Premier CCC in Europe
Volume of Activity

• ± 13000 new patients /yr
• ± 50,000 treatments /yr
• >10,000 surgical interventions /yr
• >200,000 chemotherapies /yr
• >200,000 outpatient visits

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

• Employees ± 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
IMPROVE RESEARCH ENVIRONMENT

- 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 (6000 M2)

- 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
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)
Whole tumor

Tissue
Adrenal gland biopsy

Treatment
Vinorelbine
cisplatinum
Taxol Carbo
evacizumab
Pemetrexed

Biology guided?
**Heterogeneity in Primary, Metastases (organ) and Evolution (time)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Tissue</th>
<th>Adrenal gland biopsy</th>
<th>Lung +</th>
<th>Bone +</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Whole tumor</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2003</td>
<td>Tumor Bank</td>
<td>Adrenal gland biopsy</td>
<td>Lung +</td>
<td>Bone +</td>
</tr>
<tr>
<td>2005</td>
<td>Vinorelbine</td>
<td>Taxol Carbo bevacizumab</td>
<td>Pemetrexed</td>
<td>Biology guided?</td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>cisplatinum</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

**Surgery T1N1**

- Adrenal gland +
- Lung +
- Bone +
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
Molecular profiling
Identification of the molecular alteration
Targeted therapy according to the molecular profile
Tumor Specimen
Molecular profiling
Precision Medicine: identify-hit the target
Overview of the PCM Program

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

**Short term Developments**

- Tumor or metastasis Biopsy
- High throughput molecular analyses (arrays or NGS)
- Targeted therapy

**New technologies**

- NGS, WES
- CTC, circDNA

**Mechanisms of resistance**

- New targets

**Developing algorithm**

- For drug sensitivity Bioinformatics

**Mid- term perspectives**

- Randomized trials personalized medicine improves outcome

**Randomized trials**

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

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Pilot study</th>
<th>1st Gener Trials</th>
<th>2nd Gener</th>
<th>Randomized trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustave Roussy monocentric</td>
<td>MSN Lung/Mel Besse/Robert 540/600</td>
<td>No NGS</td>
<td>NGS</td>
<td>MATCH-R(WES) (SORIA) =/600</td>
</tr>
<tr>
<td>Gustave Roussy/Unicancer multicenter</td>
<td>preSAFIR (ANDRE) 108/108</td>
<td>MOSCATO (SORIA) 700/900</td>
<td>WES</td>
<td>SAFIR01 (ANDRE) 427/427</td>
</tr>
<tr>
<td>Gustave Roussy/WIN multicenter</td>
<td></td>
<td>SAFIR02 Lung/Soria =/600</td>
<td></td>
<td>SAFIR02 Breast/Andre 220/600</td>
</tr>
<tr>
<td>L Bérard/Lyon Curie</td>
<td></td>
<td></td>
<td></td>
<td>SHIVA (Letourneau)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MOST</td>
</tr>
</tbody>
</table>

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

FUNDING TOTAL ~50 Million: Fondation GR (10) + Buidling (15), IHU (6), INCA (6), ARC (3), WINconsort (4), EU-FP7 (3)
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

Funded by INCA
Sanger 30 genes, then NGS
Pre-SAFIR
N=108

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

Target identification

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

Funded by French NCI
Sponsor: UNICANCER

André et al ESMO 2012, Lancet Oncol 2014
Inclusions

Recruitment completed between May 2011 and August 2012

High level of expectation

Accrual

scheduled

planned targeted therapies

423

120
Molecular alterations

- Targetable alterations
- Rare alterations

% of patients with available genomic result

- mutations
- copy number alterations

IN THE END ONLY 12% gets targeted therapy

André et al, Lancet Oncology 2014
MOSCATO: MOlecular Screening for CANcer Treatment Optimization

Histological analysis → Molecular analysis
CGH, NGS --- WES
Gene-panel sequencing

21 – 14 calendar days
CGH+NGS - WES

TARGET IDENTIFIED IN 45-50%
Targeted therapy in 20-25%
700 / 900 PATIENTS IN 2 Years
Ongoing clinical programs (SAFIR01, MOSCATO, MSN): 3000 patients within 3 years

Tumor or metastasis Biopsy

High throughput molecular analyses (arrays or NGS)

