

The Clinical-Translational- Basic Research Continuum

ESMO-ASCO Symposium, Madrid 2014



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Gustave Roussy Comprehensive Cancer Center
Cancer Campus Grand Paris, France

Premier CCC in Europe

Volume of Activity

- \pm 13000 new patients /yr
- \pm 50.000 treatments/yr
- >10.000 surgical interventions/yr
- > 200.000 chemotherapies/yr
- \geq 200.000 outpatient visits

- 560 beds (including 90 outpatient beds/chairs)
- 220 specialists FT + 200 PT

- Employees \pm 3000

- Budget: 300 millions Euros
- Research: 70 millions Euros

Key Clinical Missions

- **Tertiary / Highly Complex Medicine**
- **Rare Tumors (> 20%)**
- **Care integrated with Clinical Research**
(~4000 pts/yr in Clinical Trials)
- **Early Drug Development**
 - (680 pts included in 2013 : ~20% of CR program)

**INTEGRATION of RESEARCH and CARE to
create TOMORROWS MEDICINE**

- **~ 4000 patients expected in clinical trials in 2014**
 - 2010: 2166 pts
- **28% of new patients in clinical trials**
 - 1/3 Pharma fully sponsored
 - 1/3 Gustave Roussy - led multicenter academic trials
 - 1/3 Gustave Roussy - single institution academic studies
- **Early Clinical Trials/Drug Development**
 - **2013 Creation of Department of Drug Development**
 - **Head: Jean Charles Soria**
 - **In 2010: 226 pts**
 - **In 2013: 682 pts**

- 30 Research Groups (Inserm, CNRS, Gustave Roussy)
- 400 Researchers, 240 Technicians
- **Basic Research**
 - Research Building 1 and 2 (each 5000 M2)
 - 2013 MolMed TR Research Building 3 (6000M2)
- **Translational Research**
 - Additional Laboratories in Hospital Building
 - Tumor Immunology / Biomarkers / Genetics etc..

Decision December 2011 – Inauguration June 2013

New Research Building 6000 M2

- 1 floor for TR / Molecular Medicine
- 1 floor for 10 new Research Groups (recruited from MSK, Harvard, CNIO, Stanford, etc)
- 1 floor for Biostat/Bioinformatics and Oncology Education



Ecole Doctorale des Sciences de Cancer

- 5000 student hours
- MD/PhD programs
- New Medical/Paramedical Professions
- Onco-Nursing

International programs

- Mahgreb/ Saoudi Arabia / Gulf
- Kazakhstan
- Latin America
- International MD/PhD program

CHOOSE Amongst **KEY AREAS** in Cancer Research

- **Omics and Precision Cancer Medicine**
- **Immunology/Immunotherapy**
- **Epigenetics**
- **Haemato/MDS/IPS-Stem cells**
- **Cell Death Mechanisms**
- **EMT – MET / Plasticity**
- **Functional Imaging**
- **Bioinformatics and BIG DATA**
- **Nanotechnology**
- **Radiobiology – New Drugs+RT**
- **Prevention**

Choose Research Lead Programs

- **Clinical Research Machine**
 - ~ 4000 pts/yr = ~30% all pts
 - Precision medicine trials +++
 - Early Drug Development +++
- **Basic Research**
 - Cell Death Mechanisms (Guido Kroemer)
 - Tumor Immunology (Laurence Zitvogel)
 - Haemato-Oncology (William Vainschenker)
- **Translational Research**
 - Precision Cancer Medicine (**transversal**)
 - Jean Charles Soria / Fabrice Andre (**Lung/Breast**)
 - Robert/Vagner /Eggermont (**Melanoma**)
 - Solary / Bernard (**Haemato**)

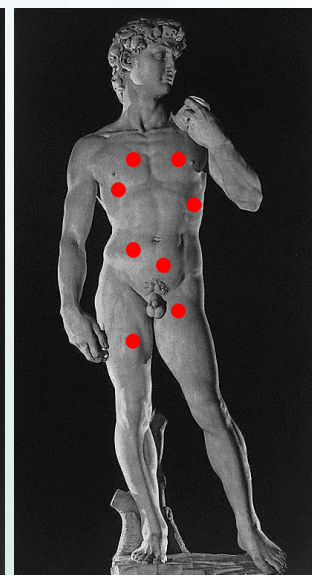
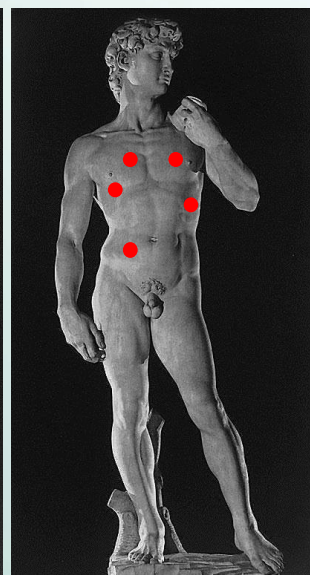
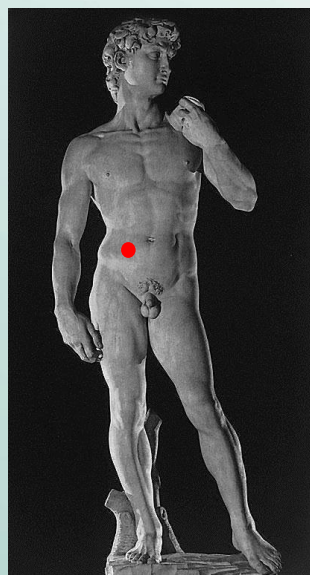
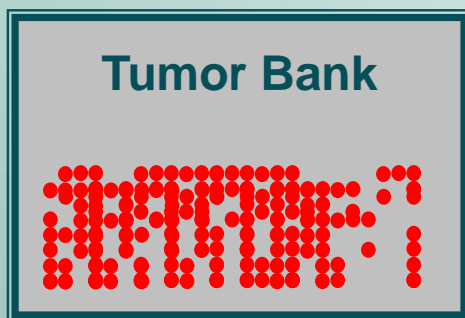
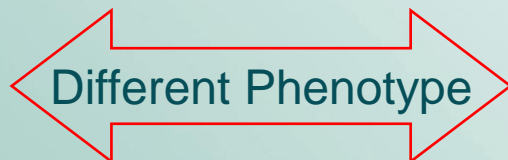
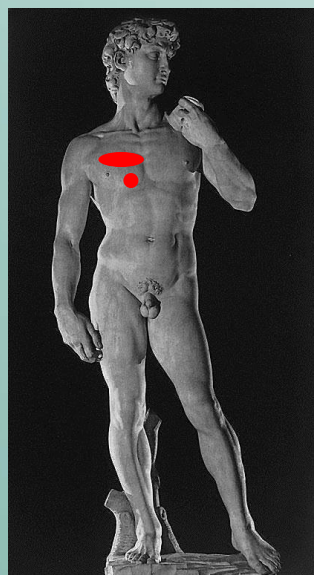


Surgery T1N1

Adrenal gland +

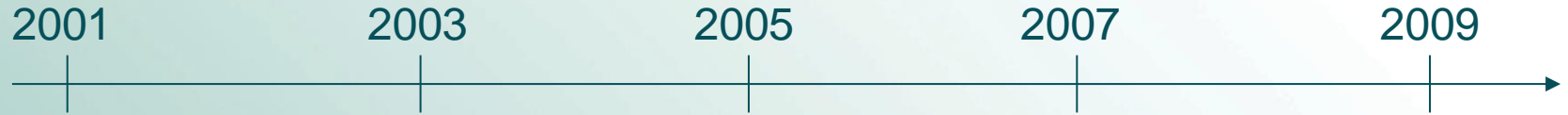
Lung +

Bone +

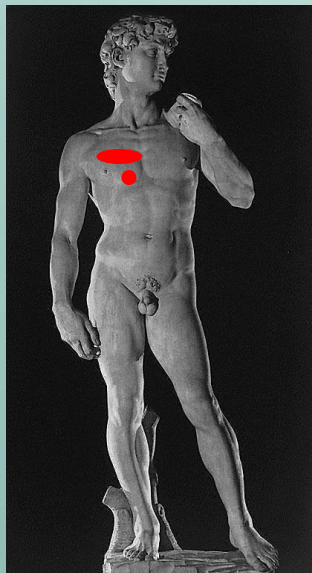


Whole tumor	<i>Tissue</i>	Adrenal gland biopsy	-	-
Vinorelbine cisplatinum	<i>Treatment</i>	Taxol Carbo bevacizumab	Pemetrexed	Biology guided ?

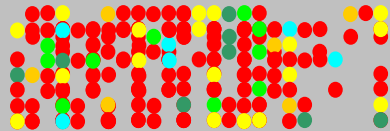
Heterogeneity in Primary, Metastases (organ) and Evolution (time)



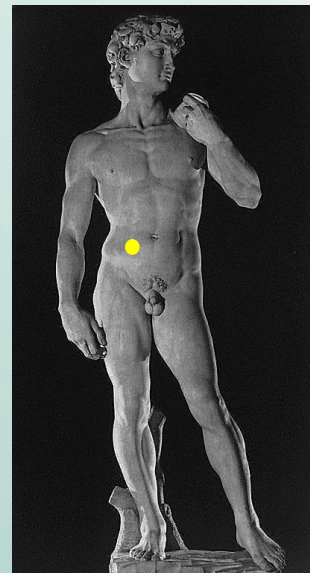
Surgery T1N1



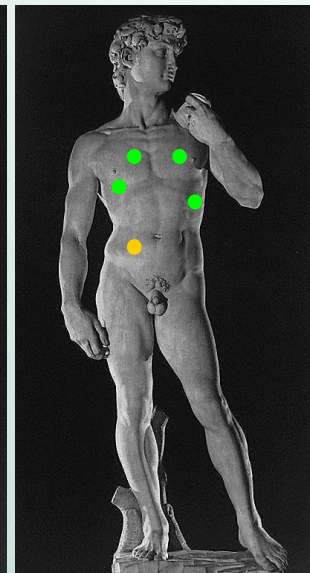
Tumor Bank



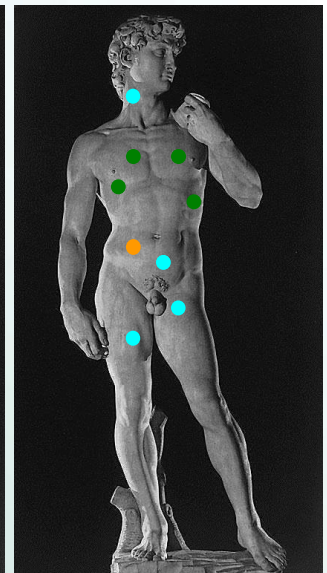
Adrenal gland +



Lung +



Bone +

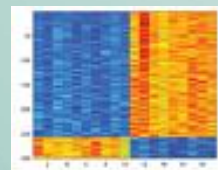


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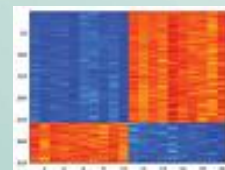
Patient Heterogeneity



