Essais de médecine personnalisée en cancérologie

Jean-Charles SORIA
Cancer patients 2.8 M / year in the EU

Cured

Local failure

Not cured

Distant failure
Cancer patients 2.8 M / year in the EU

Cured

Not cured

Local failure

Distant failure

Genomics applications:
- Expanding actionability
- Developing new algorithms
Cancer patients 2.8 M / year in the EU

Cured

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

Not cured

Local failure

Distant failure
Circulating Tumor DNA

- MicroRNA
- Aneuploidy
- Methylation DNA
- Rearrangements
- Mitochondrial DNA
- DNA Point mutation
Standard anti-cancer therapy has reached a plateau
The molecular circuitry of cancer cells is better understood.
Working Hypothesis

Drugs that target the molecular mechanisms involved in cancer progression improve outcome in the absence of genomic instability.
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”!

(*New Engl J. Med 2010*)

(*New Engl J. Med 2010*)
Precision Medicine: To identify and hit the target

- Molecular profiling
- Tumor Specimen
- Identification of the molecular alteration
- Targeted therapy according to the molecular profile
Ongoing precision medicine programs in France:
9 trials (high throughput genomics)

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Pilot study</th>
<th>1st generation trials</th>
<th>Randomized trials</th>
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</thead>
<tbody>
<tr>
<td>Unicancer</td>
<td>preSAFIR</td>
<td>SAFIR01 (Andre, ASCO2013)</td>
<td>SAFIR02 breast</td>
</tr>
<tr>
<td>Gustave Roussy / WIN</td>
<td>(Arnedos, EJC, 2012)</td>
<td>MOSCATO (Hollebecque, ASCO 2013)</td>
<td>SAFIR02 lung</td>
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<tr>
<td>L Berard Lyon</td>
<td></td>
<td>WINTEGER</td>
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<td>Curie Institute</td>
<td></td>
<td></td>
<td>MOST</td>
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<td></td>
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<td>SHIVA (Letourneau TAT 2014)</td>
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Unified Database: Pick-up the winner targets

2nd generation Algorithm for Personalized medicine

Overall: >3,000 planned patients (all tumor types), >1,000 already included
Breast Cancer: >1,000 planned, >90 already treated with targeted therapies
Outline

– Molecular screening programs
– 2nd generation precision medicine trials
Molecular screening programs: Concept

Molecular screening with High Throughput Genomics

Target identification

Trial A
Trial B
Trial C
Trial D

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

Andre, Delaloge, Soria, J Clin Oncol, 2011
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
Identification of a targetable Genomic Alteration by a multicentric multidisciplinary team

Whole genome CGH array (gene copy numbers)
Sanger sequencing hot spots PIK3CA/AKT1

Targeted therapy according to the genomic profile at the time of PD

Biopsy metastases in patients PR/SD under treatment 2 Frozen samples 1 FFPE sample
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 Lefevre, 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.
423 patients enrolled

407 with biopsy results

403 biopsy samples assessed

299 samples with DNA suitable for genomic analysis*
  2 CGH array alone
  281 CGH array and Sanger sequencing
  16 Sanger sequencing alone

195 patients with targetable genomic alterations

55 patients received matched therapy
  52 driven by genomics
  3 HER2 amplification on CGH array

16 excluded because no biopsy result

4 excluded because metastatic breast cancer not confirmed

104 excluded
  91 low percentage of tumour cells
  8 no frozen material
  5 other reasons

21 excluded
  16 CGH array results deemed uninterpretable
  2 not enough DNA for Sanger sequencing
Targetable alterations that led to treatment proposition

High frequency of rare targetable genomic alterations

- PIK3CA mutation
- CCND1 amplification
- FGFR1 amplification
- AKT1 mutation
- FRS2, EGFR, RPTOR, MDM2 amplifications
- PIK3CA, FGFR2, AKT2 amplifications
- IGF1R, ALK, MET amplifications

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

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Objective response</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>SD &gt; 16 weeks</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>OR + SD &gt; 16 weeks</td>
<td>12 (28%)</td>
</tr>
<tr>
<td>Progression within 16 weeks</td>
<td>32 (72%)</td>
</tr>
<tr>
<td>Ongoing therapy SD &lt; 16 weeks</td>
<td>4</td>
</tr>
<tr>
<td>Erbb2 conversion (n=4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 OR</td>
</tr>
<tr>
<td></td>
<td>1 long term SD (10 months)</td>
</tr>
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</table>

