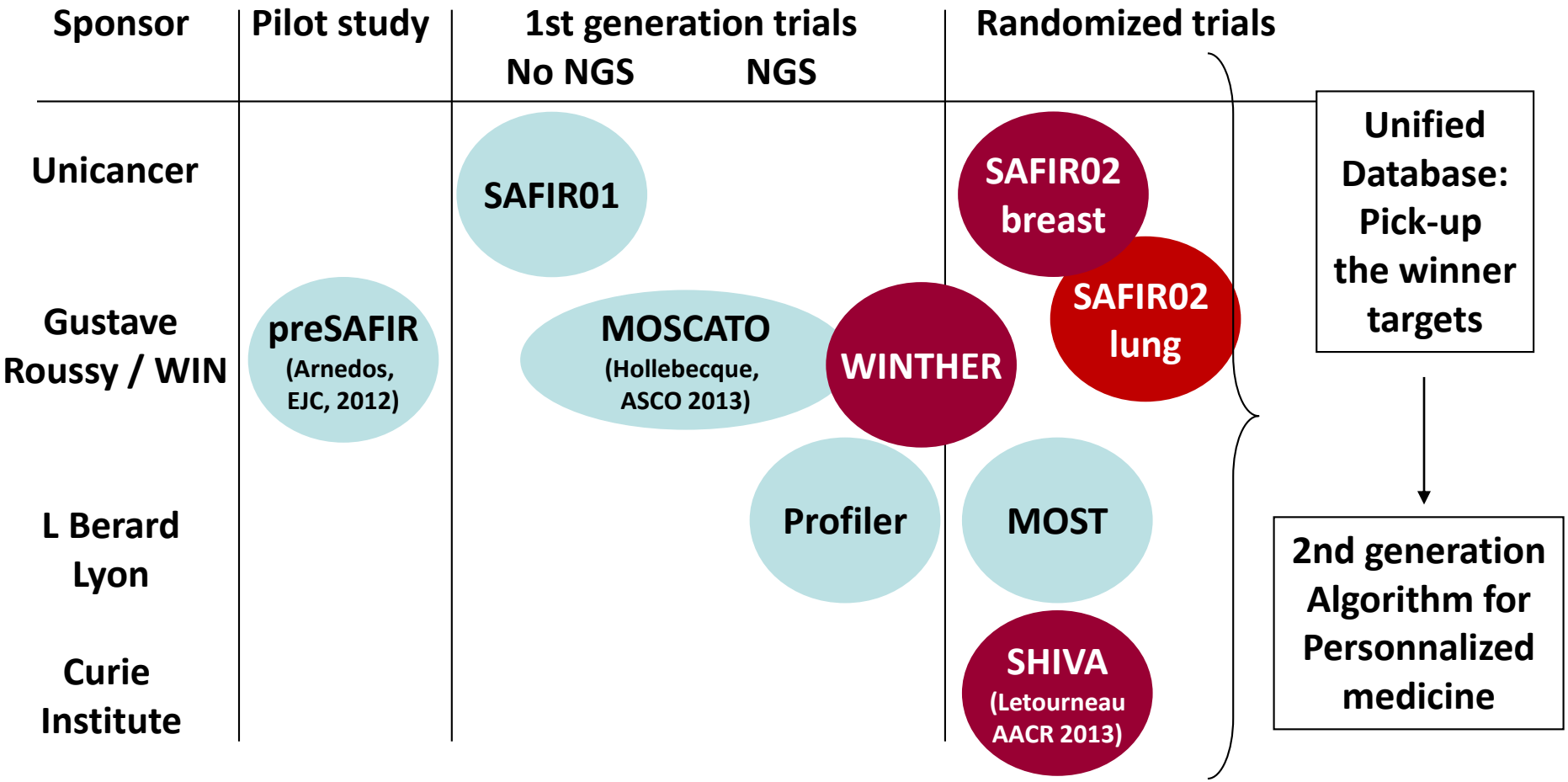
Database + Preclinical studies

Algorithm for Personalized medicine → **Trials testing algorithm**

Tursz, Nat Rev Clin Oncol, 2011

Personalized medicine:
Evaluation of bioinformatic algorithms to identify the targets

Ongoing precision medicine programs in France



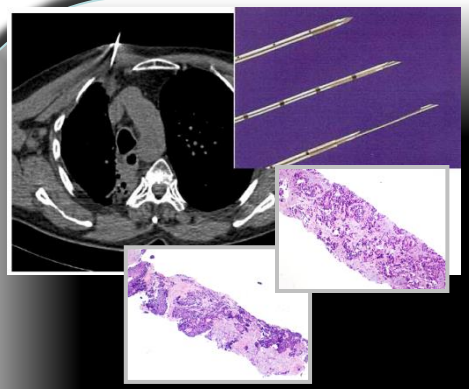
Overall : >3 000 planned patients (all tumor types), >1000 already included

Breast Cancer: > 1 000 planned, >90 already treated (preSAFIR / SAFIR / MOSCATO)