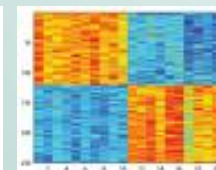
Inter- and Intratumor !! Tumor Molecular Heterogeneity



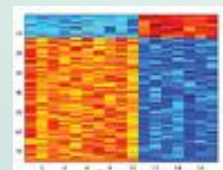
RAS



EGFR



MYC



MET

Rational Genomics: “Molecular Portraits” for targeted therapy allocation

**Rapid Development through Clinical Trials
focus, time pressure, culture, infrastructure**

Examples of Current Clinical Trials

Complexity of trials increases rapidly

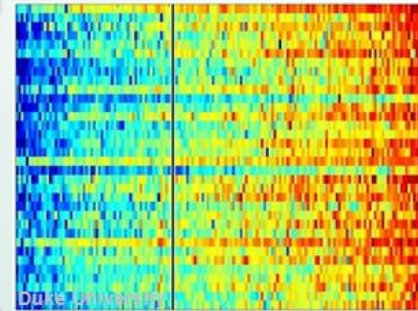
Precision Medicine: identify-hit the target



Tumor Specimen



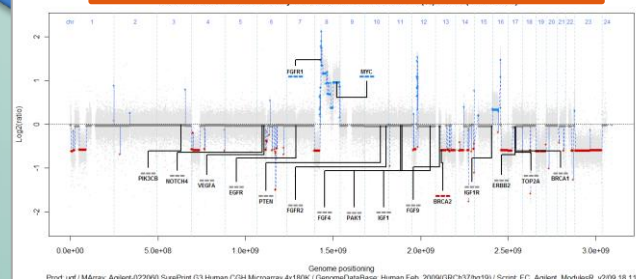
Molecular profiling



Targeted therapy according
to the molecular profile

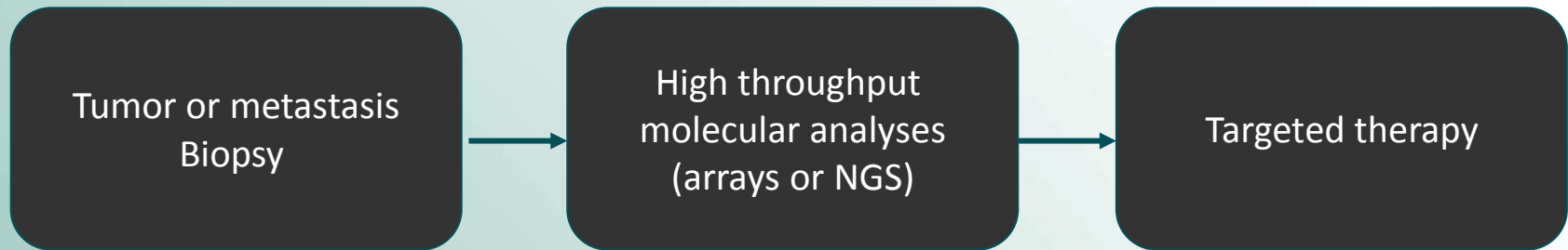


Identification of the molecular
alteration

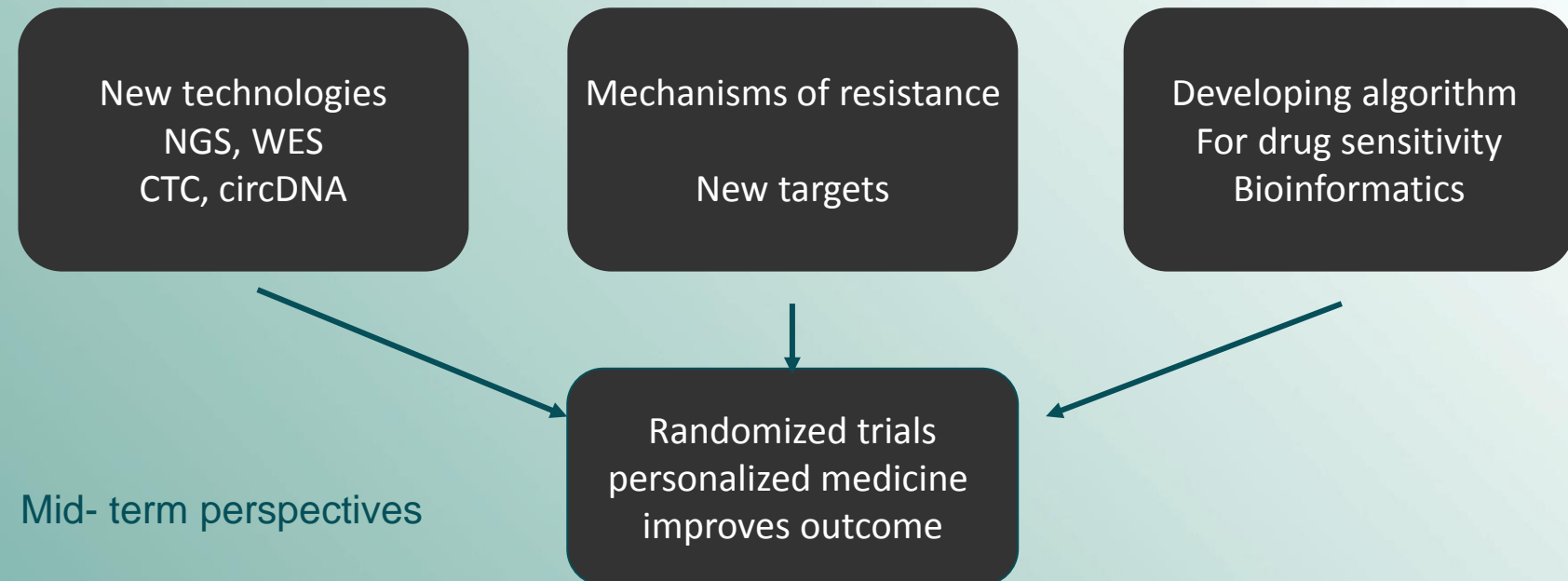


Overview of the PCM Program

Ongoing clinical programs (*SAFIR01*, *MOSCATO*, *MSN*): 3000 patients within 3 years

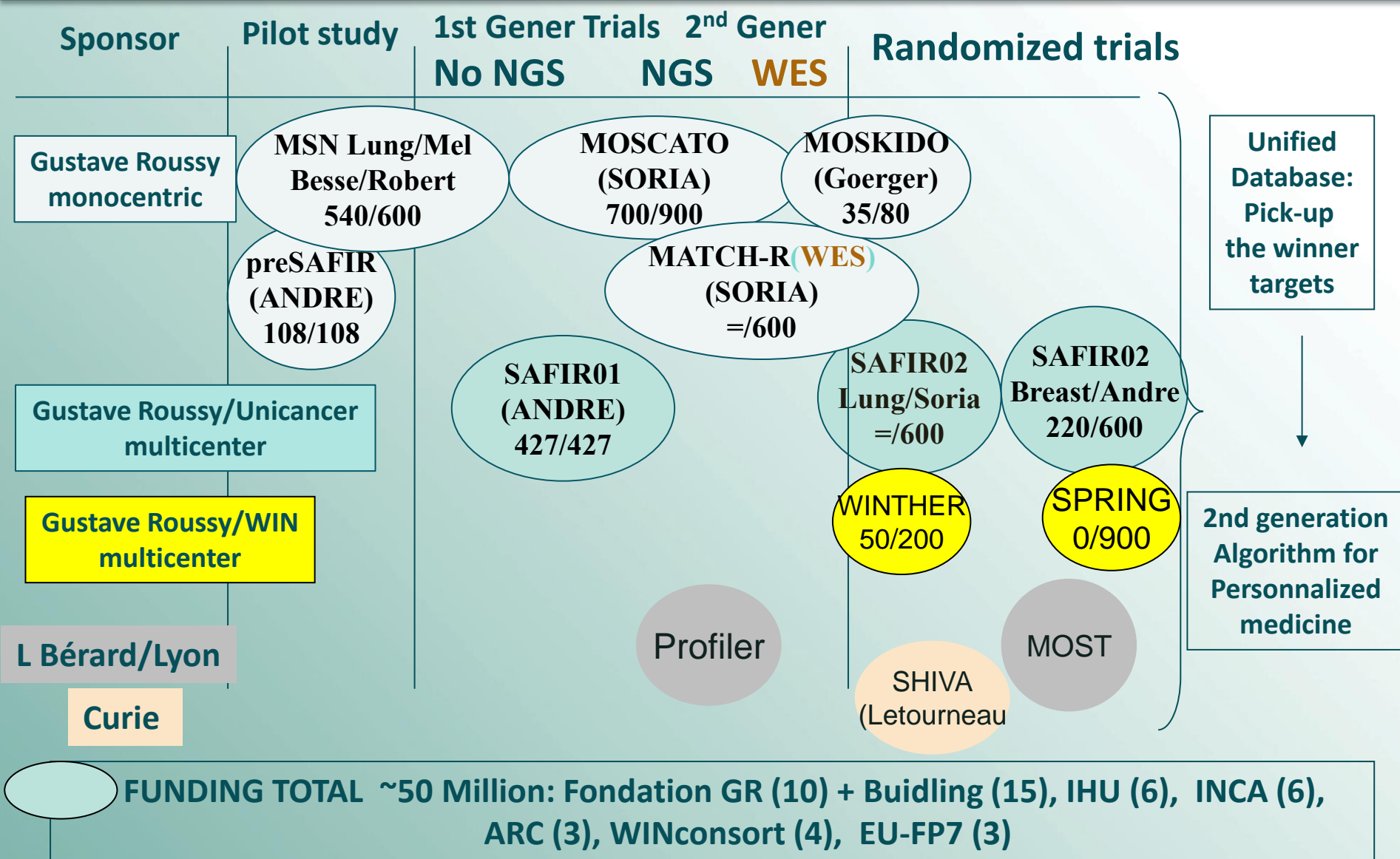


Short term Developments



Mid- term perspectives

Since 2010: Ongoing precision medicine programs 15 GR-initiated trials (high throughput genomics)



SAFIR01 Molecular Screening in Breast Cancer

Which candidate target ?

Biopsy of metastatic sites
Frozen sample
CGH/hot spot mutations
(PIK3CA/AKT)*

eligible for phase I
N= 400

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

FGFR1
FGFR2
FGF4 amp

NOTCH amp

PIK3CA / AKT / PTEN
alteration

Genetic
instability

VEGFA
amplification

PAK1 ampli

**Target
discovery**

Trial A

Trial B

Trial C

Trial D

Trial E

Trial F

Trials X,Y...

