How INCa is supporting the development of personalized medicine

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The Cancer Plan 2009-2013

Main axis of the cancer plan:

The development of personalized medicine
The French Cancer Plan: The road to personalized medicine

- **Patient centered approach**
  - Personalized therapeutic project (PPS)
  - Organized structures for specific cares
    - Oncogeriatric centers/ Oncopeadiatric centers/ Young adults and adolescent centers
    - Rare tumors networks (23 specialized networks)
    - Oncogenetic consultations and laboratories (70 sites)

- **Tumor centered approach**
  - Molecular diagnosis of tumors
    - Molecular genetic platforms
    - Next generation sequencing
  - Clinical and research implications
    - Access to targeted therapies
    - Early phase clinical trials
The tumor based approach: the way to “personalized medicine”

A reality or a goal?
Toward molecular subsets of cancers

Why identification of biomarkers so important?
- improve knowledge on oncogenic pathways
- diagnosis
- prognosis: improve risk stratification to guide treatment strategies
- development of targeted therapies
National commitment to nationwide provision of molecular tests

Measure 21.
Guarantee equal access to innovative and existing treatments.

21.2 Develop cancer molecular genetics hospital platforms and expand access to molecular testing.
France organisation of molecular centres for personalized medicine

The programme is operated and funded by the INCa/Ministry of Health

- **Objectives**
  - Perform molecular testing for all patients
  - Whatever the healthcare institution status (public hospitals, private hospitals…)
  - Perform high quality tests
  - For leukemia and solid tumours

- **28 regional centres**
  - Partnerships between several laboratories
  - Regional organization
  - Cooperation between pathologists and biologists
Rapid access to innovation

Mid 2008: EMA approvals for panitumumab and cetuximab for patients with wild type KRAS tumours

- INCa started to allocate €2.5M to the 28 centres at the end of 2008

June 2009: gefitinib approvals by EMA for patients with activating mutations of EGFR in their tumors

- INCa started to allocate €1.7M to the 28 centres at the end of 2009
Sparing cost for the health insurance

Example of gefitinib treatment in lung cancer

EGFR testing for lung cancer patients

€ 1.7M

15 000 patients -
(gefitinib treatment: 8 weeks DFS; Mok 2009)

1 724 patients +
(gefitinib treatment: 38 weeks DFS; Mok 2009)

€ 69M

Spared cost of gefitinib treatment

€ 35M

Cost of gefitinib treatment
Predictive tests for targeted therapies prescription

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Cancer type</th>
<th>Targeted therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCR-ABL translocation</strong></td>
<td>Chronic Myeloid Leukemia/ Acute Lymphoblastic Leukemia</td>
<td>Imatinib, nilotinib, dasatinib</td>
</tr>
<tr>
<td><strong>KIT</strong> and <strong>PDGFRA mutations</strong></td>
<td>GIST</td>
<td>Imatinib, nilotinib, dasatinib</td>
</tr>
<tr>
<td><strong>HER2 amplification</strong></td>
<td>Breast and gastric cancers</td>
<td>Trastuzumab, lapatinib (breast)</td>
</tr>
<tr>
<td><strong>KRAS mutations</strong></td>
<td>Colorectal cancer</td>
<td>Panitumumab and cetuximab</td>
</tr>
<tr>
<td><strong>EGFR mutations</strong></td>
<td>Lung cancer</td>
<td>Gefitinib and erlotinib</td>
</tr>
<tr>
<td><strong>ALK translocations</strong></td>
<td>Lung cancer</td>
<td>Crizotinib</td>
</tr>
<tr>
<td><strong>BRAFV600 mutation</strong></td>
<td>Melanoma</td>
<td>Vemurafenib</td>
</tr>
</tbody>
</table>
Nationwide provision of molecular tests

- Molecular tests (all): **155,000 patients in 2011**
- Predictive tests for access to targeted therapies: **55,000 patients in 2011**
Is this personalised medicine?

Stratified or precision medicine
An increasing number of biomarkers for each patient

**Actionable molecular alterations**
- Lung cancer
  - gefitinib
  - erlotinib
  - crizotinib

**Prognosis**
- AML

- Implementation of Next Generation Sequencing (NGS) for clinical use in the 28 molecular genetics centres
  - Implementation ongoing for the investigation of a panel of genes
  - Medium term: analysis of whole exome or genome
Proof of concept for molecularly guided therapy: prospective trials for the future

Need to demonstrate that sequencing tumours (Exome-Whole GS) is of interest for treatment decision:

- A national cooperative randomized study in early metastatic patient in some tumour types
- Comparing therapeutic decision based on NGS to current diagnostic procedures including defined genetic tests
- With the help of Pharmas to provide drugs already in phase 2 trials
Organizing clinical research in the sequencing era?

Increasing number of targeted therapies to evaluate

All cancers become niches
The early phase network is composed of 16 early phase clinical trials centers: CLIP$^2$ funded by INCa and La Fondation ARC
Current situation

- Molecule identification
- Agreement
- Call
- Project selected
- Clinical Trial on going

Projects:
- Novartis: 2 projects
- Pfizer: 3 projects
- Roche: 2 projects
- Lilly: 2 projects
- Transgene: 1 project (GA201 On Hold)
- Sanofi: 1 project

Discussion on going
Next objectives are to increase the number of available molecules and to collaborate with Union to an implementation of this model in European countries.

Increase Number of molecules provided by pharma and propose calls for proposals on a regular basis.

EPAAC WP8 expand this public/private partnership at European level as way of innovative method of cancer research coordination.