Goal: To generate optimal algorithm for individualized therapy

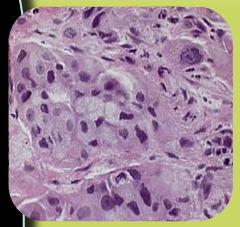
WINTHER concept

Patient with metastatic cancer



TUMOR BIOPSY & MATCHED NORMAL TISSUE BIOPSY

Histology Control

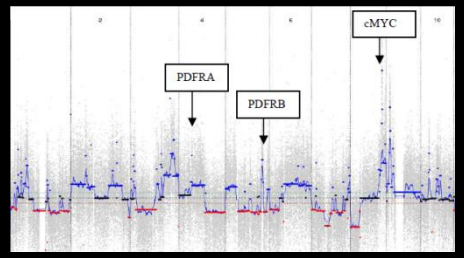


% of cancer and normal cells

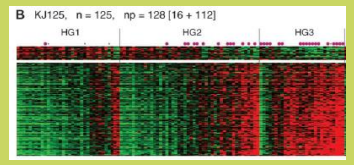
MOLECULAR PROFILING

Mutational aberrations

CGH



Transcriptomic Aberrations

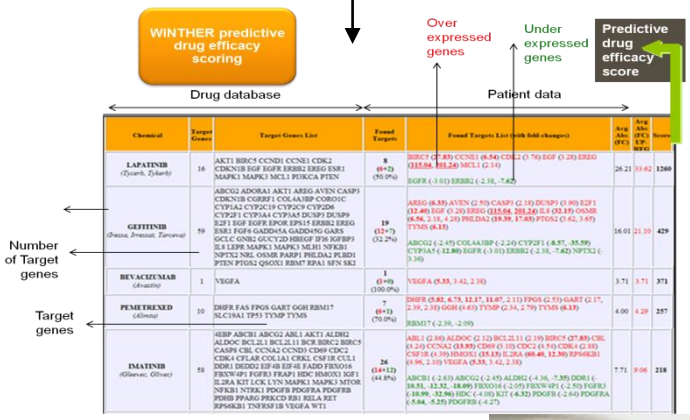


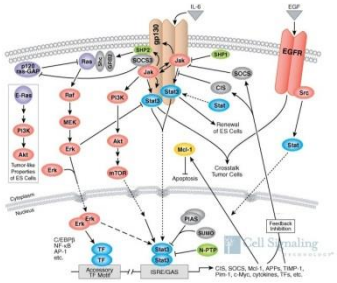
WINTHER concept

Computational tools – Algorithm and genes_drugs database

3. Genetic distance converted into drugs scoring

Individual Drug efficacy Scoring Statement



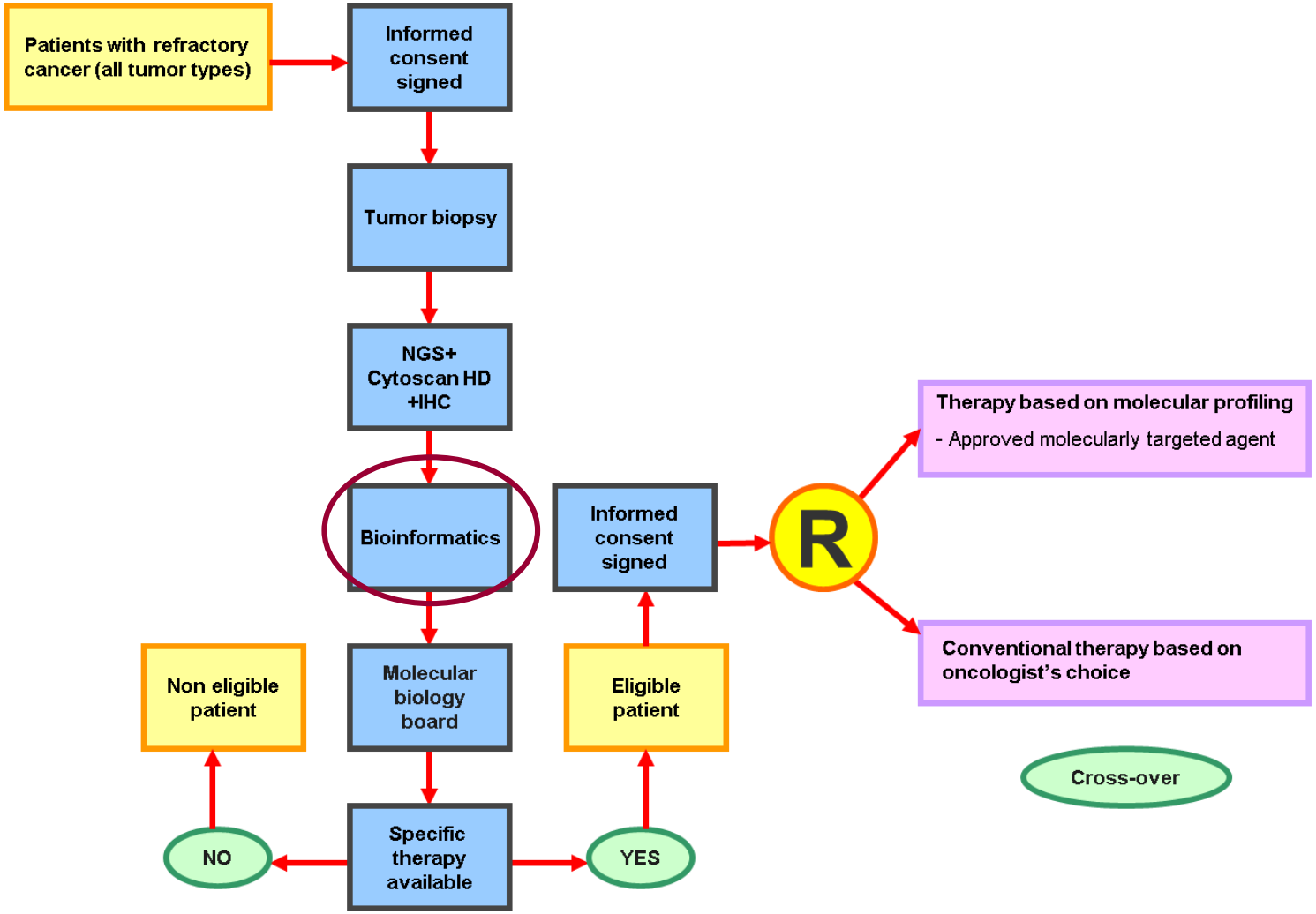


Doctor's decision

RATIONAL TREATMENT BASED ON HOLISTIC BIOLOGICAL INVESTIGATIONS

Personalized Medicine trials: testing the algorithm for target identification

SHIVA trial



C. LeTourneau BJC 2014

Treatment algorithm

Targets	Molecular alterations	Targeted therapies
KIT, ABL1/2, RET	Mutation/Amplification	Imatinib
PI3KCA, AKT1 AKT2/3, mTOR, RICTOR, RAPTOR PTEN STK11 INPP4B	Mutation/Amplification Amplification Homozygous deletion Heterozygous deletion + mutation or IHC Homozygous deletion Heterozygous deletion + mutation Homozygous deletion	Everolimus
BRAF	Mutation/Amplification	Vemurafenib
PDGFRA/B, FLT3	Mutation/Amplification	Sorafenib
EGFR	Mutation/Amplification	Erlotinib
HER-2	Mutation/Amplification	Lapatinib + Trastuzumab
SRC EPHA2, LCK, YES1	Mutation/Amplification Amplification	Dasatinib
ER, PR	Protein expression $\geq$10% IHC	Tamoxifen or Letrozole
AR	Protein expression $\geq$10% IHC	Abiraterone

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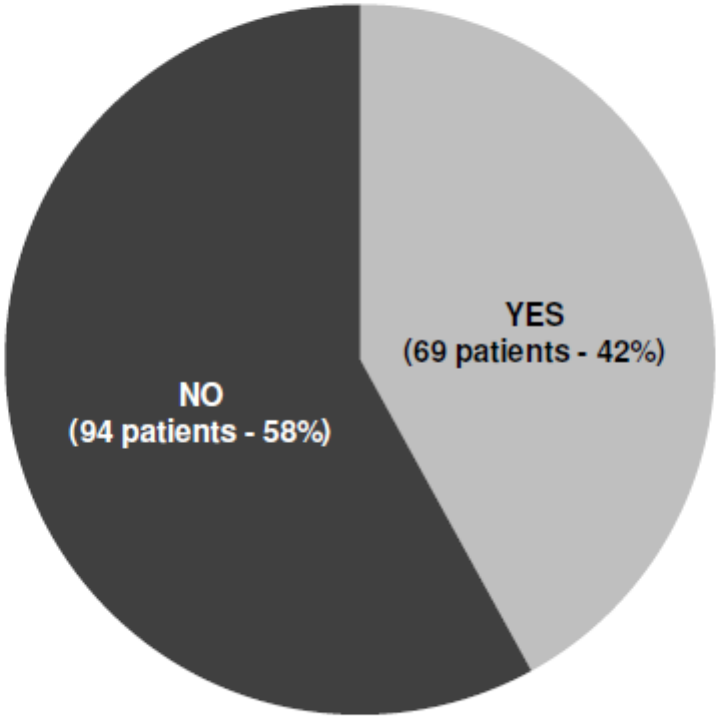
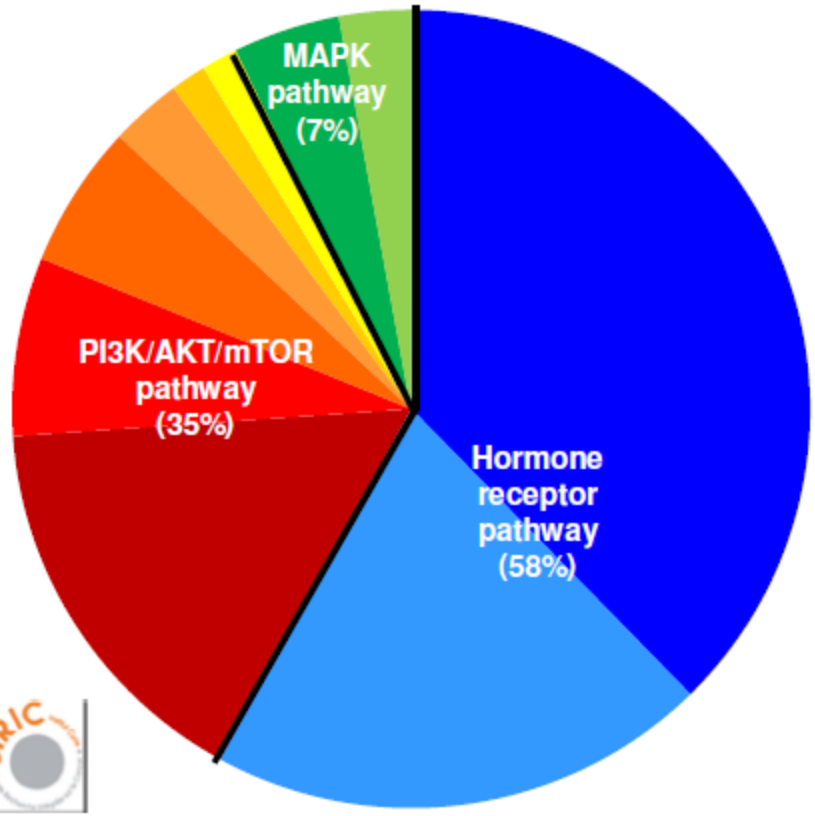
Proportion of patients eligible for randomization



Molecular alterations retained for the randomization



- AR
- ER/PR
- PI3KCA mutation
- PTEN loss/deletion
- AKT amplification/gain
- PI3KCA mutation + PTEN loss
- STK11 mutation & loss
- AKT gain + STK11 loss
- PDGFRA amplification/gain
- HER2 amplification/gain

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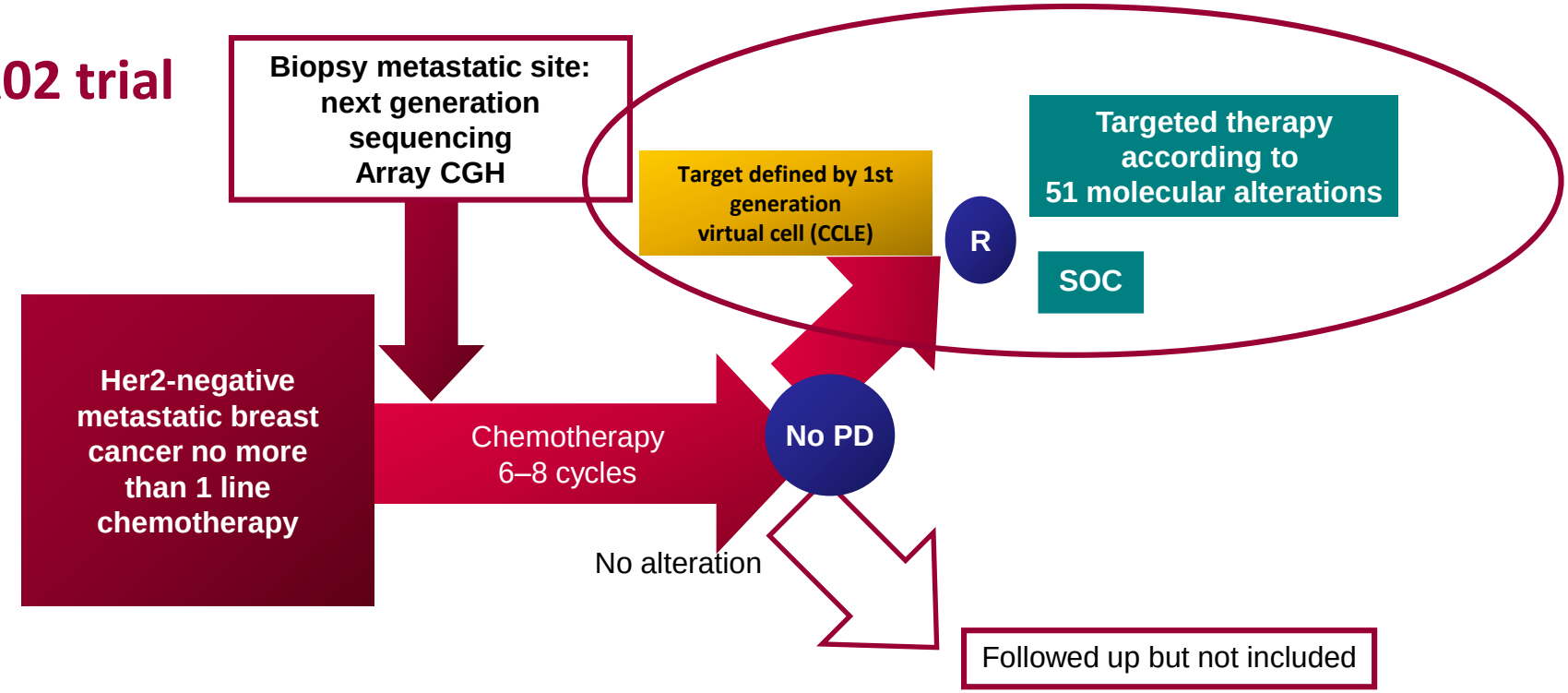
Personalized Medicine trials: testing the algorithm for target identification