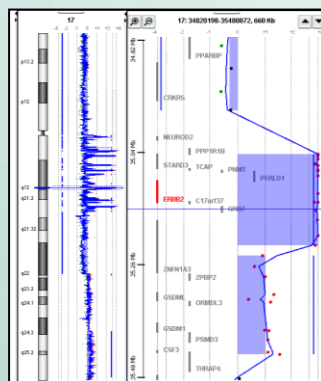
Funded by **INCA**
Sanger 30 genes, then NGS

SAFIR 01 Trial Design

Pre-SAFIR
N=108



**Target
identification**



Whole genome array
CGH
hot spot mutations
(PIK3CA/AKT)

PD

targeted therapy



18 centers
5 platforms

SAFIR01
Metastatic breast cancer
Biopsy of metastatic sites
Frozen sample

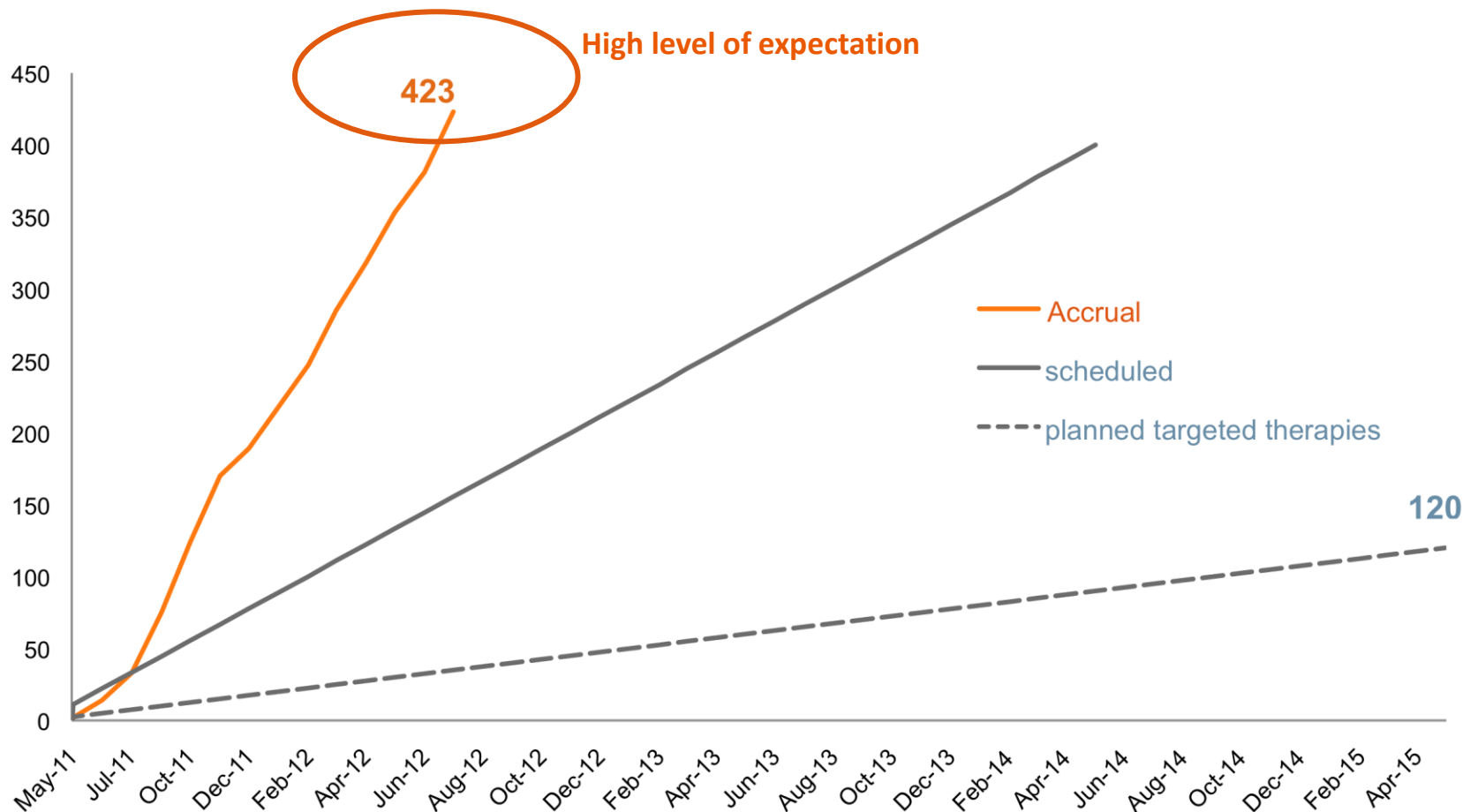
No PD under treatment
N=400

Primary Objective:
%patients treated
according to the
molecular profile

Funded by French NCI
Sponsor: UNICANCER

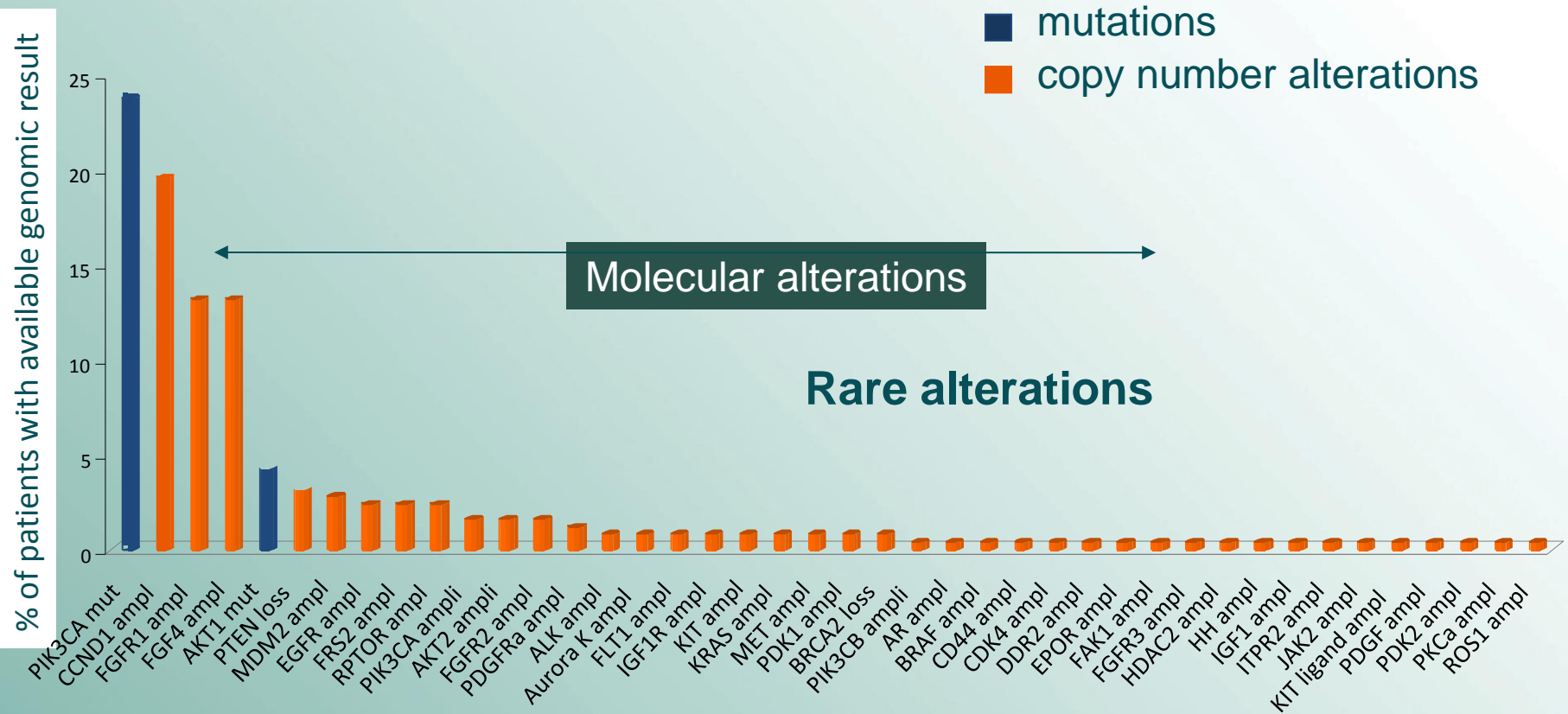
André et al ESMO 2012, Lancet Oncol 2014

