Innovative Molecular Targets and Cancer Therapeutics

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Institut Bergonié
Innovative Molecular Targets and Cancer Therapeutics

One Priority:
Improving access to tailored treatment and innovative drugs for cancer patients from the Aquitaine Region
Work Package 1:
Predictive biomarkers and cancer database

Main objective:
Identification of predictive biomarkers to improve tailoring of anti-cancer therapies
Work Package 1:  
**Predictive biomarkers and cancer database**

Development of research programs which aimed to

- identify predictive signature of response to anti-cancer therapies
- create datasets (clinical and molecular) that will be available to the scientific community

**Input of the SIRIC:** developing strategic partnership that will bring together the multidisciplinar expertise and resources needed

- to identify such signatures in three major tumor types: breast cancer, soft-tissue sarcomas, renal cell carcinoma

→ **Sharing staff and molecular platforms,** reinforcing the bioinformatics department

- To create a renal cancer tumor bank and database similar to that already developed for soft-tissue sarcomas

→ **Sharing experience and methodological skills from sarcoma investigators**
Work Package 1:
Predictive biomarkers and cancer database

**Doxorubicin**
75 mg/m² q3wk
165 patients (first + second steps)

**Trabectedin**
1.3 mg/m² 3-h q3wk
OR
1.5 mg/m² 24-h q3wk
205 patients (first + second steps)

EORTC agreement to send tumor blocks after histological central review and share clinical data

**Genomic and Bioinformatic Analysis**

- Validation of the previously published signature (trabectedin)
  (Italiano et al., Cancer 2011)
  - ERCC5, ERCC1 and BRCA1 mRNA expression (qRT-PCR)
  - Genotyping of ERCC5, ERCC1 and BRCA1 SNPs

- Identification and Validation of SNP-based signatures for trabectedin and doxorubicin
  Illumina's HumanOmniExpress- BeadChip arrays

Grant obtained from the Association pour la Recherche contre le cancer (2012): 300 KE
SIRIC support: bioinformatics, statistician
Work Package 1: Highlights

National Renal Cancer Database: Patients data and Tumor bank

- Official approval by regulatory authorities (CNIL): April 2013
- 2100 patients included by 2016
- Several projects in the starting blocks: RoPaN, CARLA, CARARE....
Work Package 2
New drugs and tumor targets: proof of concept clinical trials

Main objective:
Improving access to phase 1 and early phase 2 trials
Early Phase I Unit (Institut Bergonié)

Main objective:
120 patients in Phase 1 trials in 2018
• Task2.1: Setting up innovative academic projects

• Task2.2: Creating a new balance of more industry-sponsored trials relative to academic studies to ensure sufficient funding to support own clinical/translational research enterprise
Work Package 2
Task 1: Innovative academic early phase trials

Early phase Trials Units labelled by the French NCI: CLIP2 Network
Work Package 2
Task 1: Innovative academic early phase trials

CLIP2 Network: Academic Early Phase 2 Studies

- Broaden development in relevant tumor types
  - Industry focus on limited number of indications dictated by market considerations
- Combinations of targeted agents a high priority
  - 8 phase I/II trials initiated since 2012
- Explore
  - Alternative methods of drug administration
  - Mechanism of Action/Proof of Principle/Biomarkers
- Mass of solicitation request: French (every 3 months) and US NCI
Early Phase Trials: Collaboration NCI / INCa

1: Firms ask NCI (through CTEP) for a specific development of one of their agents by NCI investigation centres

2: NCI/CTEP issue a « mass solicitation request » to US centres opened now to INCa

3: INCa solicits the French network (16 centres CLIP²) on this specific “letter of intent” (protocol synopsis)

4: Answers from the French centres are reviewed by INCa

5: The French letters of intent are submitted to NCI/CTEP by INCa for formal review

6: If approved by NCI, the project is submitted to the firm for definite approval: Full protocol, drug importation to France as well as patients accrual will follow
Early Phase Trials: Collaboration NCI / INCa


A. Italiano¹, A. Le Cesne², C. Bellera³,⁴, S. Piperno-Neumann⁵, F. Duffaud⁶, N. Penel⁷, P. Cassier⁸, J. Domont², N. Takebe⁹, M. Kind¹⁰, J.-M. Coindre¹¹, J.-Y. Blay⁸ & B. Bui¹

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Work Package 2
Task 1: Innovative academic early phase trials

HIGHLIGHTS:

