Personalized Medicine
A nationwide initiative for an equal access to cancer treatment in France

Fabien CALVO – Deputy Director General
The challenges of targeted therapies in cancer

- Molecular genetics deciphers severe frequent cancers into specific rare cancers with specific treatment
- Molecular characteristics redefine tumor classification for molecular targeted therapies
- Ensuring equity of access to innovation
- Offering the best treatment to patients considering the cost–effectiveness ratio
The shift of paradigm: towards molecular subsets of cancers

Molecular subsets of colorectal cancer: 18,000 patients

Molecular subsets of non small cell lung cancer: 16,000 patients
Molecular characteristics redefine tumor classification for molecular targeted therapies

The shift of paradigm: molecular alterations shared in several cancers

One drug is now efficient for the treatment of several « rare cancers »

Imatinib has granted European market approval 2001 for:

- Chronic myeloid leukemia and acute lymphoblastic Leukemia => BCR-ABL translocation
- Gastrointestinal Stromal Tumors => cKIT expression
- Hypereosinophilic Syndrome => FIP1L1/ PDGFR re-arrangements
- Myelodysplastic-Myeloproliferative Diseases => PDGFR re-arrangements
- Precursor Cell Lymphoblastic Leukemia-Lymphoma
- Dermatofibrosarcoma
Ensuring equity of access to innovation: France organisation of molecular platforms for personalised medicine

Provides nation-wide molecular diagnostic tests

The programme is operated by the INCa/Ministry of Health since 2006

**Objectives**

- Perform molecular testing for all patients;
- Whatever the healthcare institution status (public hospitals, private hospitals...);
- Perform high quality tests;
- Leukemia, solid tumours

**28 regional platforms**

- Partnerships between several laboratories located in University hospitals and cancer centres
- Regional organization
- Cooperation between pathologists and biologists
Predictive tests for targeted therapies prescription

<table>
<thead>
<tr>
<th>BCR-ABL translocation:</th>
<th>Chronic Myeloïd Leukemia/ Acute Lymphoblastic Leukemia</th>
<th>Imatinib prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- BCR-ABL detection</td>
<td></td>
<td>1- Imatinib prescription</td>
</tr>
<tr>
<td>2- BCR-ABL quantification</td>
<td></td>
<td>2- Monitoring of minimal residual disease</td>
</tr>
<tr>
<td>3- ABL mutation</td>
<td></td>
<td>3- Resistance to Imatinib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KIT and PDGFRA mutations</th>
<th>GIST</th>
<th>Imatinib prescription</th>
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<thead>
<tr>
<th>HER2 amplification</th>
<th>Breast and gastric cancers</th>
<th>Trastuzumab prescription</th>
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<tr>
<th>KRAS mutations</th>
<th>Colorectal cancer</th>
<th>Panitumumab and cetuximab prescription</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>EGFR mutations</th>
<th>Lung cancer</th>
<th>Gefitinib and erlotinib prescription</th>
</tr>
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<tr>
<th>EML4-ALK translocations</th>
<th>Lung cancer</th>
<th>Crizotinib prescription</th>
</tr>
</thead>
</table>

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<tr>
<th>BRAF mutation V600E</th>
<th>Melanoma</th>
<th>Vemurafenib prescription</th>
</tr>
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</table>
Benefit for all patients

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

- For all patients
- free of charge for patients & hospitals
- compensation of local pathologists for sample shipments

⇒ Ensure that all patients effectively benefit from molecular testing
Rapid access to innovation

Offer each patient in France an equal access to molecular tests as soon as a new targeted therapy is available

Mid 2008 : EMA approvals for Erbitux® and Vectibix® for patients with wild type KRAS tumours

⇒ INCa allocated €2.5M to the 28 platforms at the end of 2008

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

⇒ INCa allocated €1.7M to the 28 platforms at the end of 2009
Offering the best treatment to patients considering the cost – effectiveness ratio:

Growth spending of drug therapy expenditure since 2004 in France (public hospital sector)

Source: ATIH-PMSI MCO base updated 2005-2008 / infography INCa and base 2009/ infographyINCa
Offering the best treatment to patients considering the cost – effectiveness ratio:

Targeted therapy represents 57 % of the cost of anticancer drugs (public hospital sector)

Source : ATIH-PMSI MCO base 2009/ infography INCa
From 2004 to 2010:

- **31 new drugs** in oncology got a first market approval in Europe.
- adapted to **49 therapeutic indications**
- Almost **half** of those new drugs are **targeted therapies**.