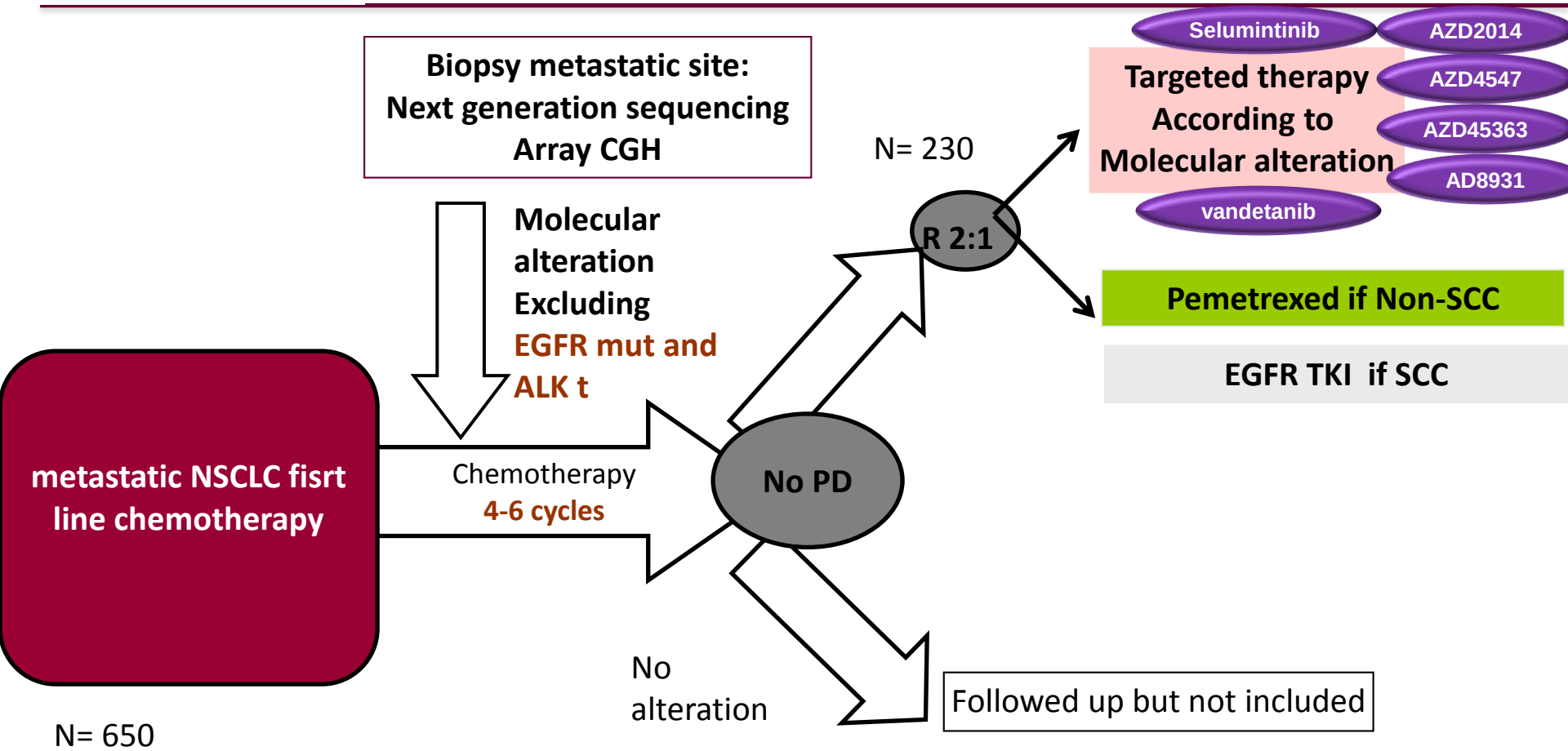
SAFIR02 trial



- 210 randomised, around 400 screened
- Hypothesis: median PFS 3 to 6 months
- Sister trial in lung cancer

- Sponsor: UNICANCER
- Funding: FONDATION ARC
- Pharma partner: AZ
- Algorithm validated on encyclopaedia cell lines

SAFIR 02lung-IFCT1301

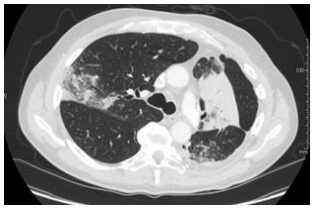


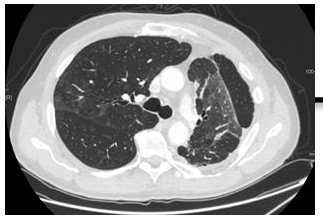
All histologies

Ethics approval sept 2013; ANSM approval oct 2013, FPI april 2014

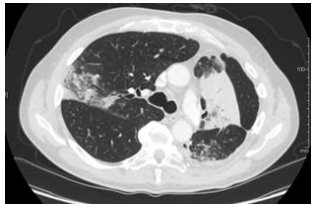
MATCH-R trial

Patients with + biomarker tumor exposed to a targeted therapy and an initial response



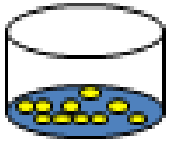


Sensitive



Resistant

In vitro Cell lines



Mouse avatar

Tumor biopy or effusion

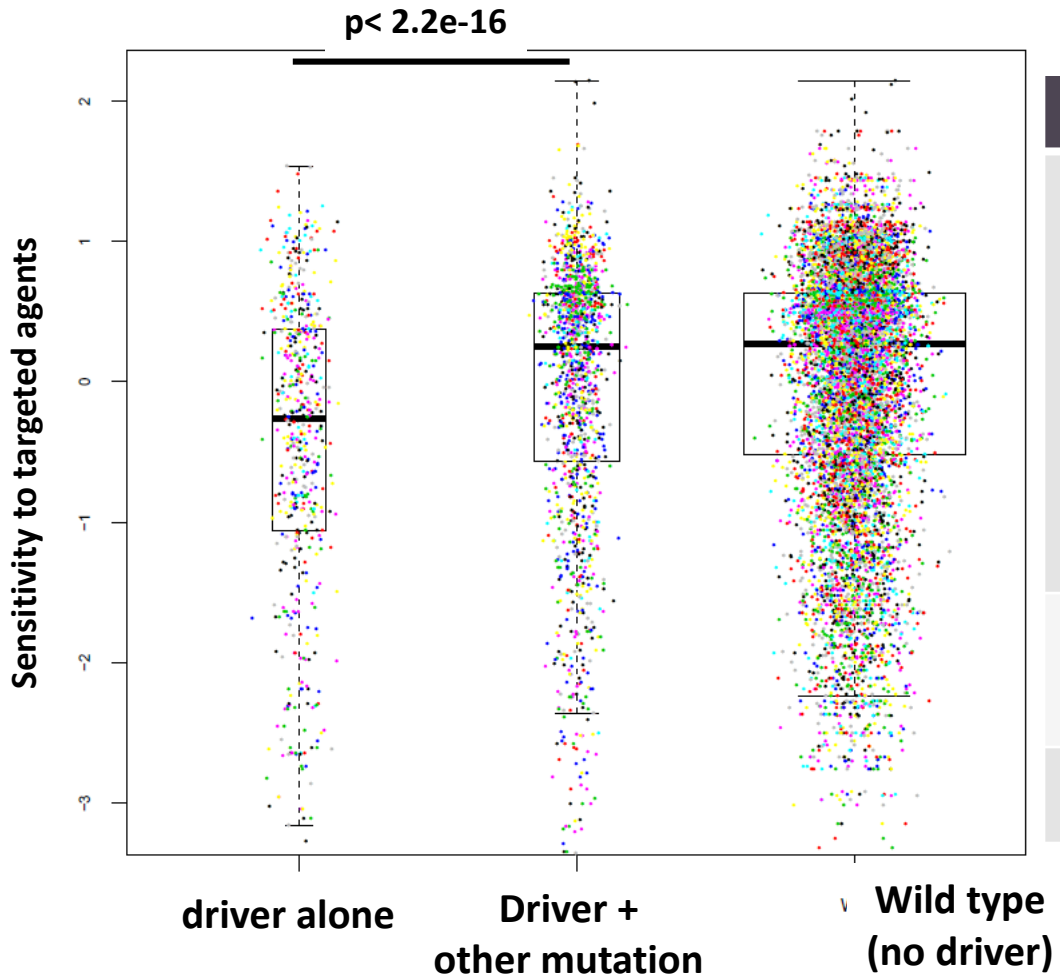
Plan

- Le contexte conceptuel
- Essais de 1ère génération et acquis
- Les essais de 2ème génération
- Enjeux et défis d’avenir

General goals of tumour molecular profiling

- Tumour molecular profiling can help decipher cancer biology at the individual level and identify:
  - Oncogenic drivers and predictors of efficacy
  - **Lethal subclones & intratumor heterogeneity**
  - Mutagenesis processes & DNA repair defects
  - Dialogue between cancer cells and immune system

Co-existing mutations: a major challenge?