Inclusions



Recruitment completed between May 2011 and August 2012

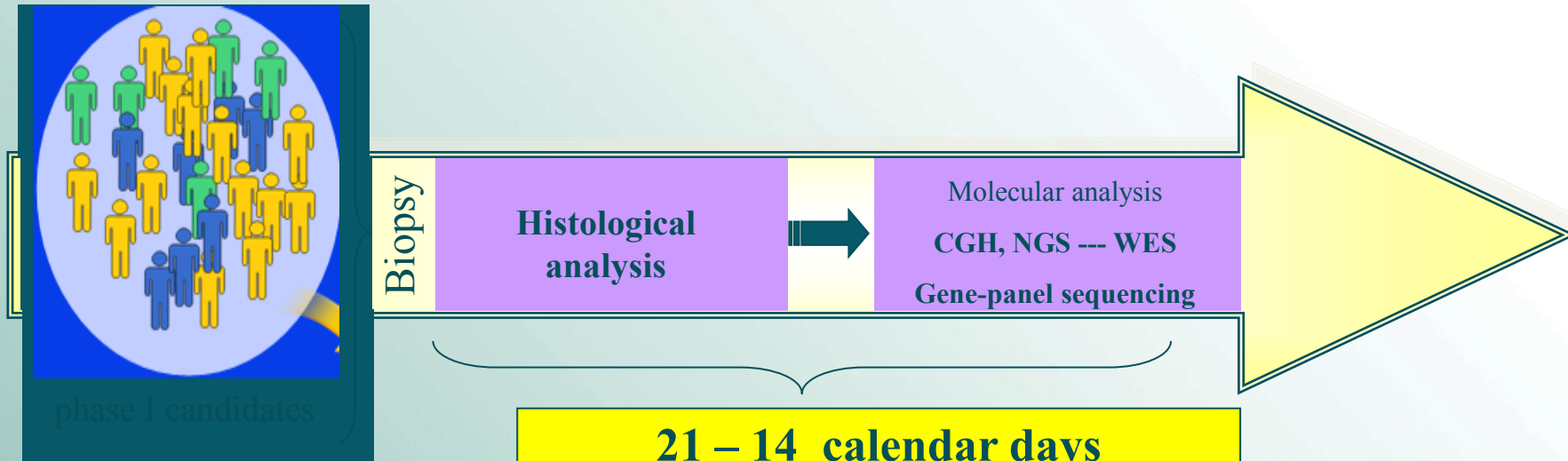
Targetable alterations



**IN THE END ONLY 12% gets
targeted therapy**

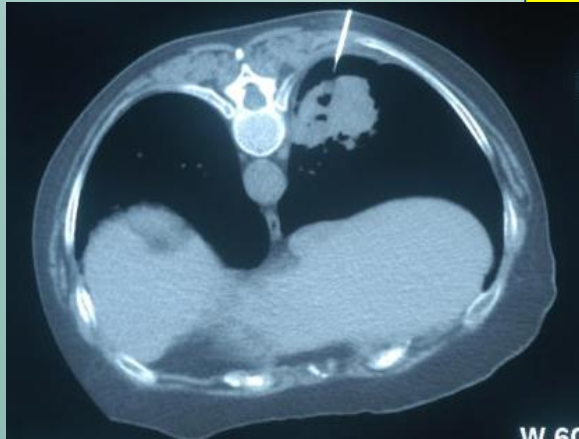
André et al, Lancet Oncology 2014

MOSCATO: MOlecular Screening for Cancer Treatment Optimization



21 – 14 calendar days

CGH+NGS - WES



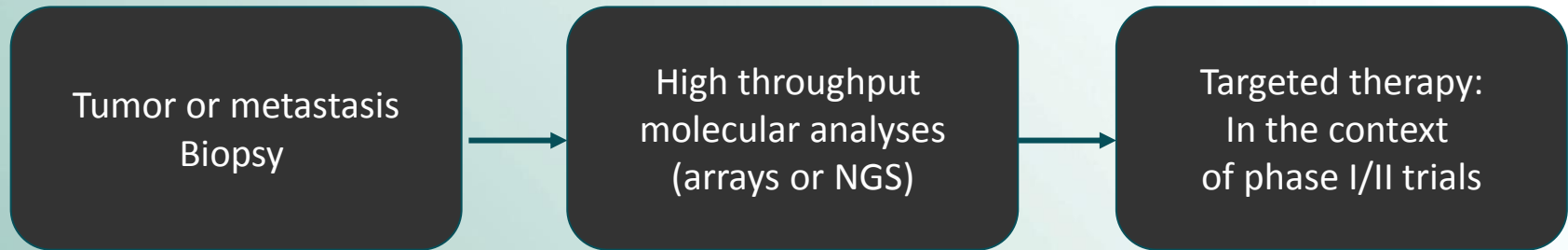
TARGET IDENTIFIED IN 45-50%

Targeted therapy in 20-25%

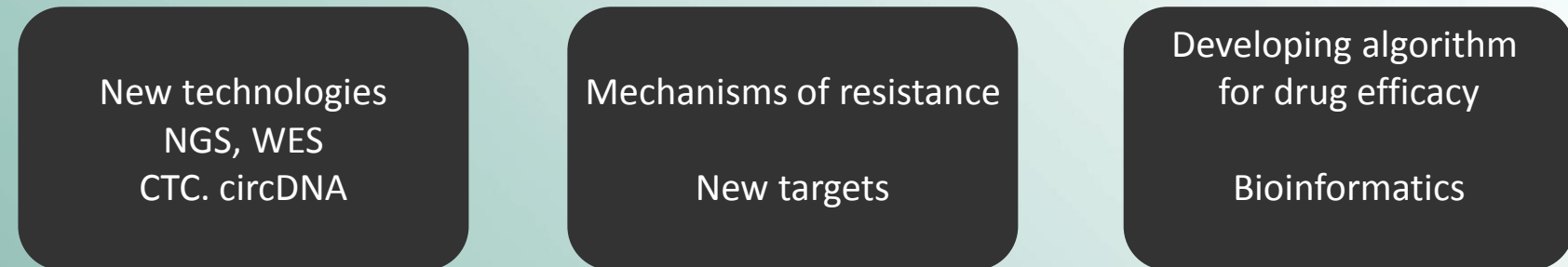
700 / 900 PATIENTS IN 2 Years

Overview of the Molecular Medicine Program

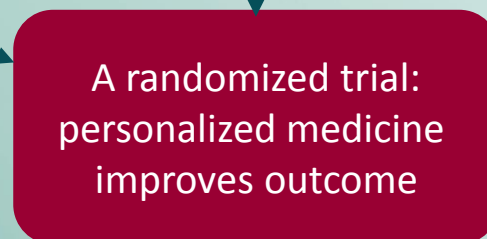
Ongoing clinical programs (*SAFIR01*, *MOSCATO*, *MSN*): 3000 patients within 3 years