Targets picked-up: EGFR amplification, AKT gene alteration, FGF-amplified BC, IGF1R amplification
Efficacy data on patients treated with therapy matched to genomic analysis.
MOSCATO-01 prospective molecular screening program

- Monocentric (Gustave Roussy)
- Target Accrual = 900 patients
• 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.
High-throughput molecular profiling using ‘on-purpose’ biopsies

CGH array Agilent
(180K, Whole genome coverage)

Ion Torrent PGM – Life Technologies
(Ampliseq CHP2 + custom
n=74 genes, Dec 2013)

FGFR1 amplification

DNA extraction
10 – 50 ng

Multiplex PCR
1450 amplicons
IonTorrent/PGM
(> 500X coverage)

Torrent_Suite v2.2
Confirmed by Sanger Sequencing

Standardized Report
Patients characteristics

- 420 advanced or metastatic cancer patients
- Eligible for phase I/II trials
- Median previous lines = 3 (range: 1-9)
- Distribution of the tumor types:

Of note, were excluded:
- EGFR TKI naïve NSCLC patients with EGFR mutation, Crizotinib naïve ALK translocated NSCLC pts
- Endocrine therapy naïve breast cancer patients with ER/PR positive expression
- BRAF inhibitor naïve melanoma patients with BRAF V600E mutation
- Anti-EGFR naïve colorectal cancer patients with KRAS and NRAS wild-type mutation profiles
- Anti-HER2 naïve breast and gastric cancer pts with HER2 + status
Ferte et al AACR 2014, oral presentation
Main molecular aberrations

Ferte et al AACR 2014, oral presentation
Main actionable aberrations

Mutations (24%)
Copy number alterations (76%)
Main non-actionable* molecular aberrations

* At the time of the trial
Best response rate (RECIST) in oriented and treated patients (n=85)*

Overall Response Rate (CR + PR) = 15%
Tumor Control Rate (CR + PR + SD) = 81%

* Excluding classical ALK, EGFR, BRAF, HER2, ER/PR alterations
Tumor Growth Rates (TGR)

Before Baseline Tumor evaluation

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 $P = 5.3 \times 10^{-5}$

Ferte et al. AACR 2014, oral presentation
Most of the biopsies are suitable for Molecular analysis

Biopsies characteristics
(based on 215 Needle biopsies)

Mean % of Tumor cells

- ≥ 30
- [10-30]
- [0-10]

Mean % of tumor cells
52±27%

CGH and NGS

NGS only

No molecular analysis

Most of the biopsies are suitable for Molecular analysis
Distribution of the Percentage of tumor cells according to the site of biopsy

Biopsies characteristics  
(based on 215 Needle biopsies)

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)

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

• Molecular screening programs allow enrichment of phase I/II trials in patients presenting genomic alteration

• Optimal programs include NGS in the context of broad availability of bioactive drugs

• Preliminary results suggest that targeting FGFR1 amplification, FGF3 amplification, AKT1 mutations, EGFR amplification could be associated with tumor response in breast cancers

• Molecular screening programs feed database to develop algorithms for personalized medicine
Outline

– Molecular screening programs
– 2nd generation precision medicine trials
Assessing tumour biology at the single sample level

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

Oncogenes

Genomic scar: DNA repair defect

TcR repertoire immune system

Intratumour heterogeneity

Intratumour heterogeneity
Precision Medicine: From Molecular screening to personalized medicine trials

Molecular screening

High throughput Genomics

Test drug in a Biomarker-defined population

Treat A

Treat B

Treat C

Tt d, e...