	In Cell lines
Source	• **GDSC (**Genomics of Drug Sensitivity in Cancer) 80 drug-gene-alteration pairs for 20 drugs and 19 targetable genes • **CCLE** (Cancer Cell Line Encyclopedia) 16 drug-gene-alteration pairs for 4 drugs and 5 targetable genes
Gene alteration	• **Mutation** • **Amplification (CNV > 4)** • **Loss (CNV < 2)**
Drug response	**nAUC** (Scaled AUC)

Each color represent one drug/target couple

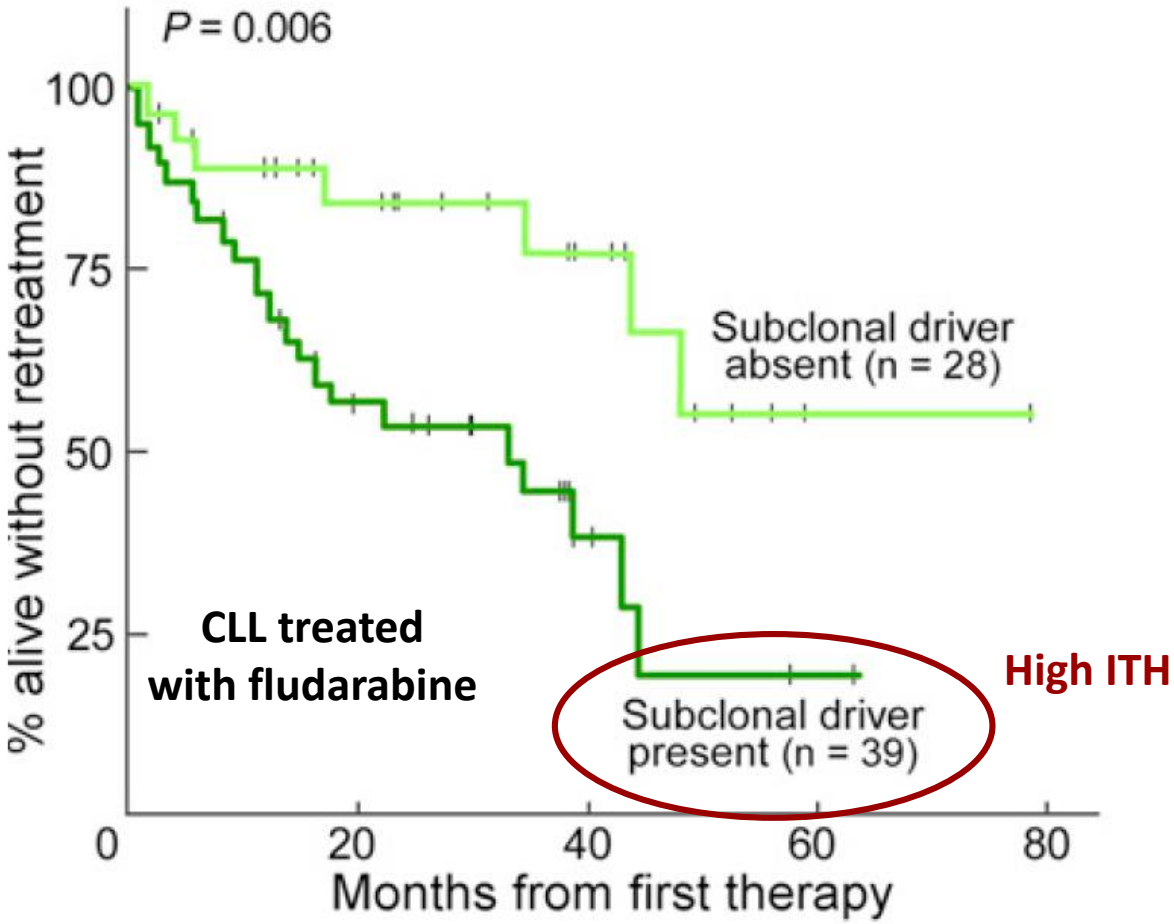
Co-existing mutations are associated with resistance

Lefebvre & Yu Cancer Pharmacogenomics and Targeted Therapies 2014

How the use of genomic tests could help avoiding resistance ?

- Does intratumor heterogeneity predict resistance to therapy ?
- Is it possible to detect the lethal subclone in primary tumor using deep sequencing… and kill it ?
- Is it possible to detect the appearance of lethal subclone by using circulating DNA… and kill it ?

Does intratumor heterogeneity predict resistance to therapy ?

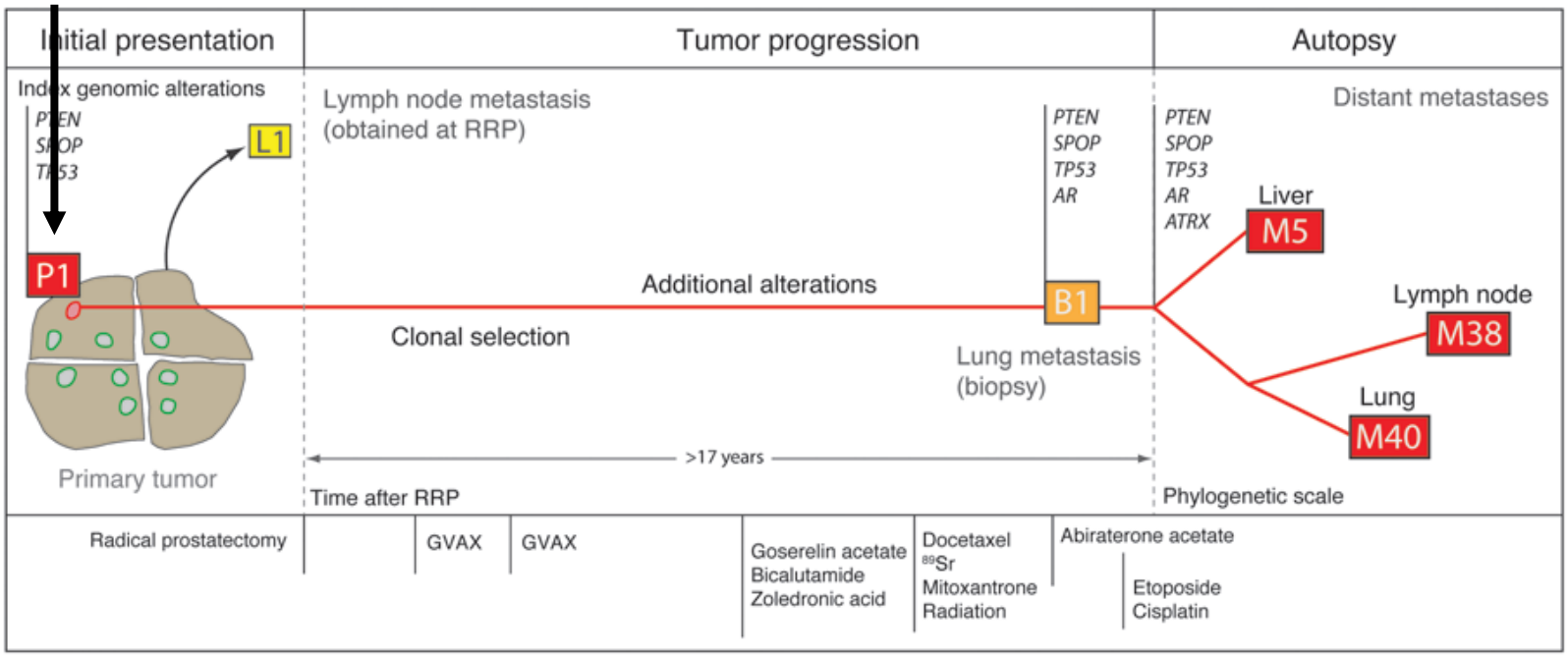


Intratumor heterogeneity could define a disease resistant to therapy

Landau, Cell, 2014

Is it possible to detect the lethal subclone in primary tumor ?