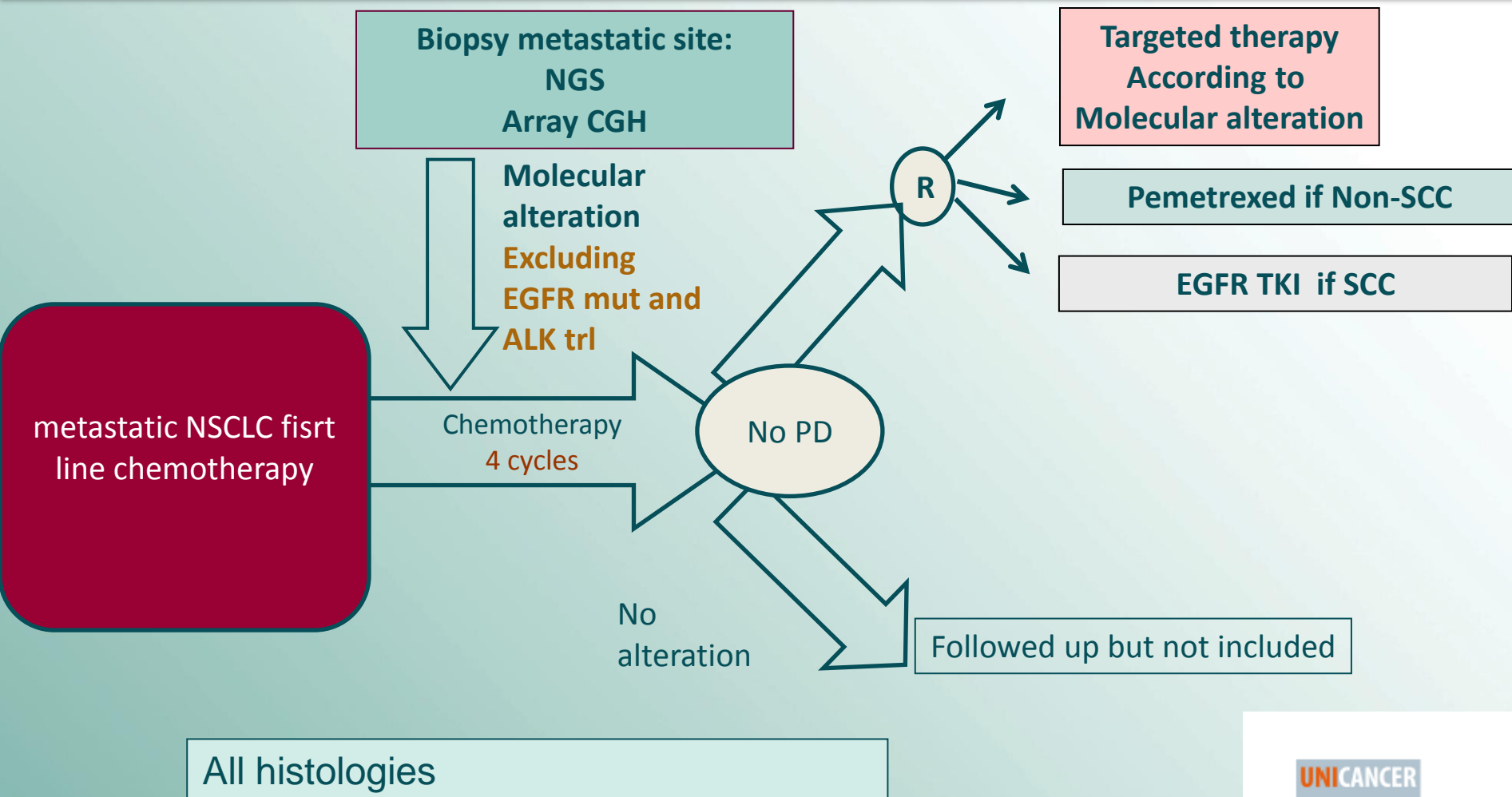
Short term Developments



Mid- term perspectives



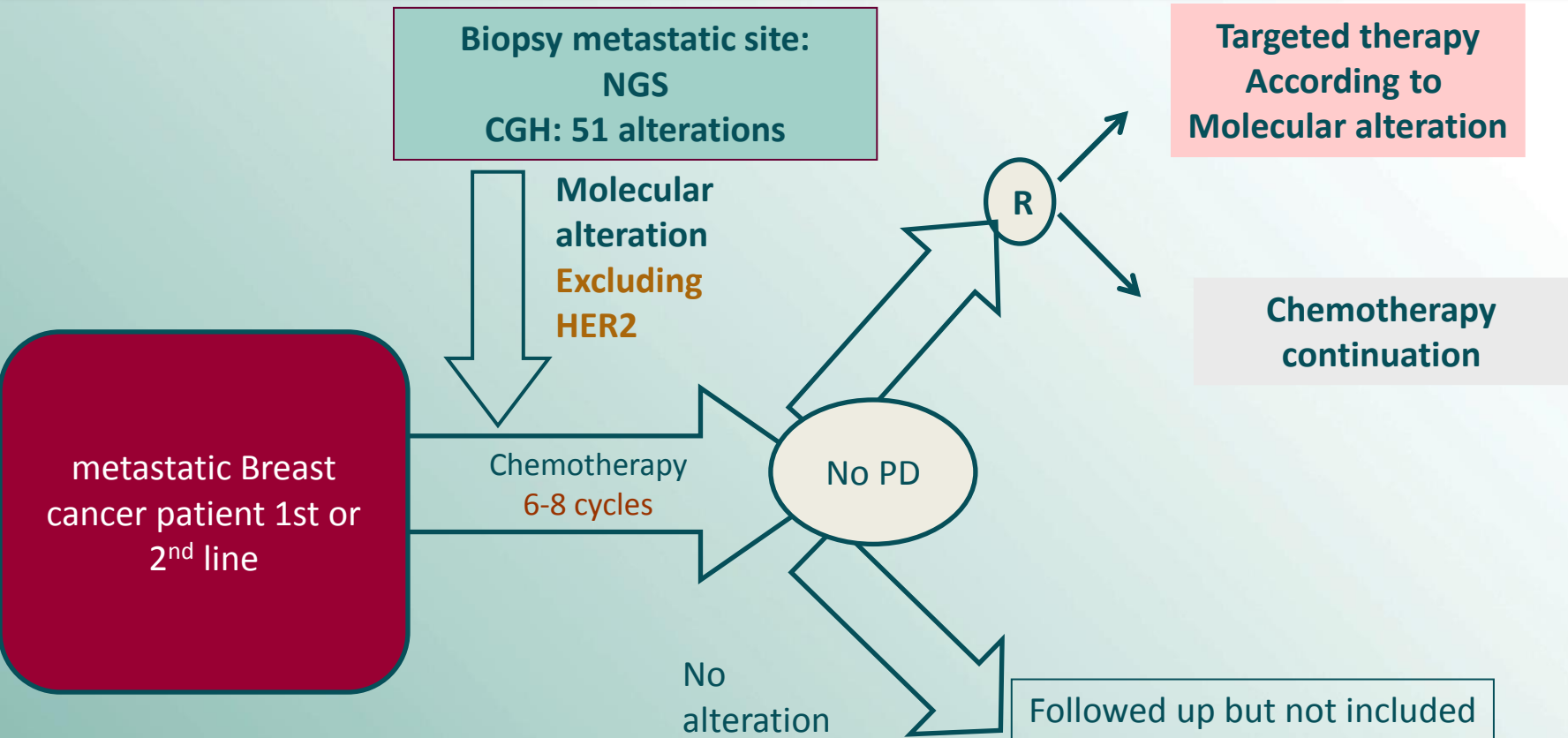
RANDOMIZED TRIAL: SAFIR 02 LUNG



Get COMPLETE PIPELINES

Genetic abnormality	Gene location	Squamous Cell Carcinoma	Adenocarcinoma	Therapeutic intervention
PIK3CA amplification[3q26.3	33%	6%	AZD2014 (TORC1/2)
FGFR1 amplification[8p12	22%	1%	AZD4547 (FGFR)
PTEN mutation	10q23.3	10%	2%	AZD8186 (PI3Kbeta)
MET amplification	7q31.1	3-21%	3-21%	Volitinib
PTEN loss	10q23.3	8-20%	8-20%	AZD8186 (PI3Kbeta)
KRAS mutation[12p12.1	6%	21%	AZD6244 (MEKi)?? Or combo with AZD2014
LKB1 mutation	19p13.3	5%	23%	AZD2014 (TORC1/2)
HER 2 amplification	17q11.2-q12; 17q21	3-5%	5-9%	AZD 8931 (pan-HER)
PIK3CA mutation	3q26.3	3%	3%	AZD2014 (TORC1/2)
RET translocation	10q11.2	2 %	1 %	AZD6474 (VEGFR, EGFR, RET)
BRAF mutation	7p34	2%	1-3%	AZD6244 (MEKi)
AKT1 mutation	14q32.32	1%	Very rare	AZD5363 (Akt)
MET mutation	7q31.1	1%	2%	Volitinib
HER2 mutation	17q11.2-q12; 17q21	1%	2%	AZD 8931 (pan-HER)

RANDOMIZED TRIAL: SAFIR 02 BREAST

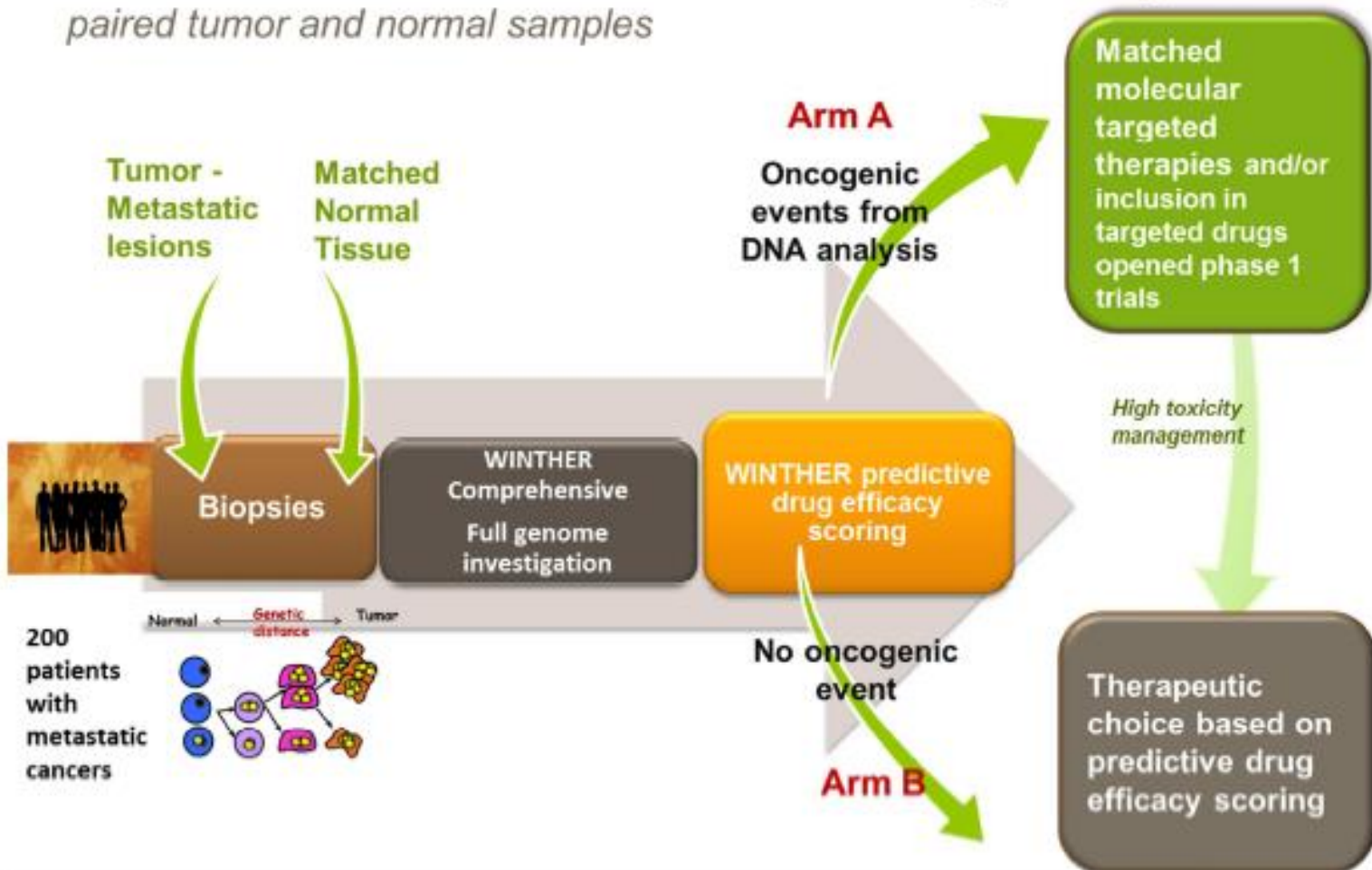


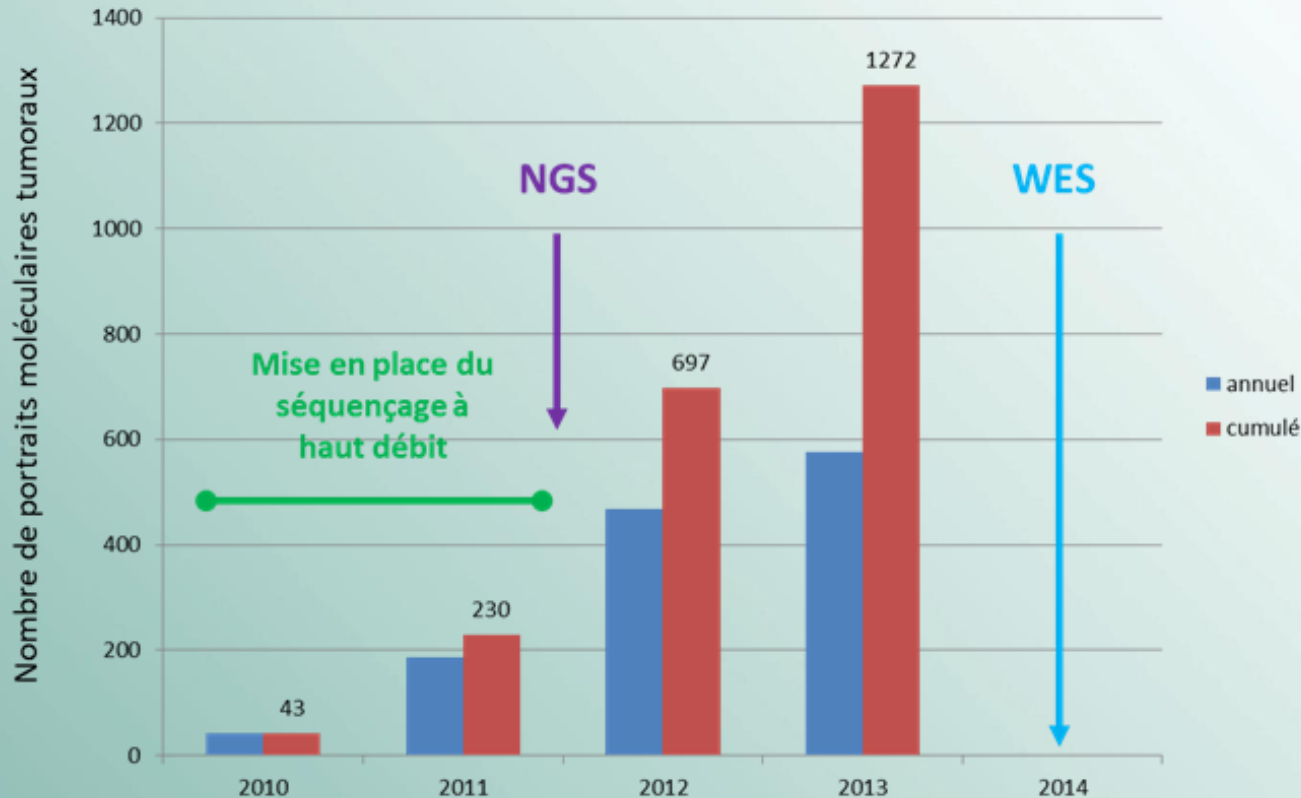
WIN Consortium Trial deals with ALL patients TRANSCRIPTOME and Algorythm for ARM B

Fig. 2

Global concept of WINTHER

Selection of Individualized treatments based on biological analysis of paired tumor and normal samples





**1330
Molecular
Portraits
in 2.5 yrs**

Techniques

Séquençage à haut débit

Next Generation Sequencing (NGS)