Database + Preclinical studies

Algorithm for Personalized medicine

Trials testing algorithm

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

Personalized medicine: Evaluation of bioinformatic algorithms to identify the targets

Andre, J Clin Oncol, 2011

Tursz, Nat Rev Clin Oncol, 2011
Interpreting genomic data at the individual level: the Virtual Cell Project

Does the use of the algorithm improve outcome?
Ongoing precision medicine programs in France

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

MOLECULAR PROFILING

Mutational aberrations

CGH

% of cancer and normal cells

Transcriptomic Aberrations
WINOTHER concept

Computational tools – Algorithm and genes_drugs database

Individual Drug efficacy Scoring Statement

Doctor’s decision

RATIONAL TREATMENT BASED ON HOLISTIC BIOLOGICAL INVESTIGATIONS

3. Genetic distance converted into drug scoring
WINTHER Participants

Cancer Centers

Gustave Roussy [France]
Jean-Charles Soria, Coordinating PI

MD Anderson Cancer Center [USA]
Lia Tsimberidou, PI

VHIO [Spain]
Jordi Rodon, PI

Chaim Sheba Medical Center [Israel]
Rannan Berger, PI

McGill Segal Cancer Center [Canada]
Wilson Miller

UCSD Moores Cancer Center [USA]
Razelle Kurzrock

Technology Partners

Foundation Medicine
Gary Palmer
NGS

Agilent Technologies
V Lazar
Gene Expression, miRNA

Ben Gurion University
Eitan Rubin
WINTHER Data Analysis
Recruitment

Rapid Accrual

Currently 2-3 pts / week
From April 16 to July 2, 2013

32 Consents

5 Screening Fails

8 biopsies yet to be performed

19 Biopsies

7 Logistical Failures

3 biopsies July 2, 2013

9 Analyzed

1 pt included in another therapeutic clinical study
1 pt with rapid worsening condition
1 pt withdraw consent
2 pts with normal tissue not obtainable

1 inappropriate choice of normal tissue
6 Tumor tissues < 60% of T cells

IGR-1011 Breast cancer
IGR-1012 Oral squamous cell carcinoma
IGR-1013 Colon cancer
IGR-1016 Lung ADK
IGR-1019 Kidney cancer
IGR-1027 Oral squamous cell carcinoma
Personalized Medicine trials: testing the algorithm for target identification

**SAFIR02 trial**

- **Biopsy metastatic site:**
  - Next generation sequencing
  - Array CGH

- **Her2-negative metastatic breast cancer no more than 1 line chemotherapy**

- **Chemotherapy**
  - 6–8 cycles

- **Target defined by 1st generation virtual cell (CCLE)**

- **Targeted therapy according to 51 molecular alterations**

- **No PD**

- **Followed up but not included**

- **Hypothesis:** median PFS 3 to 6 months

- **210 randomised, around 400 screened**

- **Sister trial in lung cancer**

- **Sponsor:** UNICANCER

- **Funding:** French charity

- **Pharma partner:** AZ

- **Algorithm validated on encyclopaedia cell lines**
Biopsy metastatic site:
Next generation sequencing
Array CGH

Chemotherapy
4-6 cycles

No alteration

Molecular alteration
Excluding EGFR mut and ALK t

R 2:1

N= 230

Targeted therapy
According to Molecular alteration

EGFR TKI if SCC

Pemetrexed if Non-SCC

No PD

Followed up but not included

metastatic NSCLC first line chemotherapy

N= 650

All histologies

Ethics approval sept 2013; ANSM approval oct 2013, FPI april 2014
Personalized Medicine trials: testing the algorithm for target identification

SHIVA trial

Patients with refractory cancer (all tumor types) → Informed consent signed → Tumor biopsy → NGS+ Cytoscan HD +IHC → Bioinformatics → Informed consent signed → Therapy based on molecular profiling
- Approved molecularly targeted agent

Non eligible patient → Molecular biology board → Eligible patient → Specific therapy available → Conventional therapy based on oncologist’s choice → Cross-over
Conclusions

• The establishment of a comprehensive tumor molecular profile is safe, feasible and compatible with clinical practice
• A molecular alteration matching an approved drug available in the SHIVA trial was present in 42% of patients
• Accrual is expected to finish this year
• Results should be available in 2016
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 biopsy or effusion
Summary

- Molecular screening programs speed-up drug development and stratified medicine

- They identify FGFR, FGF, AKT1, EGFR as potential targets in BC

- Optimal molecular screening should:
  - Be performed in strong connection with pharma companies to secure drug access
  - Use NGS

- Personalized medicine trials are starting and will evaluate 1st generation genomic algorithm for oncogene de-addiction

- Research on bioinformatic algorithms will allow defining oncogenic drivers at the individual level