Lethal clone present in a minority of cells in the primary tumors



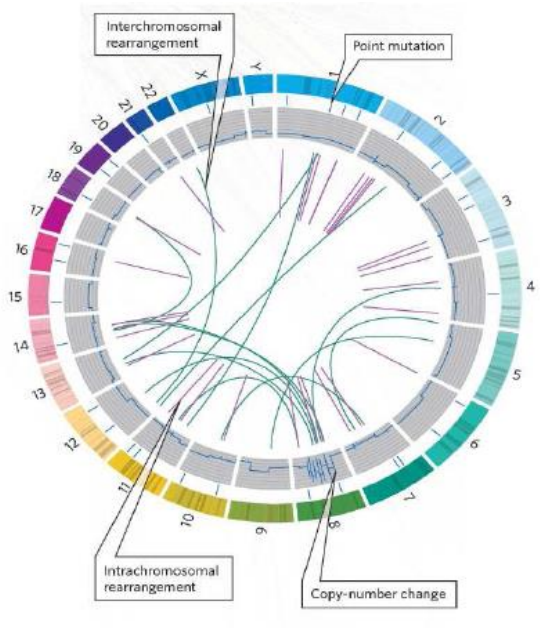
Ultradeep sequencing could detect the lethal minority subclone in primary tumor

Hafner, J Clin Invest, 2013

Bridging oncogene de-addiction with complementary systems

Oncogenes

TcR repertoire immune system



Genomic scar: DNA repair defect

Intratumour heterogeneity

As each genomic landscape is unique, we do not have any more homogenous cohorts to register a drug in a population

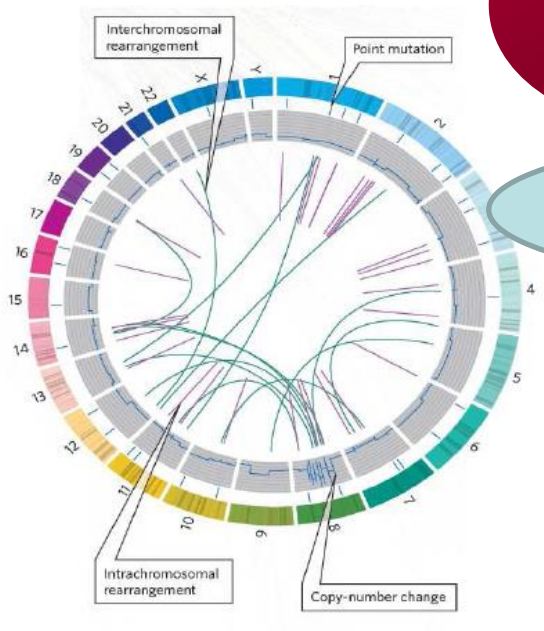
Third generation trials

Oncogenes

TKI

TcR repertoire immune system

Immunecheckpoints



Genomic scar: DNA repair defect

DDR modulators

Intratumour heterogeneity

Ultradeep Seq cfDNA

Challenges of tumour molecular profiling

- The optimal technology is yet to be universally adopted
- The optimal setting for analysis (metastatic vs locoregional vs resected) is still debated
- Best patient population to enroll (refractory, sensitive…) TBD

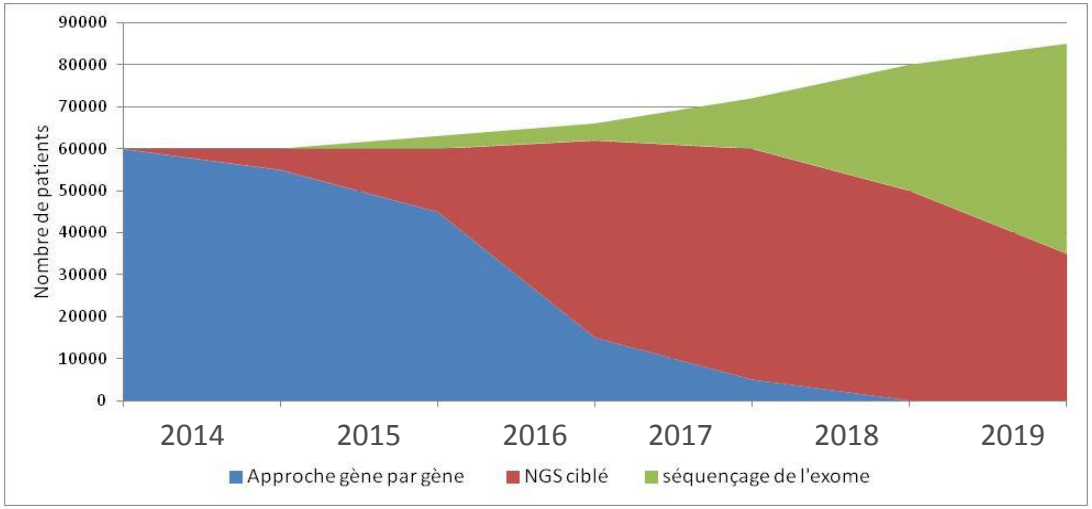
Soutien de l'INCa au déploiement du NGS

2013 : Appel à projets INCa → Structuration du séquençage de nouvelle génération à visée diagnostique en cancérologie

Perspectives 2015/2016 :

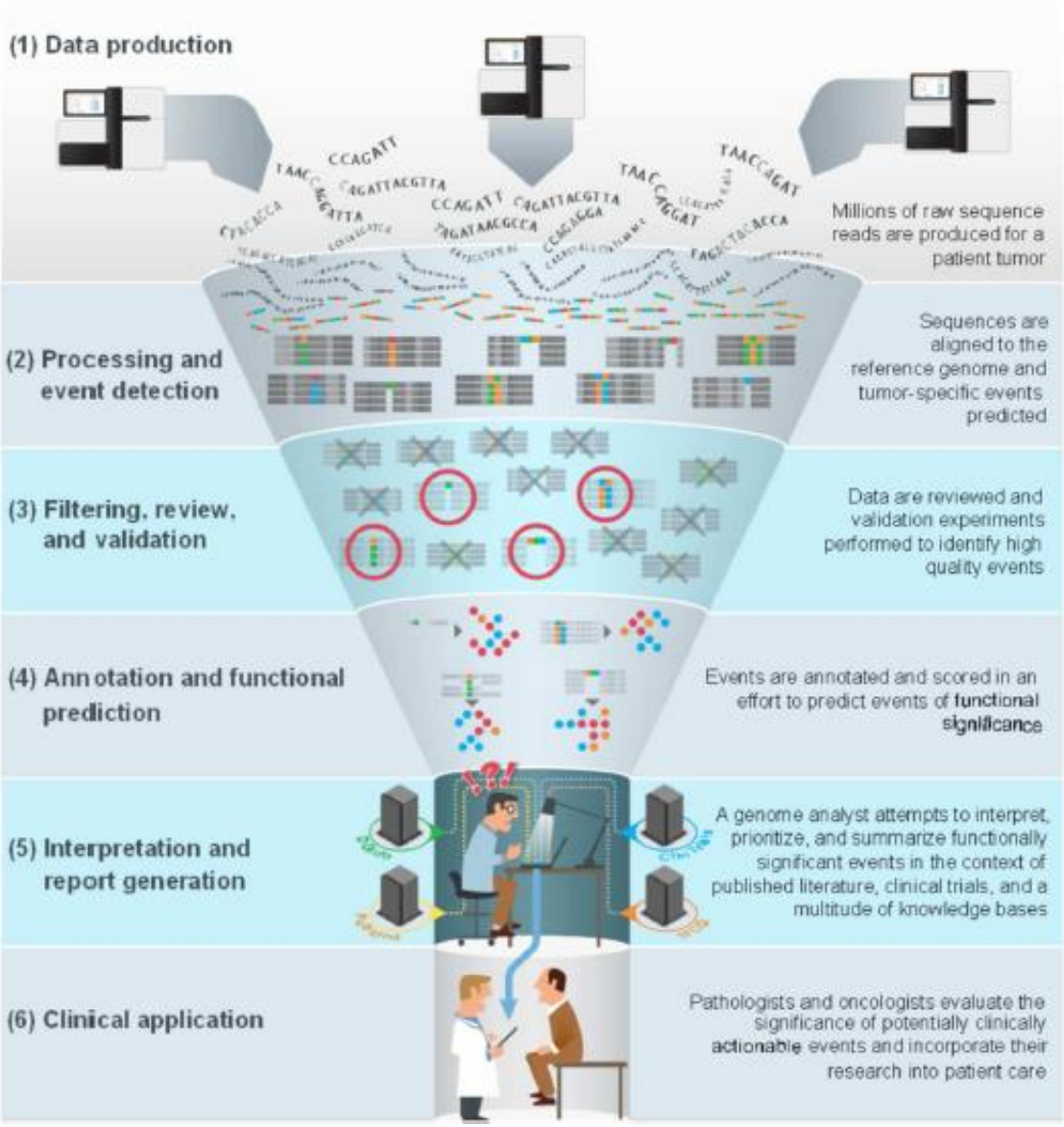
→ Déploiement du programme à l'échelle nationale pour permettre l'accès au NGS ciblé sur tout le territoire

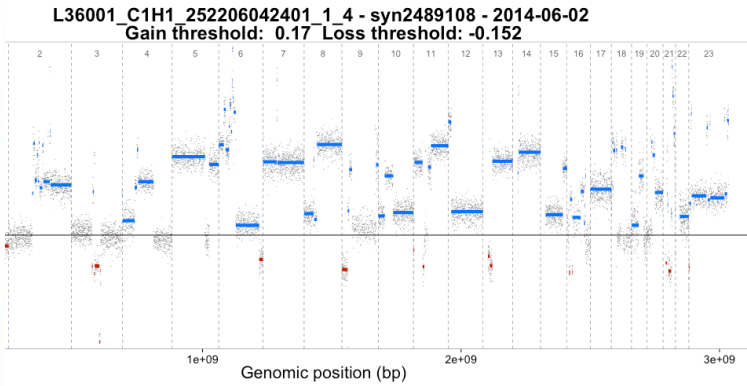
→ Anticiper le séquençage de l'exome en pratique clinique (phase pilote au travers des essais cliniques guidés par la génomique)

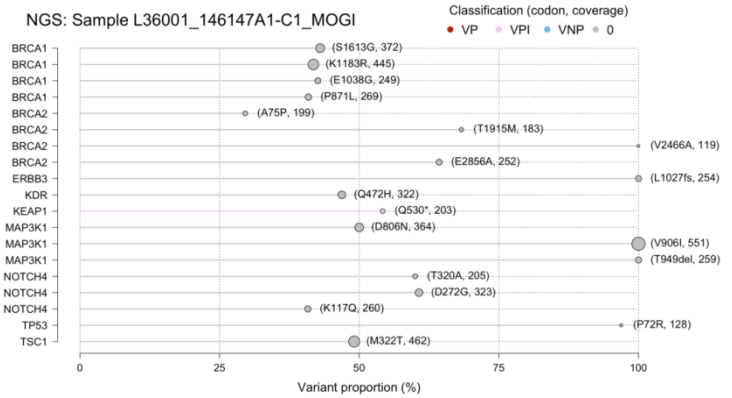


A Buzyn

SAFIR 02 lung-IFCT1301 data interpretation challenge







Good et al. Genome Biology 2014, 15:438

Amplifications focales d'oncogènes (CGH)

- **Taille maximun < 10 Mb (100 gènes)**
- **Fold change > X8 et/ou LogRatio > 2**
- A interpréter (au cours du MTB) en fonction de :
  - la cellularité tumorale
  - la qualité de la CGH
  - de la ploïdie (Puce SNP Affimetrix)
  - *versus* génome entier (valeur « Log »)
  - *versus* le bras chromosomique
  - *versus* la région subcentromérique (valeur « relativeLog »)

I Bieche

How do we define actionability?