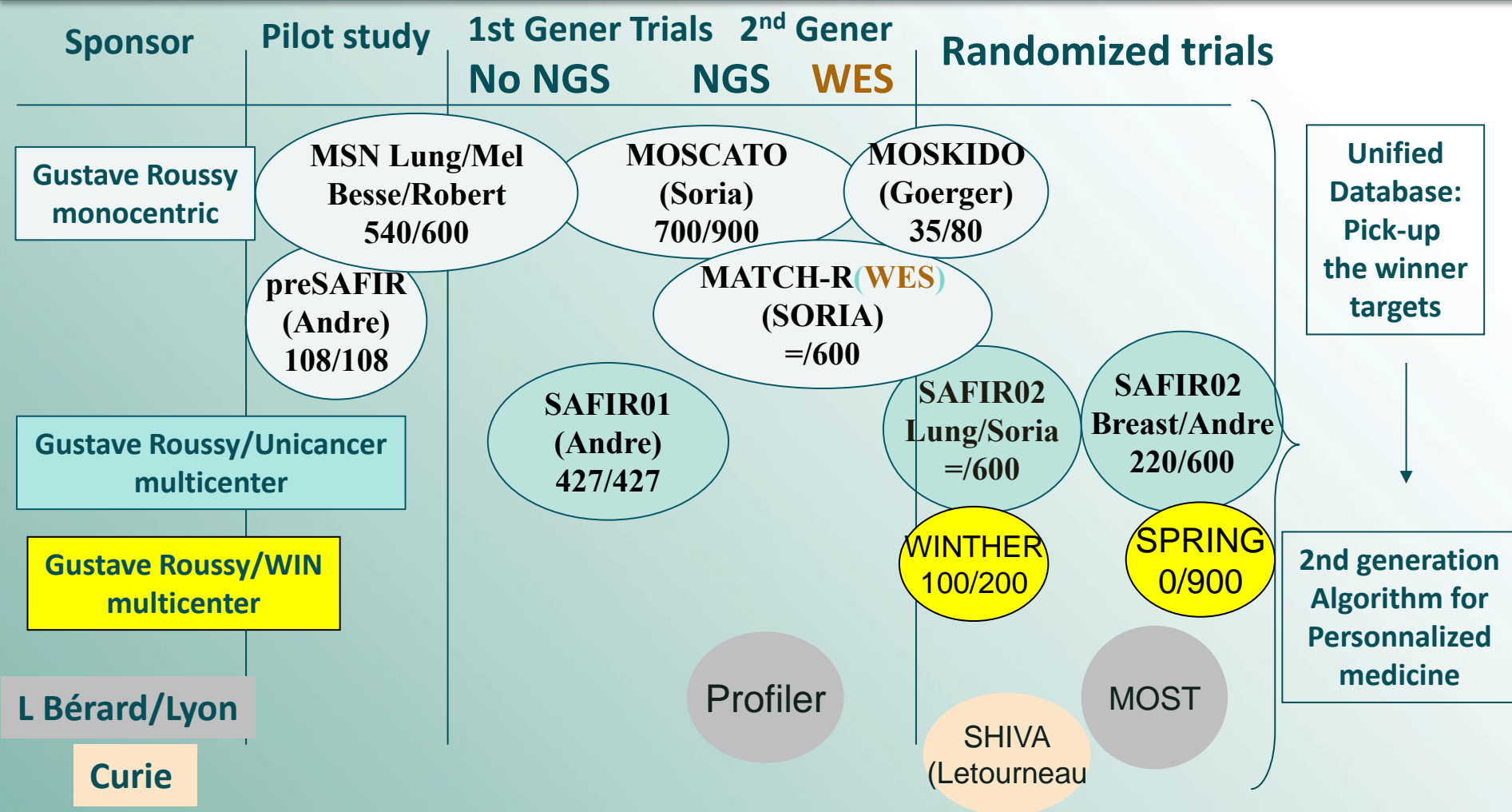
Whole Exome Sequencing (Wes)

30 gènes

70 gènes

100000 gènes

Since 2010: Ongoing precision medicine programs 15 GR-initiated trials (high throughput genomics)



FUNDING TOTAL ~50 Million: Fondation GR (10), MCM Building (15), IHU (6), INCA (6), ARC (4), Philanthropia (2), WINconsort (4), EU-FP7 (3)