New trials planned to start by in 2013-2014

- **CYCLIGIST**: Safety and efficacy of PD-0332991 in patients with GIST refractory to imatinib and sunitinib (sponsor: Institut Bergonié, Funding French NCI)
- **MetroMAJX**: Phase I study of JX-594 and metronomic cyclophosphamide in breast cancer and sarcoma patients (sponsor: Institut Bergonié, Funding French NCI)
- **METZOLIMOS**: Phase I study of metronomic cyclophosphamide, methotrexate, sirolimus and zoledronic acid in osteosarcoma patients (sponsor: Institut Bergonié, Reliable Cancer Therapies)
- **CABOSARC**: Phase 2 study of cabozantinib in relapsed osteosarcoma and ewing sarcoma (sponsor: Institut Bergonié, Funding French NCI, Drug provided by the US NCI)

Total grant > 2 100 000 Euros
Work Package 2
Task 2: Developing Industry-sponsored studies

- An increasing amount of sponsored research is coming from pharmaceutical companies for clinical trials targeted to a specific mutation.
- A modest amount of molecular screening is now being done in routine practice.
- We are anticipating a future when all incoming patients will be offered their “mutational smorgasbord” data in order to make them ready to enroll in a clinical trial matching their profile.
<table>
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<tr>
<th>Study Type</th>
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<td><strong>First in human subjects</strong></td>
<td>A Study of AG-120 as Monotherapy in Patients With Advanced Solid Tumors</td>
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| **Combinations of approved + new agents** | - Phase I/II study of LY2228820 with radiotherapy plus concomitant TMZ in the treatment of newly diagnosed glioblastoma  
- A Phase 1b, open-label, dose escalation study of the safety, tolerability and efficacy of LY2780301 (a p70/Akt inhibitor) in combination with Gemcitabine in Patients with Advanced or Metastatic Cancer  
- A Phase I, multi-centre, open-label study in patients with solid tumors to assess the tolerability of S-222611 in combination with various anticancer agents and to examine their pharmacokinetics.  
- A randomised phase II study of LY2228820 plus Tamoxifene in breast cancer patients.  
- A Phase II, Open-label, Study in Patients with BRAF V600E-Mutated Rare Cancers with Several Histologies to Investigate the Clinical Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib |
| **New agents in special populations**  | - An Open-label, Non-randomised, Multicentre, Comparative, Phase I Study to Determine the Pharmacokinetics, Safety and Tolerability of Olaparib following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumours and Normal Hepatic Function or Mild or Moderate Hepatic Impairment  
- An Open-label, Non-randomised, Multicentre, Comparative, Phase I Study of the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumours and Normal Renal Function or Renal Impairment |
Improving inclusion even in rare molecular « niches »: Molecular Screening Program

Routine molecular screening (NGS) starting January 2014:
- Ion AmpliSeq™ Comprehensive Cancer Panel
- Comparative genomic hybridization
- Immunohistochemistry: EGFR, HER2, ALK, MET, GLI, p-AKT, PTEN
Improving inclusion even in rare molecular « niches »: Collaboration network

Pre-Screening in partner centers to improve inclusion even in rare molecular « niches »
Work Package 2
Task 3: Developing Translational Research

- Special focus on mechanisms of secondary resistance to innovative agents tested in the clinical setting
- Example: Mechanisms of secondary resistance to MDM2 inhibitors
- Other projects: secondary resistance to PI3K/MTOR, FGFR2 pathway
### Work Package 2: Publications

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W.P. 3 Development of Innovative Imaging Solution for Accurate Early Assessment of Tumor Response to Targeted Therapies

*Three axis of research*

One objective: *Early assessment of tumor response*

Academic collaborations: « Translational research and advanced imaging Laboratory » (University of Bordeaux), PET research unit (University hospital centre of Bordeaux)

Private partners: Siemens, General Electric, Appolo Medical Imaging, IBA-CisBio
W.P. 3 Development of Innovative Imaging Solution for Accurate Early Assessment of Tumor Response to Targeted Therapies

Potential Input of the SIRIC

• Favoring the development of new imaging agents, methods and applications in cancer with translation to appropriate clinical trials.

• Provide organizational support for integration of imaging research programs in early phase trials conducted by the phase 1 units of the SIRIC
Key Objectives for 2014

- WP1- Validation of the predictive signature to trabectedin
- WP1- first studies from the renal cancer database published
- WP2: New success to a solicitation mass from the French/US NCI
- WP2: Implementation in routine of molecular screening for phase 1 patients
- WP2: Increase by 20% the number of patients included in industry sponsored phase 1 trials
- WP3: First study to be designed with DCE-US as an early marker of chemotherapy efficacy in breast and sarcoma patients
Acknowledgement

- Phase 1 medical staff: A. Italiano, A. Ravaud, M. Toulmonde,
- Molecular platform/Pathology: JP. Merlio, I. Soubeyran
- Informatics / Bio-informatics: C. Lucchesi
- Methodology of Clinical Trials: S. Mathoulin, C. Bellera
- Database: JC Bernhard, A Ravaud
- Imaging: F. Cornelis, M. Kind, J. Palussière,
- Translational Research Unit: B. Fourneau, A. Laroche, V. Chaire