Annals of Oncology Advance Access published October 24, 2014

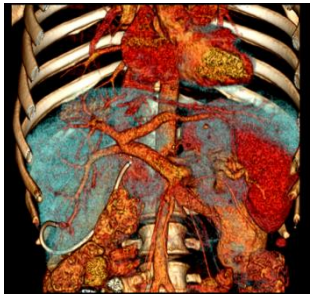
Prioritising Targets for Precision Cancer Medicine

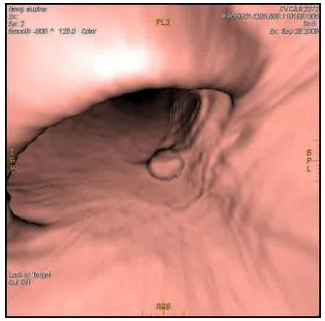
Fabrice Andre[1], Elaine Mardis[2], Max Salm[3], Jean-Charles Soria[1], Lillian L. Siu[4], Charles Swanton[3,5]

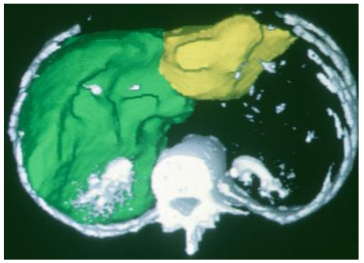
How do we define actionability?

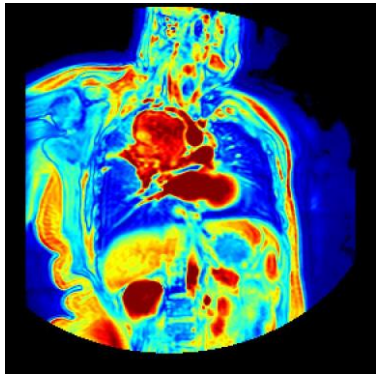
TABLE 4 Level Evidence Scale for target prioritization

Level of evidence	A	B	C	Clinical implications
I : Molecular alteration validated in several robust early phase trials or at least one phase III randomized trials	Alteration validated in the disease under consideration, targeted therapies have shown to be uneffective in patients who are lacking the genomic alteration	no evidence that the therapy does not work in the absence of the molecular alteration	Level I molecular alteration, but not in the disease under consideration.	A/B: patients must be treated with the targeted therapy C: patients must enter clinical trials testing the targeted therapy
II: Molecular alteration suggested in single and underpowered phase I/II trials	Alteration validated in the disease under consideration, targeted therapies have shown to be uneffective in patients who are lacking the genomic alteration	no evidence that the therapy does not work in the absence of the molecular alteration	Level I molecular alteration, but not in the disease under consideration.	patients must enter clinical trials testing the targeted therapy
III : Target suggested by preclinical studies	Preclinical studies include human samples, cell lines and animal models	preclinical studies that lack either cell lines or animal models	NA	Inclusion in clinical trials is optional
IV: Target predicted but lack of clinical or preclinical data	Genomic alteration is a known cancer related gene	Genomic alteration is not known as cancer related gene	NA	Inclusion in clinical trials is optional