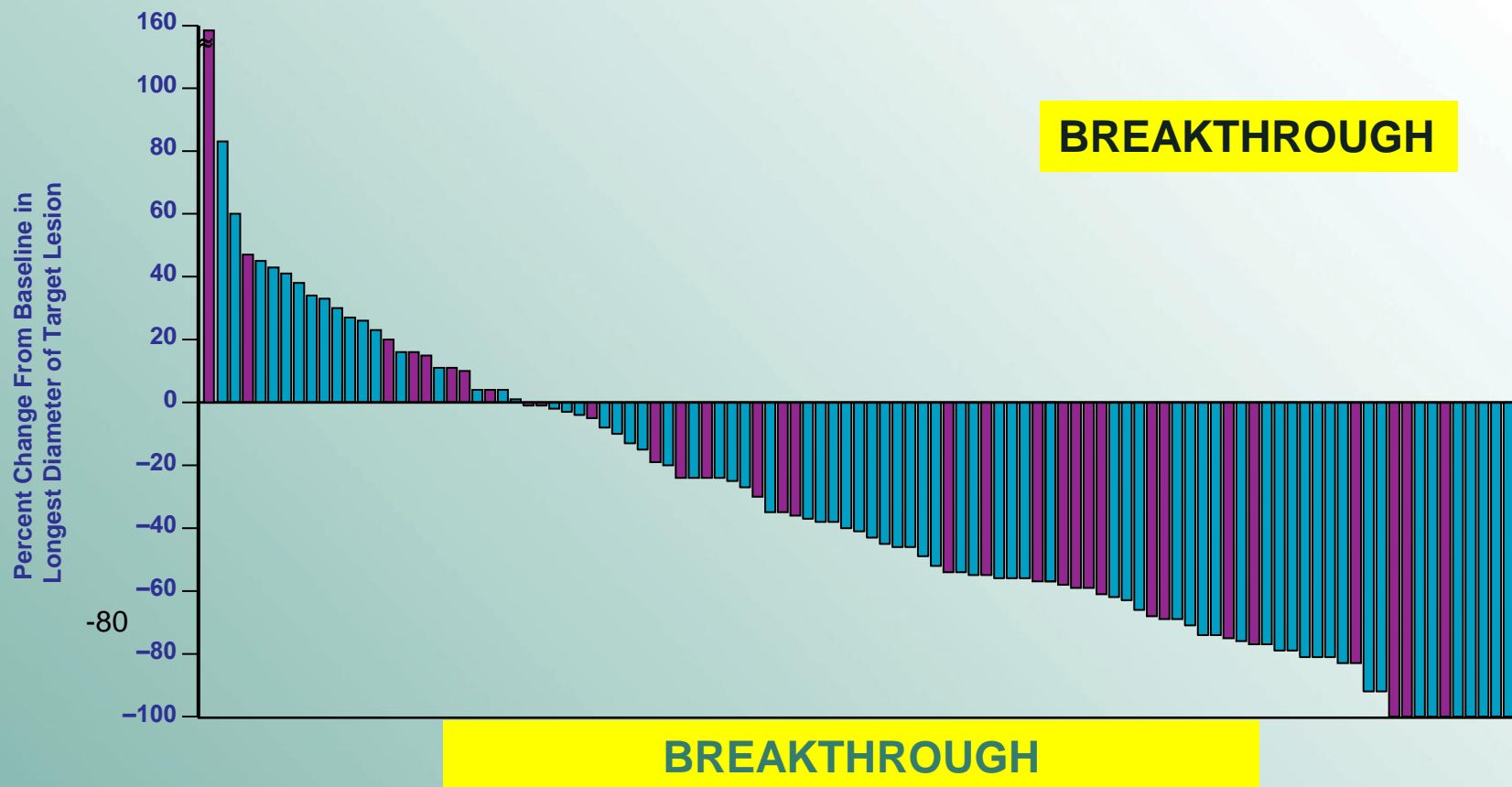
THE MELANOMA PARADIGM

MUTATION DRIVEN DRUG DEVELOPMENT

INNOVATIVE IMMUNOMODULATION



BREAKTHROUGH ACTIVITY IN STAGE IV MELANOMA

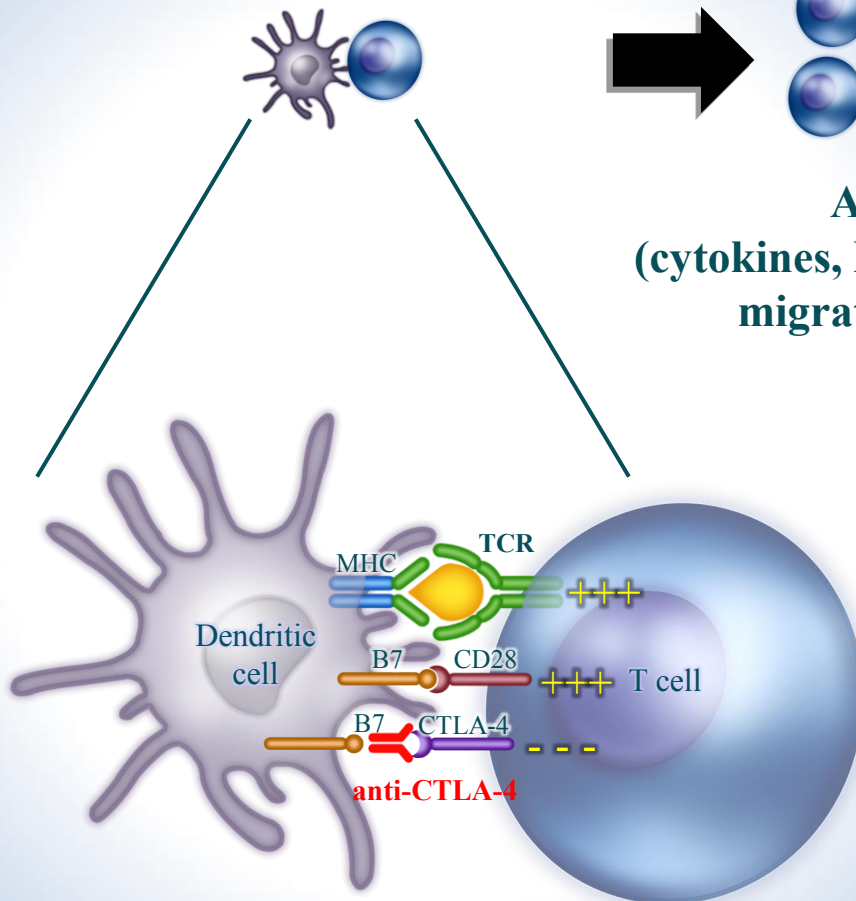


CTLA-4 and PD1/PDL1

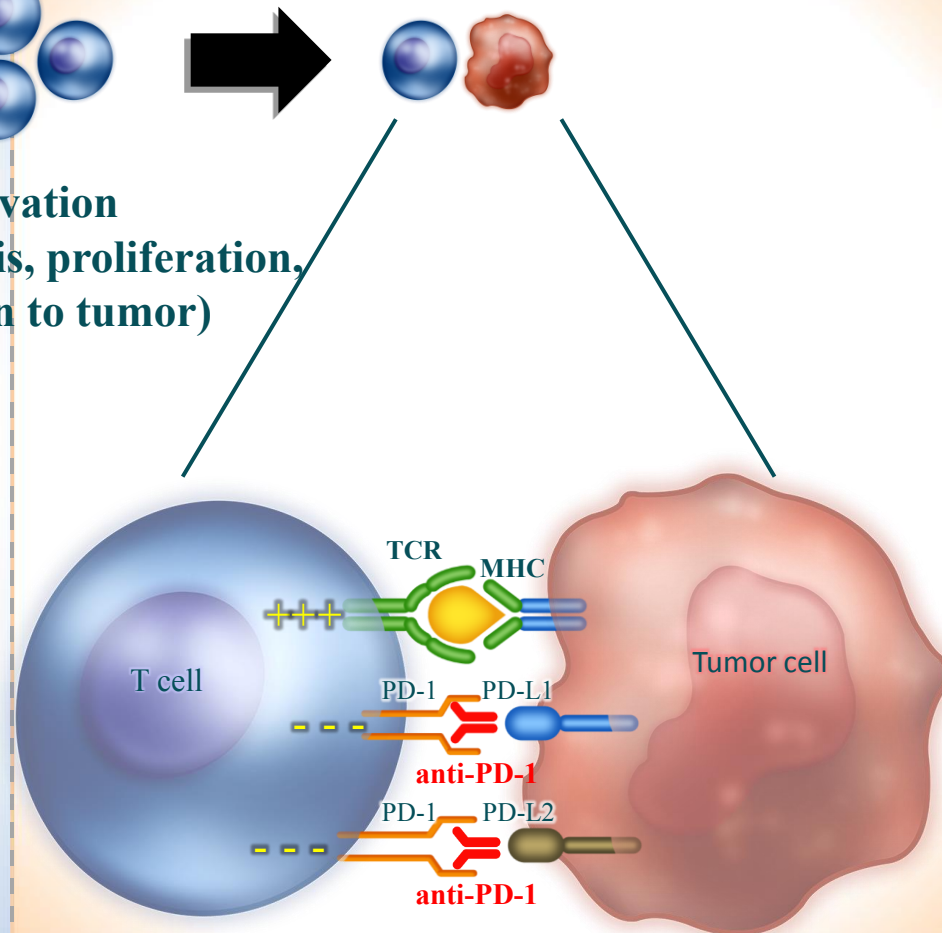
Mostly CENTRAL in LNN

Mostly PERIPHERAL
Tumor Microenvironment

Activation
(cytokines, lysis, proliferation,
migration to tumor)



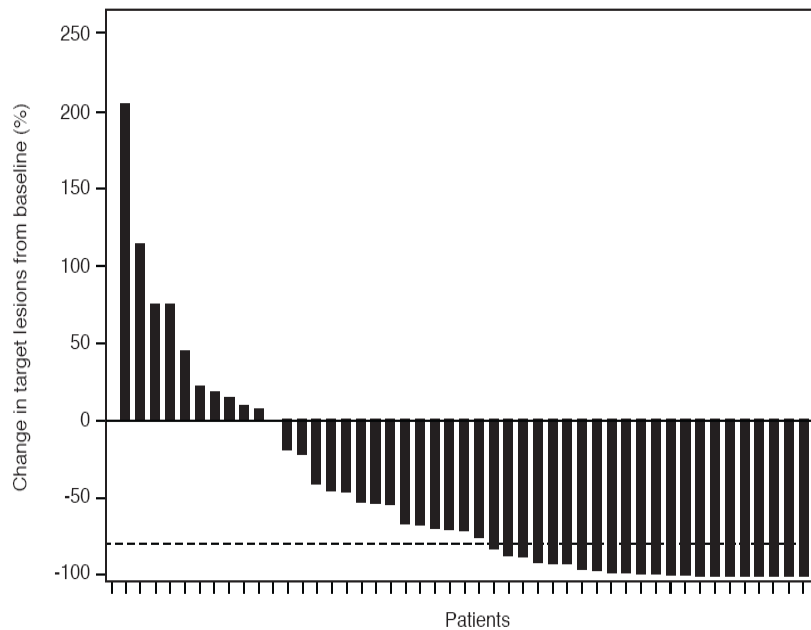
CTLA-4 Blockade (ipilimumab tremelimumab)



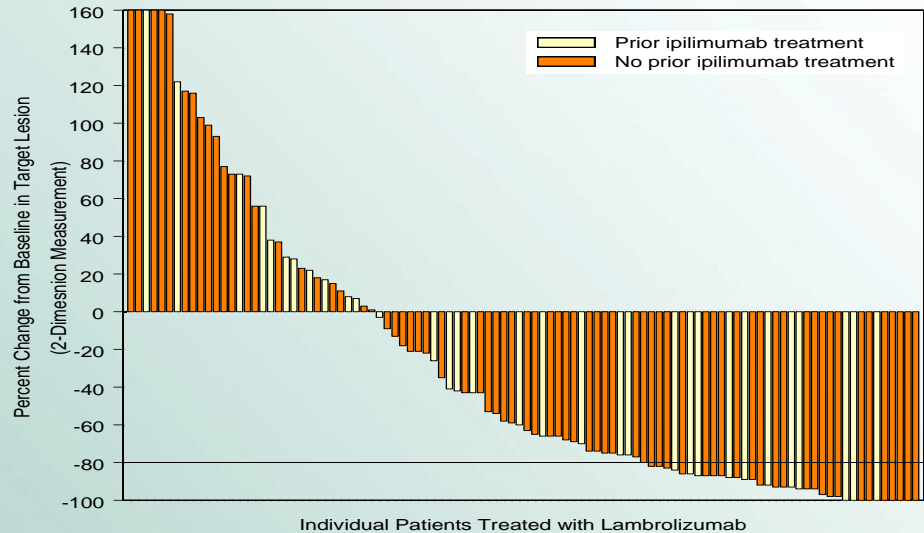
PD-1 Blockade (nivolumab, lambrolizumab)