Targeted therapy: In the context of phase I/II trials

Short term Developments

New technologies
NGS, WES
CTC. circDNA

Mechanisms of resistance
New targets

Developing algorithm for drug efficacy
Bioinformatics

A randomized trial: personalized medicine improves outcome

Mid-term perspectives
Biopsy metastatic site: NGS Array CGH

Molecular alteration
Excluding EGFR mut and ALK trl

Chemotherapy 4 cycles

No PD

No alteration

Followed up but not included

Targeted therapy According to Molecular alteration

Pemetrexed if Non-SCC

EGFR TKI if SCC

metastatic NSCLC first line chemotherapy

All histologies
<table>
<thead>
<tr>
<th>Genetic abnormality</th>
<th>Gene location</th>
<th>Squamous Cell Carcinoma</th>
<th>Adenocarcinoma</th>
<th>Therapeutic intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA amplification</td>
<td>3q26.3</td>
<td>33%</td>
<td>6%</td>
<td>AZD2014 (TORC1/2)</td>
</tr>
<tr>
<td>FGFR1 amplification</td>
<td>8p12</td>
<td>22%</td>
<td>1%</td>
<td>AZD4547 (FGFR)</td>
</tr>
<tr>
<td>PTEN mutation</td>
<td>10q23.3</td>
<td>10%</td>
<td>2%</td>
<td>AZD8186 (PI3Kbeta)</td>
</tr>
<tr>
<td>MET amplification</td>
<td>7q31.1</td>
<td>3-21%</td>
<td>3-21%</td>
<td>Volitinib</td>
</tr>
<tr>
<td>PTEN loss</td>
<td>10q23.3</td>
<td>8-20%</td>
<td>8-20%</td>
<td>AZD8186 (PI3Kbeta)</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>12p12.1</td>
<td>6%</td>
<td>21%</td>
<td>AZD6244 (MEKi)? Or combo with AZD2014</td>
</tr>
<tr>
<td>LKB1 mutation</td>
<td>19p13.3</td>
<td>5%</td>
<td>23%</td>
<td>AZD2014 (TORC1/2)</td>
</tr>
<tr>
<td>HER 2 amplification</td>
<td>17q11.2-q12; 17q21</td>
<td>3-5%</td>
<td>5-9%</td>
<td>AZD 8931 (pan-HER)</td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>3q26.3</td>
<td>3%</td>
<td>3%</td>
<td>AZD2014 (TORC1/2)</td>
</tr>
<tr>
<td>RET translocation</td>
<td>10q11.2</td>
<td>2%</td>
<td>1%</td>
<td>AZD6474 (VEGFR, EGFR, RET)</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>7p34</td>
<td>2%</td>
<td>1-3%</td>
<td>AZD6244 (MEKi)</td>
</tr>
<tr>
<td>AKT1 mutation</td>
<td>14q32.32</td>
<td>1%</td>
<td>Very rare</td>
<td>AZD5363 (Akt)</td>
</tr>
<tr>
<td>MET mutation</td>
<td>7q31.1</td>
<td>1%</td>
<td>2%</td>
<td>Volitinib</td>
</tr>
<tr>
<td>HER2 mutation</td>
<td>17q11.2-q12; 17q21</td>
<td>1%</td>
<td>2%</td>
<td>AZD 8931 (pan-HER)</td>
</tr>
</tbody>
</table>
Biopsy metastatic site:
NGS
CGH: 51 alterations

Molecular alteration
Excluding
HER2

Chemotherapy
6-8 cycles

No PD

Targeted therapy
According to Molecular alteration

Chemotherapy continuation

Followed up but not included

metastatic Breast cancer patient 1st or 2nd line
WIN Consortium Trial deals with ALL patients
TRANSRIPTOME and Algorythm for ARM B

Global concept of WINThER

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

Arm A
Oncogenic events from
DNA analysis

Arm B
No oncogenic
event

Matched molecular
targeted therapies and/or
inclusion in
targeted drugs
opened phase 1
trials

High toxicity
management

Therapeutic
choice based on
predictive drug
efficacy scoring
Program PCM*

1330 Molecular Portraits in 2.5 yrs

Techniques
- Séquençage à haut débit  30 gènes
- *Next Generation Sequencing (NGS)*  70 gènes
- *Whole Exome Sequencing (Wes)*  100000 gènes

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

**Sponsor**
- Gustave Roussy monocentric
- Gustave Roussy/Unicancer multicenter
- Gustave Roussy/WIN multicenter
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  - SAFIR02 Breast/Andre 220/600

**Randomized trials**
- WINther 100/200
- SPRING 0/900
- SHIVA (Letourneau)
- MOST

**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

<table>
<thead>
<tr>
<th>Percent Change From Baseline in Longest Diameter of Target Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>160</td>
</tr>
<tr>
<td>140</td>
</tr>
<tr>
<td>120</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>-20</td>
</tr>
<tr>
<td>-40</td>
</tr>
<tr>
<td>-60</td>
</tr>
<tr>
<td>-80</td>
</tr>
<tr>
<td>-100</td>
</tr>
</tbody>
</table>

The chart shows the break-through activity with MK-3475.
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

Individual Patients Treated with Lambrolizumab

Percent Change from Baseline in Target Lesion (2-Dimension Measurement)

Prior ipilimumab treatment
No prior ipilimumab treatment

Percent Change from Baseline in Target Lesion

Individual Patients Treated with Lambrolizumab
Overall Survival for Concurrent Therapy
Ipilimumab + Nivolumab by Dose Cohort

Survival at 1 yr from 25% to 90%
Survival at 2 yr from 12% to 80%
Survival at 5 yr from 3% to > 50%?

(Sznoll et al, ASCO 2014)
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

PRIORITIES GUSTAVER ROUSSY

• 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
  – USA: MDAnderson, MSKCC, Jefferson, UCSD
  – Canada: McGill, Pr Margaret
  – Asia: Fudan, AsanMC, YonseiMC, Singapore, 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.
Cancer Core Europe: A consortium to address the cancer care – Cancer research continuum challenge

Alexander M.M. Eggermont1*, Carlos Caldas2, Ulrik Ringborg3, René Medema3, Josep Tabernero4, Otmar Wiestler1

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2 Cambridge Cancer Centre, Cambridge, United Kingdom
3 Karolinska Institutet, Stockholm, Sweden
4 Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands
5 Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain
6 German Cancer Research Center (DKFZ), Heidelberg, Germany

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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 ‘hospital’ and a powerful translational platform, inter-compatible clinical and 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 genomics, immune-monitoring and other assessments. Importantly, all these require e-culture of data collection and data storage that provides complete longitudinal datasets to allow for effective data sharing and common data base building, and to achieve a level of comprehensiveness of data that is required for conducting outcome research, thereby informing our current understanding of cancers as communities of evolving clones. Cutting edge research and technology development serves 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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0959-8403 © 2014 Published by Elsevier Ltd.
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)
Gustave Roussy Cancer Campus Grand Paris