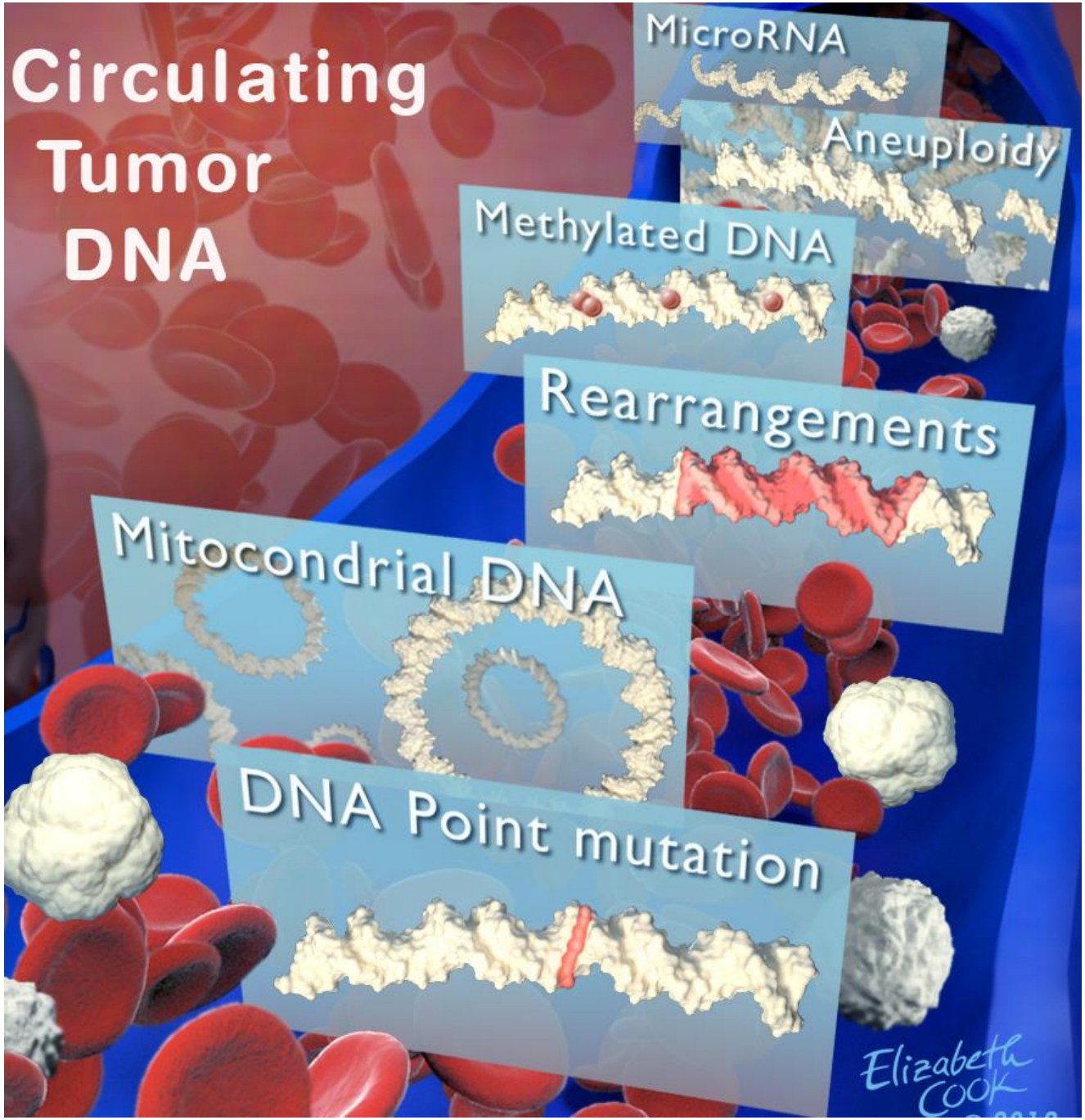




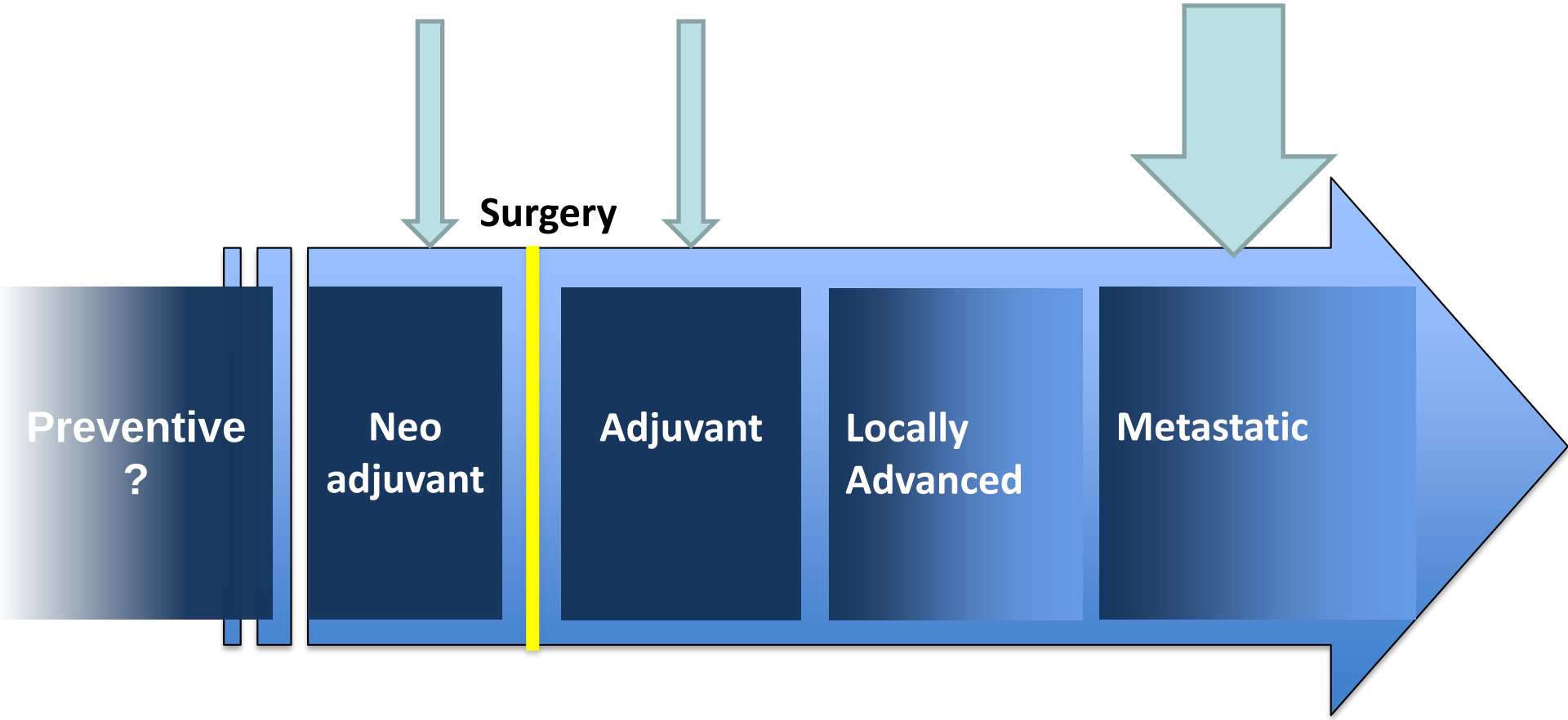




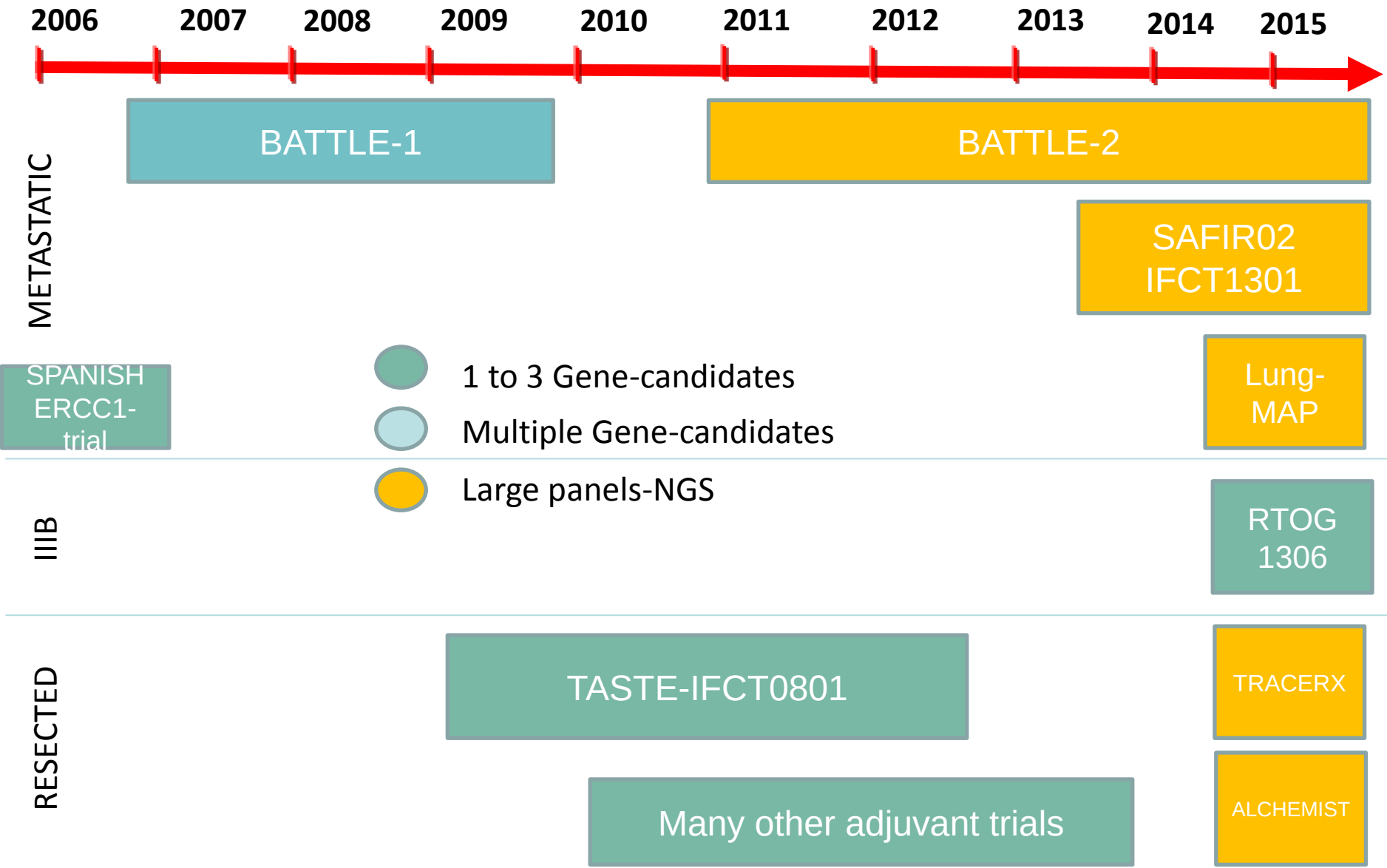
IMAGING

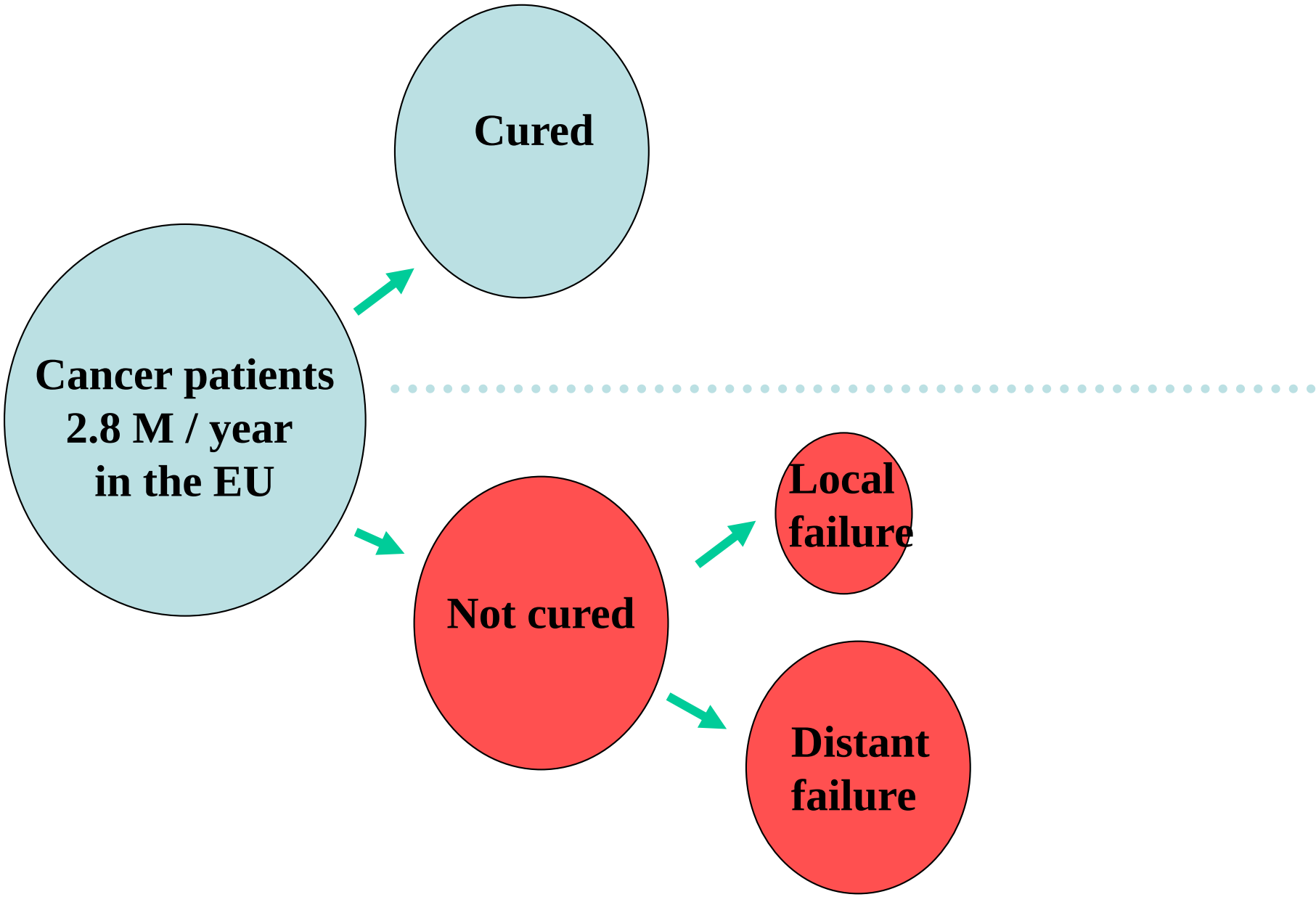

Circulating
Tumor
DNA
MicroRNA
Aneuploidy
Methylated DNA
Rearrangements
Mitocondrial DNA
DNA Point mutation
Elizabeth
COOK