Programs to be shared by CLIP²
New types of early phase of clinical trials in the era of personalized medicine

<table>
<thead>
<tr>
<th>Basket studies</th>
<th>Umbrella studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Several types of cancers share the same genetic abnormality</td>
<td>• Tumours of a specific organ can express different genetic abnormalities</td>
</tr>
<tr>
<td>• This genetic abnormality is actionable by one target therapy</td>
<td>• Allocate the treatment arm according to the type of mutation expressed</td>
</tr>
<tr>
<td>• The trial test the efficacy of the target therapy whatever the tumor type is</td>
<td>✓ <strong>Limitations:</strong></td>
</tr>
<tr>
<td>• Example : AcSé program</td>
<td>• Need to sequence the tumour genome of all tumours of a specific organ</td>
</tr>
<tr>
<td></td>
<td>• Need for several target therapies available for clinical use</td>
</tr>
</tbody>
</table>
AcSe Program

Promote access for all patients with an advanced refractory malignancy and no therapeutical alternative through academic phase II clinical trials.

Objectives

• To guarantee an equal and quick access to treatment with innovative drugs for French patients in a context of high safety and prospective data collection

• To offer a targeted therapy for patients according to the presence of a specific molecular alteration in their tumor when no clinical trial nor marketing authorisation is available
Early Access to targeted therapies: the AcSe program

- To favour secured access to MA or near to market new drugs for all patients in all authorized cancer treatment centres in France (N=835)
- Facilitated criteria of inclusion and non-inclusion
- Based on a defined molecular abnormality in any tumor type (excluding those of MA)
- Simple clinical protocol aiming at detecting efficacy and safety in new rare indications
- Stratification for Go – Stop in different tumour types
AcSe Program

A phase II clinical trial for one target therapy

Promote access for all patients with an advanced refractory malignancy in all authorized cancer treatment centres

- Molecular screening performed in the French molecular genetics platforms
- Drug provided by the pharmaceutical firm
- Withdrawal if high toxicity or no efficacy in a predefined number of patients of the same tumour type
- If efficacy signal: drug development by the pharmaceutical firm
AcSe Program

2 trials starting in 2013
200-500 patients to be included in France

- Pfizer : Crizotinib
- Roche : Vemurafenib (discussion on going with regulation agency ANSM)

Co-funding : ARC Foundation
Promotion : Unicancer
Sequencing modifies our understanding of tumours

Research tool
International Cancer Genome Consortium: ICGC

ICGC Goal: To obtain a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes which are of clinical and societal importance across the globe.

Main objectives:
• Collect ≈ 500 tumours/normal pairs from each of 50 different major cancer types
• Comprehensive genome analysis of each pair: genome, transcriptome and methylome
• Make the data available to the research community and public

The French contribution to this program is coordinated and funded by INCa for liver, breast, prostate cancer, and Ewing sarcoma.
# International cancer genomics consortium: ICGC

<table>
<thead>
<tr>
<th>Countries within the ICGC</th>
<th>Funding bodies</th>
<th>Types of tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>• Federal Ministry of Education and Research</td>
<td>• Brain</td>
</tr>
<tr>
<td></td>
<td>• German Cancer Aid</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>• National Health and Medical Research Council</td>
<td>• Ovary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pancreas</td>
</tr>
<tr>
<td>Canada</td>
<td>• Ontario Institute for Cancer Research</td>
<td>• Pancreas</td>
</tr>
<tr>
<td></td>
<td>• Ontario Ministry of Research and Innovation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Canada Foundation for Innovation</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>• Chinese Cancer Genome Consortium</td>
<td>• Stomach cancer</td>
</tr>
<tr>
<td>Spain</td>
<td>• Spanish Ministry of Science and Innovation</td>
<td>• Chronic lymphocytic leukaemia</td>
</tr>
<tr>
<td>France</td>
<td>• National Cancer Institute</td>
<td>• Breast</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prostate</td>
</tr>
<tr>
<td>India</td>
<td>• Department of Biotechnology</td>
<td>• Oral cavity</td>
</tr>
<tr>
<td></td>
<td>• Ministry of Science and Technology</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>• University of Verona · Italian Ministry of Education</td>
<td>• Pancreas</td>
</tr>
<tr>
<td></td>
<td>• University and Research</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>• RIKEN · National Institute of Biomedical Innovation</td>
<td>• Liver</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>• The Wellcome Trust · Breakthrough Breast Cancer</td>
<td>• Breast</td>
</tr>
<tr>
<td>European Union</td>
<td>• European Commission FP7</td>
<td>• Breast · Kidney</td>
</tr>
</tbody>
</table>

## Cancer genome Atlas (USA)

<table>
<thead>
<tr>
<th>Funding bodies</th>
<th>Types of tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td></td>
</tr>
<tr>
<td>• National Institutes of Health</td>
<td>• Brain</td>
</tr>
<tr>
<td>• National Cancer Institute</td>
<td>• Colon</td>
</tr>
<tr>
<td>• National Human Genome Research Institute</td>
<td>• Lung</td>
</tr>
<tr>
<td></td>
<td>• Ovary</td>
</tr>
<tr>
<td></td>
<td>• Leukaemia</td>
</tr>
</tbody>
</table>
Conclusions

- **Personalized medicine/care is a multiparametric and integrative approach**
  - Which should be the standard of care for any cancer patient
  - Taking into account several factors related to the patient or the tumour itself
  - Leading to dedicated structures or organisations

- **This initiative for targeted cancer treatment in France shows that:**
  - Innovation can be successfully integrated into the healthcare system
  - Molecular stratification is cost effective

- **The evolution of personalized medicine should change our way of performing clinical trials.**

  All these approaches are instrumental to facilitate access to the best care and improve patient’s survival and quality of life.