→ Impact on the **physician’s practice** and on the healthcare’s setting.
→ Need to have **access to molecular testing** for each patient in order to get a personalized medicine.
Funding mechanisms

Offer the best treatment to patients considering the cost – effectiveness ratio

- Seed fundings from INCa for the test set-up
- Performance and cost evaluation
- Recurrent annual fundings from the French Ministry of Health insurance
Example of gefitinib treatment: €69M spared cost for the health insurance

EGFR testing for lung cancer patients

15,000 patients -

(gefitinib treatment: 8 weeks DFS; Mok 2009)

€ 69M

1,724 patients +

(gefitinib treatment: 38 weeks DFS; Mok 2009)

€ 35M

Spared Cost of gefitinib treatment

Cost of gefitinib treatment

€ 1.7M

Example of gefitinib treatment:

- 1724 patients
- Cost of gefitinib treatment: €35M
- Spared cost for the health insurance: €69M

(gefitinib treatment: 38 weeks DFS; Mok 2009)
Some pending issues on targeted therapies

- Is increased survival a legitimate end point?

- Does tumor based molecular stratification exclude patients who could benefit from treatment?
Is increased survival a legitimate end point?

Trastuzumab for HER2 overexpressing patients with breast cancer

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Line of treatment</th>
<th>Type of administration</th>
<th>Median progression free survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H0649g</td>
<td>Second line and further</td>
<td>Monotherapy</td>
<td>3,2</td>
</tr>
<tr>
<td>H0648g</td>
<td>First line</td>
<td>Combination with chemotherapy</td>
<td>7,1</td>
</tr>
<tr>
<td>M77001</td>
<td>First line</td>
<td>Combination with chemotherapy</td>
<td>10,6</td>
</tr>
</tbody>
</table>

4-year disease-free survival: 78.6% for 1-year trastuzumab vs 72.2% for the observation group.

(Gianni Lancet Oncol. 2011)
Some pending issues on targeted therapies

• Is increased survival a legitimate end point?

• Does tumor based molecular stratification exclude patients who could benefit from treatment?
Implementation of a quality assurance programme

2 types of action:

- Elaboration of guidelines for the detection of mutations in solid tumors before targeted therapies prescription:
  - Implementation in 2011 of a national External Quality Assessment for the 28 platforms (BCR-ABL, KRAS, EGFR)

⇒ Harmonization of practices between platforms
⇒ Assurance quality optimization
Challenges ahead

- **Maintain the quality of molecular tests**
- **Anticipate the launch of new molecules**: reduction of time-to-access to molecule (In 2011, the INCa allocates €3.5M for the prospective detection of emergent biomarkers in lung cancer, colorectal cancer and melanoma).
- **Improve basic/clinical research interfaces**: Basic science to better understanding of mutations/variations/metabolic impact/redundancy of pathways and fostering translational research
- **Public/private partnerships** to optimize the implementation of new tests and sustain innovation.
Conclusions and perspectives

- This initiative for targeted cancer treatment in France shows that:
  - innovation can be successfully integrated into the healthcare system
  - molecular stratification is cost effective
  - this organization could be easily expanded in other European settings

- These platforms are key to help develop translational research and to sustain progress

- They are instrumental to facilitate access to the best care and improve patient’s survival and quality of life

- Training of medical students and professionals to personalized medicine
• 28 pathologists and molecular biologists who run these platforms and their collaborators
• INCa departments of Health Care and Research – special thanks to Fréderique Nowak in charge of this program, Valerie Thibaudeau and Christine Berling
• Our previous president, Dominique Maraninchi
• The patients to whom this national contribution is dedicated
# Economical impact of molecular testing

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Drug</th>
<th>Biomarker</th>
<th>% patients with mutation</th>
<th>Nb of tested patients</th>
<th>Number of spared prescriptions</th>
<th>Median PFS for non responders</th>
<th>Cost of treatment/patient</th>
<th>Spared cost</th>
<th>Public fundings allocated for the provision of the test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung cancer</strong></td>
<td>gefitinib</td>
<td>EGFR mut</td>
<td>10,3%</td>
<td>16722</td>
<td>15000</td>
<td>8 weeks</td>
<td>4 600 €</td>
<td>€69 M</td>
<td>€1.7 M</td>
</tr>
<tr>
<td></td>
<td>erlotinib</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td>cetuximab</td>
<td>KRAS mut</td>
<td>36%</td>
<td>17250</td>
<td>6 210</td>
<td>8 months</td>
<td>32 419 €</td>
<td>€201 M</td>
<td>€2.5 M</td>
</tr>
<tr>
<td></td>
<td>Panitumumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8 weeks</td>
<td>9 263 €</td>
<td>€57 M</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>4 weeks</td>
<td>4 390 €</td>
<td>€27 M</td>
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</table>
1- Is increased survival a legitimate end point?

Imatinib for patients with CML (BCR-ABL translocation)

After failure of interferon -α treatment

Fist line treatment

6 year-survival rate = 76% (Hochhaus, Blood 2008)

6 year-survival rate = 88% (Hochhaus, Leukemia 2009)

CML patients taking Imatinib and in remission after two years of treatment have similar mortality rates to people in general population (Gambacorti-Passerini C, JNCI 2011)