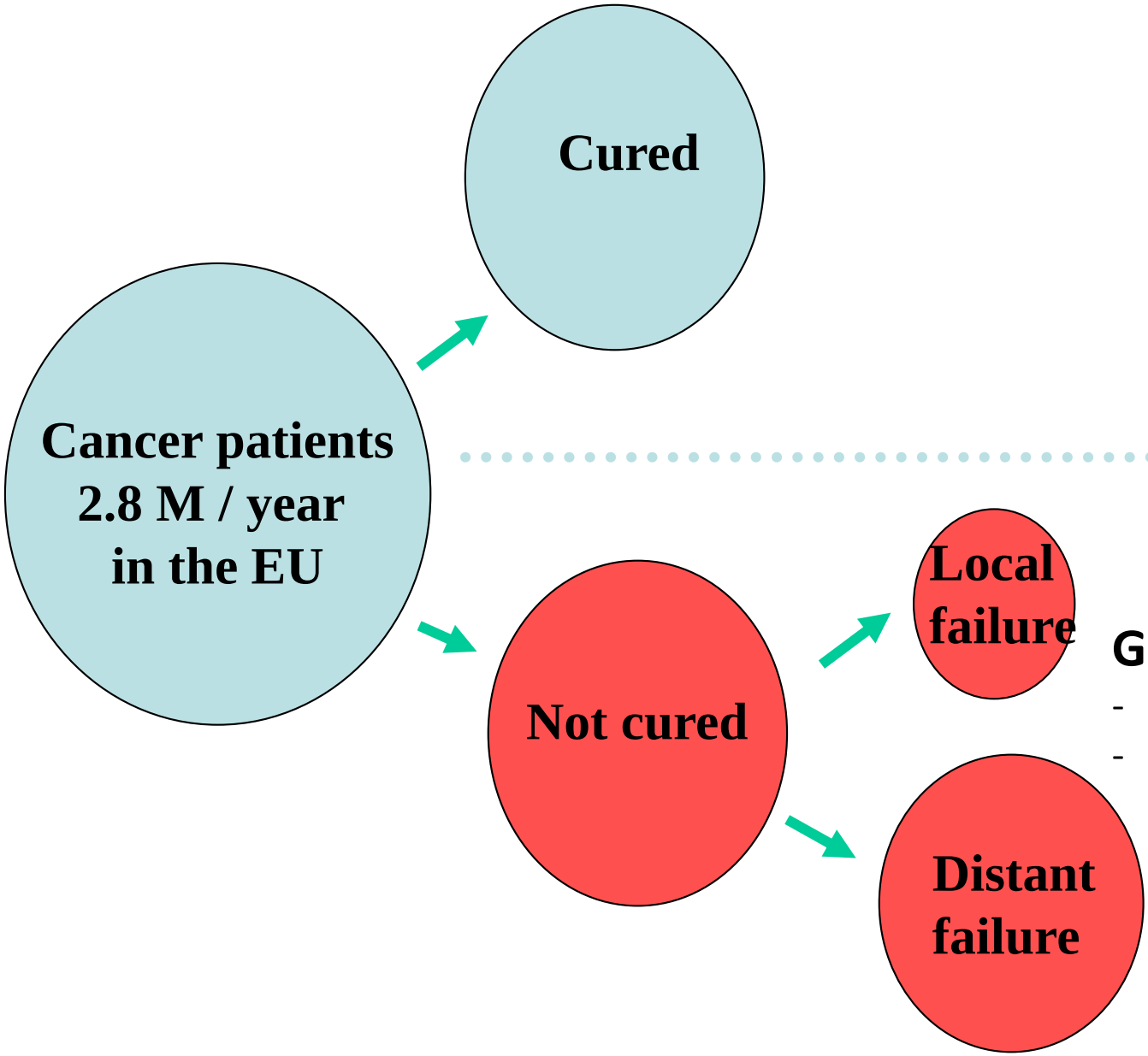
Optimal setting of molecular profiling ?



Partial perspective of molecular profiling trials in lung cancer

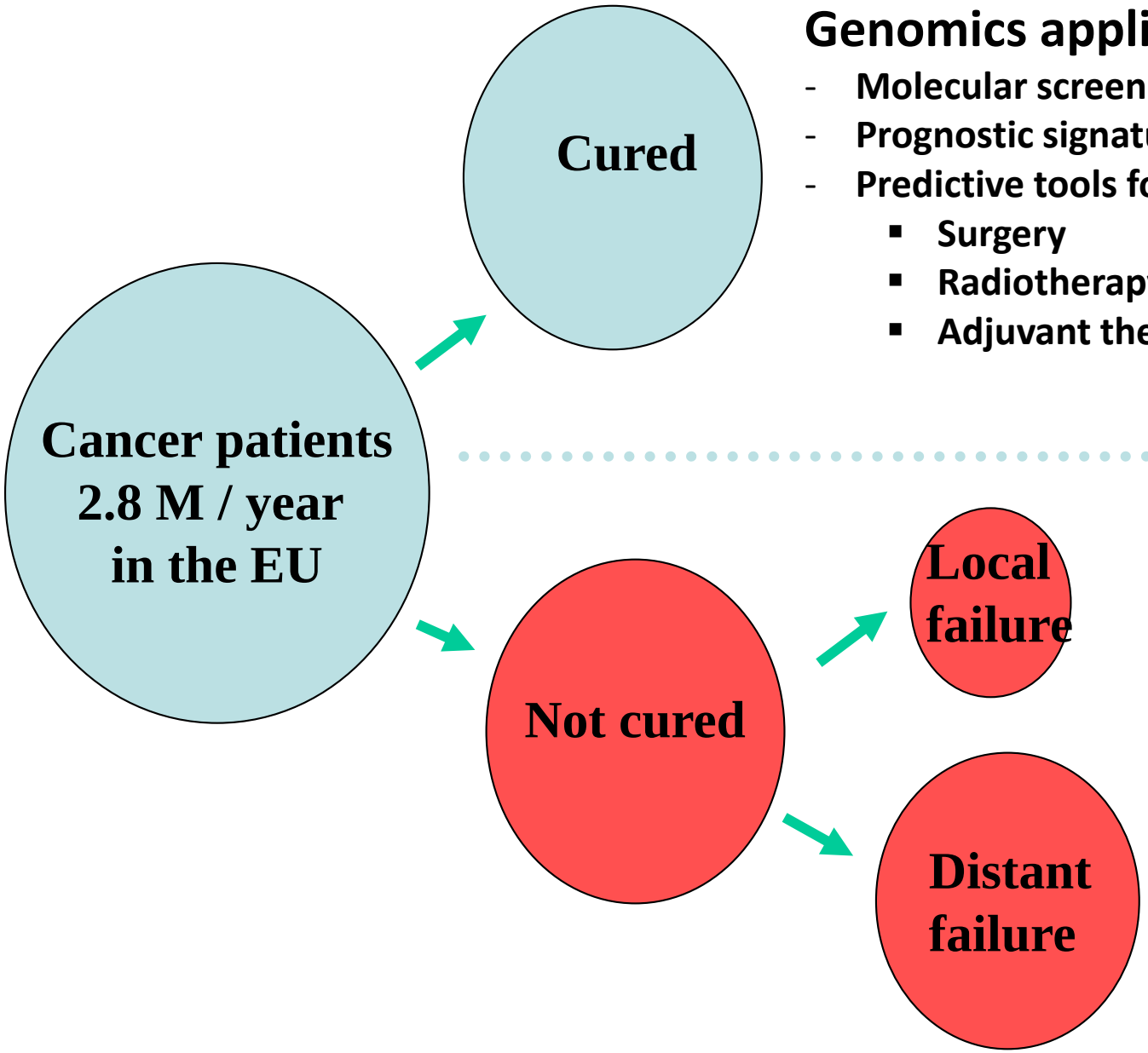



Cured
Cancer patients
2.8 M / year
in the EU
Not cured
Local
failure
Distant
failure



Genomics applications:

- Expanding actionability
- Developing new algorithms



Genomics applications:

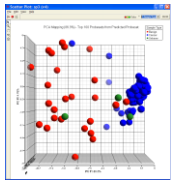
- Molecular screening programs
- Prognostic signatures
- Predictive tools for better
  - Surgery
  - Radiotherapy
  - Adjuvant therapy

Cancer Patient in the near future

Tumor Biopsy/ blood

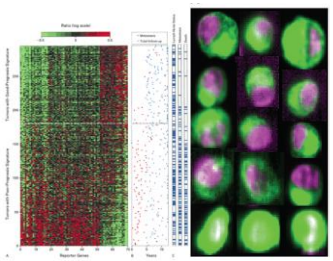
MOLECULAR PORTRAIT

Diagnostic

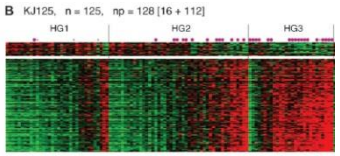


Cancer?
Yes/No

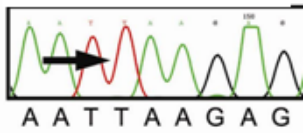
Prognosis



Chemotherapy sensitivity



Targeted therapy sensitivity



Immunotherap

PD1/PDL1
OX40
Other
Pathways
…

Need for treatment ?

Which treatment and when ?

Acknowledgements

Gustave Roussy

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J Raynaud

INCA

A Buzyn/ F Calvo
F Nowak

VHIO

Jordi Rodon