Single agent Pembrolizumab (anti-PD1) or nivolumab + ipilimumab

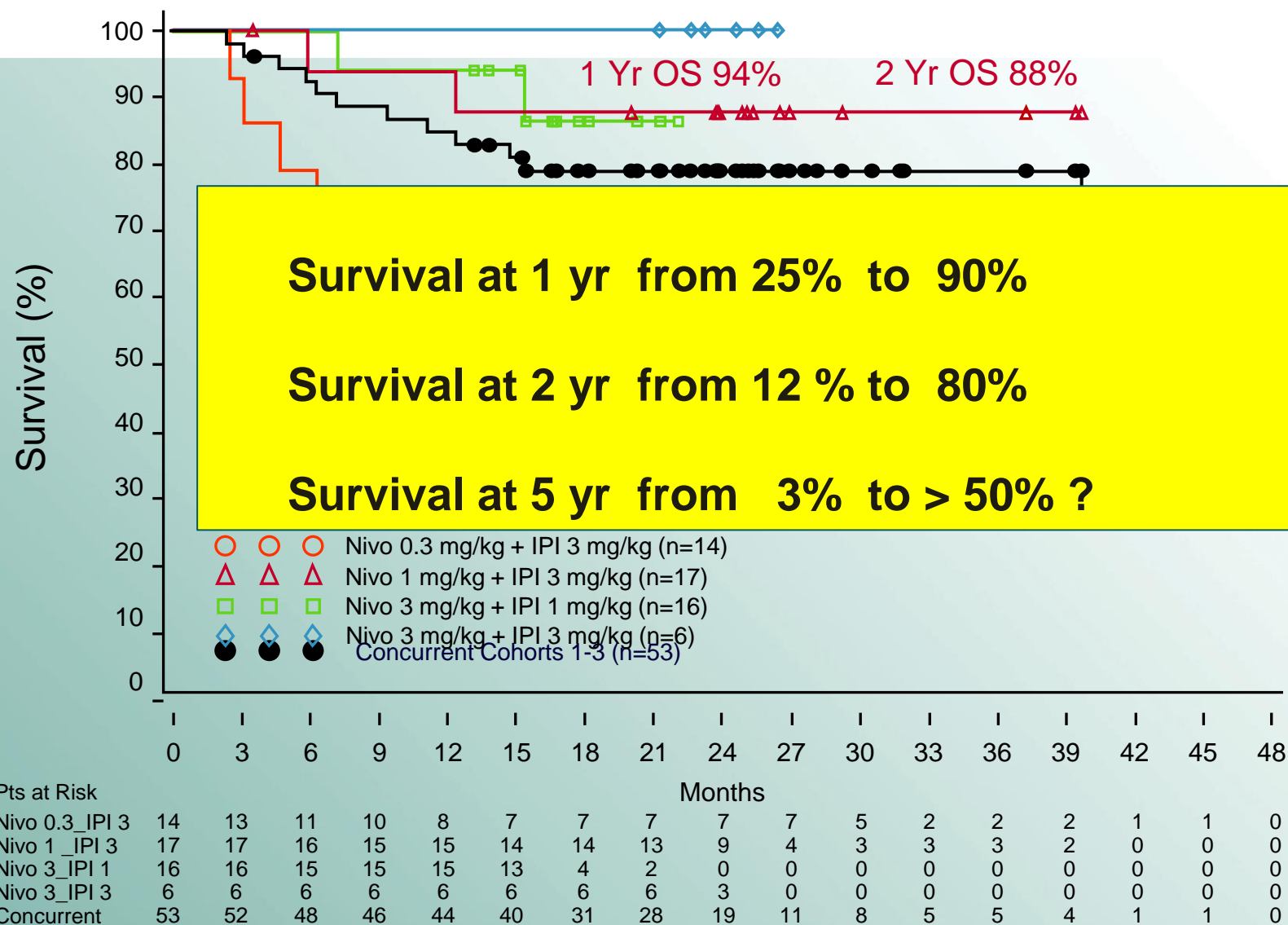
Nivolumab + Ipilimumab



Pembrolizumab Alone



Overall Survival for Concurrent Therapy Ipilimumab +Nivolumab by Dose Cohort

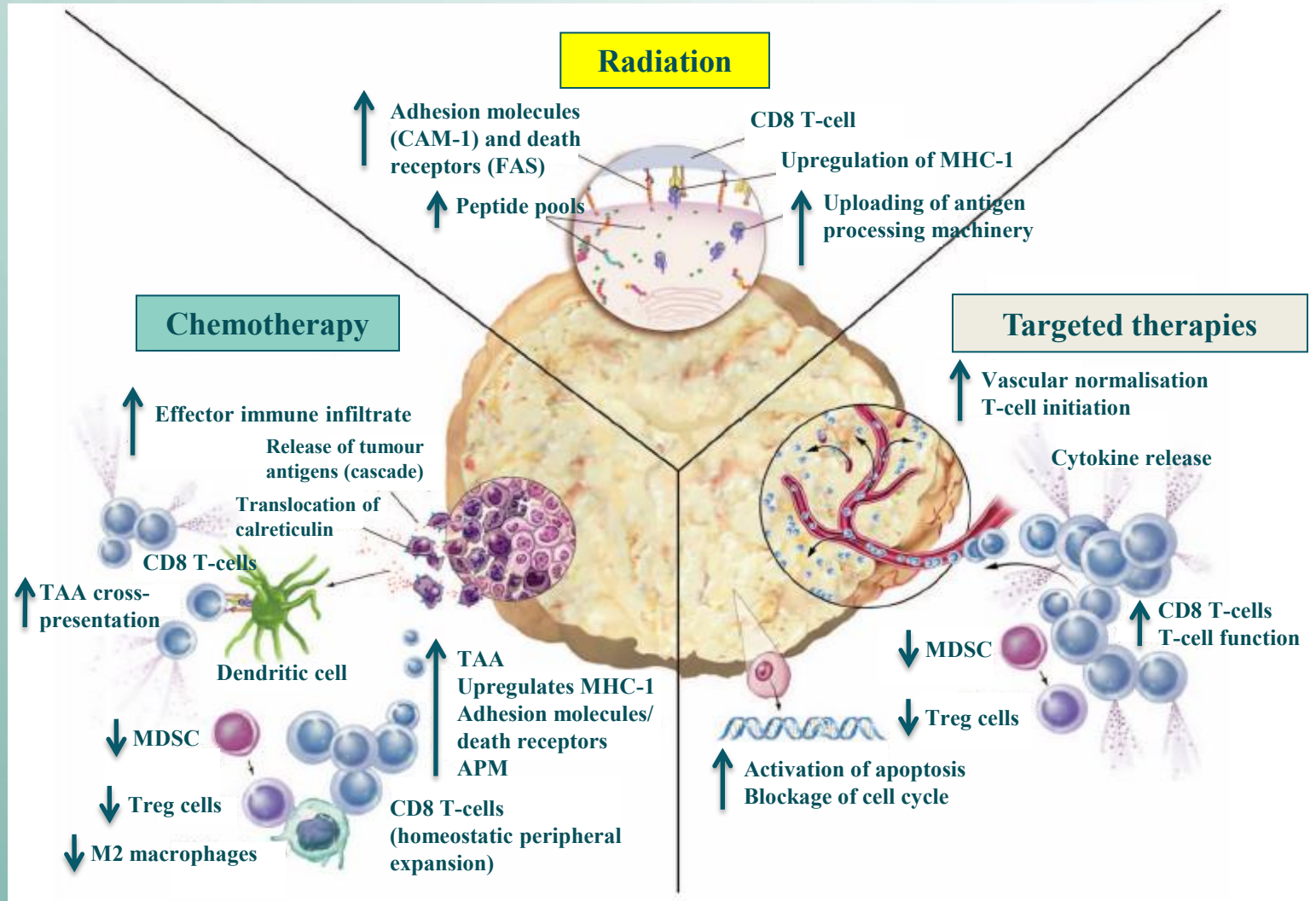


LANDSCAPE next clinical trials

- **Breaking Tolerance will get Nobel Price**
- **Immuno combos will dominate drug development for the next 5-10 years**
- **Breaking tolerance is the key prerequisite**
 - **Inhibitor–agonist combos is next step**
- **Multidrug class combos and multimodality combos may be guided by immunogenic cell death prerequisite**

Immunogenic Cell Death (Zitvogel & Kroemer)

Multiple mechanisms of synergy between the different treatment modalities



- **FIND THE MONEY**
- **IMMUNOTHERAPY PROGRAM**
 - Immunotherapist-Scientists (25-75)
 - Immunomonitoring platform + immunosignature programs
 - Combo academic trials / immunogenic cell death guided
- **PRECISION CANCER MEDICINE PROGRAM**
 - As shown
 - Tumor priority programs: Lung-Breast-Melanoma-Hemato
- **HAEMATO-ONC**
 - Vainchenker/Solary Lab – integration clinical programs
- **CONSORTIA**
 - Unicancer / WIN / Cancer Core Europe
- **From CCC to CANCER CAMPUS**

- **Gustave Roussy – MD Anderson Initiative**
 - Legal Office @ Gustave Roussy
- **Academic Members**
 - Europe: Gustave Roussy , Cambridge, DKFZ, VHIO, Istituto Tumori Milano, e.o.
 - USA: MDAnderson, MSKCC, Jefferson, UCSD
 - Canada: McGill, Pr Margaret
 - Asia: Fudan, AsanMC, YonseiMC, Singapoure, Mumbai
 - Middle East: Hadassah, Sheeba, Ben Gurion, KHCC
- **PHARMA**
 - Pfizer, AstraZeneca, Takeda (millenium), Novartis, Lilly, e.o.
- **TECH/Diagnostics**
 - Agilent, LifeTech, GE, Oracle, e.o.
- **PAYORS**
 - Blue Shield / Blue Cross
- **Patient Organizations**
 - Various
- **Cancer Organizations**
 - CRUK, EORTC, e.o.



Position Paper

Cancer Core Europe: A consortium to address the cancer care – Cancer research continuum challenge

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KEYWORDS

Cancer care
Research
Continuum
Consortium
Europe

Abstract European cancer research for a transformative initiative by creating a consortium of six leading excellent comprehensive cancer centres that will work together to address the cancer care-cancer research continuum.

Prerequisites for joint translational and clinical research programs are very demanding. These require the creation of a virtual single 'e-hospital' and a powerful translational platform, inter-compatible clinical molecular profiling laboratories with a robust underlying computational biology pipeline, standardised functional and molecular imaging, commonly agreed Standard Operating Procedures (SOPs) for liquid and tissue biopsy procurement, storage and processing, for molecular diagnostics, 'omics', functional genetics, immune-monitoring and other assessments. Importantly also it requires a culture of data collection and data storage that provides complete longitudinal data sets to allow for: effective data sharing and common database building, and to achieve a level of completeness of data that is required for conducting outcome research, taking into account our current understanding of cancers as communities of evolving clones. Cutting edge basic research and technology development serve as an important driving force for innovative translational and clinical studies. Given the excellent track records of the six participants in these areas, Cancer Core Europe will be able to support the full spectrum of research required to address the cancer research-cancer care continuum. Cancer Core Europe also constitutes a unique environment to train the next generation of talents in innovative translational and clinical oncology. © 2014 Published by Elsevier Ltd.

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E-mail address: alexander.eggermont@gustaveroussy.fr (A.M.M. Eggermont).

VIRTUAL E-HOSPITAL

60.000 New pts/yr, 250.000 pts treated, > 1 Million consultations

- **COMMON SOPs**
 - (tissue procurement, biobank, functional imaging, molecular screening methods, bioinformatic pipelines, etc)
- **SHARE DATA (common data bases)**
- **DEVELOP PRECISION MEDICINE**
 - Innovative Trials, attractive partner for pharma/biotech etc
- **OUTCOME RESEARCH**

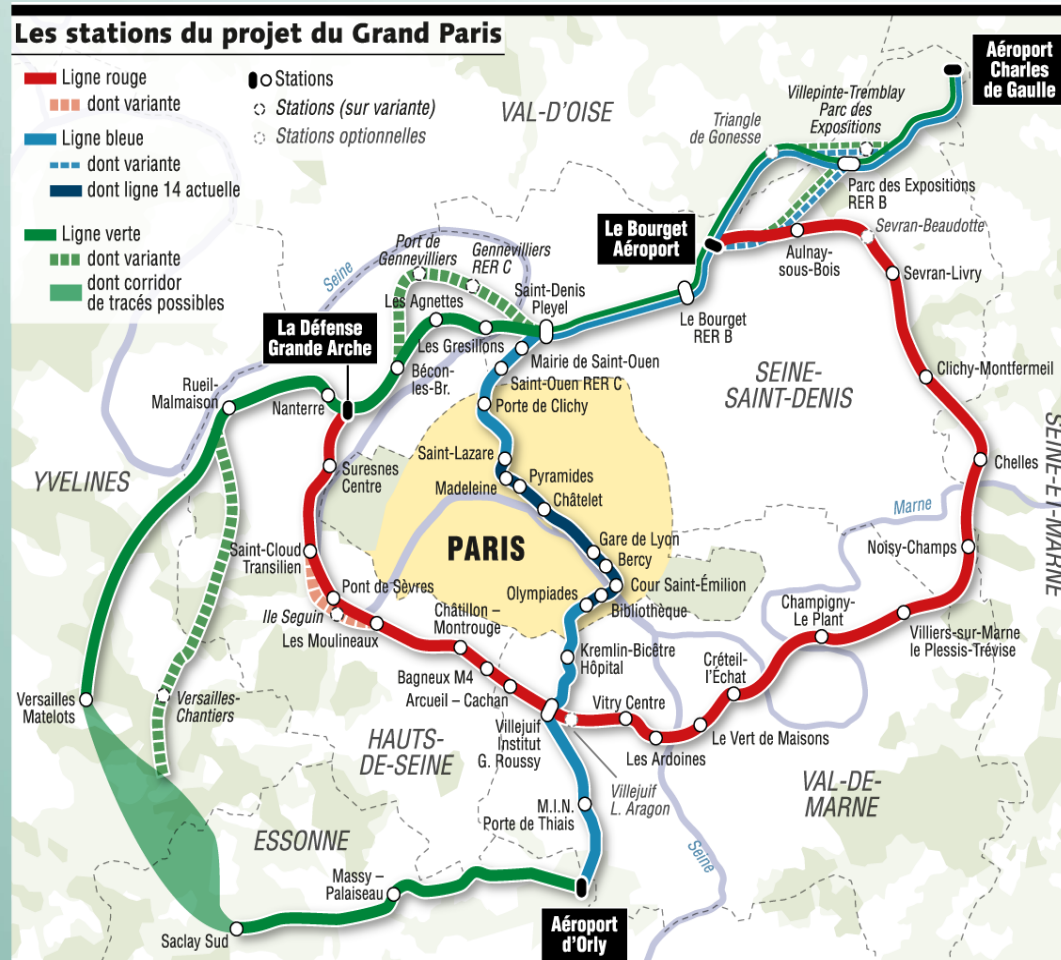
Comprehensive Cancer Center Towards a Cancer Campus



Alexander EGGERMONT. MD, PhD
*Gustave Roussy Comprehensive Cancer Center
Cancer Campus Grand Paris, France*

From CCC to CANCER CAMPUS

At Cross Road of the Two most important Metro Lines (2018)



2025

