PRESS INVITATION

Launch of PIONEER, a major international research project in lung cancer

Thursday 23 November 2017, 13:00 pm
Boardroom of Aix-Marseille University Faculty of Medicine
27 Boulevard Jean Moulin, 13 385 Marseille cedex 5

Immunotherapy is becoming a game-changer in the treatment of cancers, including one of the most serious: non-small-cell lung cancer (NSCLC). However to date, only 20% of these patients respond favorably to the first available immune-modulating antibodies: PD-1 immune checkpoint inhibitors.
An international team of researchers and clinicians from academia and industry and coordinated by Prof. Fabrice BARLESI gave itself 5 years to better understand, predict and overcome these resistances. Laureate of the third "University-Hospital Research in Health" call for projects of the program "Investments for the Future"[1], this major project, called PIONEER, is being launched on 23 November in Marseille.

Press meeting agenda

12:30 pm
Lunch

13:00 pm
Introduction
Prof. Yvon BERLAND, President of Aix-Marseille University (AMU).

13:10 pm
Overcoming resistance to PD-1 immune checkpoint inhibitors in lung cancer, a three-fold challenge
Prof. Fabrice BARLESI, Professor of Medicine at AMU, Head of multidisciplinary oncology and therapeutic innovations department at AP-HM, Coordinator of the Marseille center for early

[1] 10 new winners and 74.5 M€ for the 3rd University-Hospital Research in Health call for projects. Press release of French Ministry of Health and Solidarity, Ministry of National Education, of Higher Education, Research and Innovation and of the Commissariat-General for Investment, 26 July 2017.

clinical testing in cancer CLIP2 (AP-HM, INCa), Coordinator of the Pioneer project and co-founder of Marseille Immunopole

13:20 pm
Evaluating in clinical setting new associations of immunomodulatory molecules
Dr. Nathalie VAROQUEAUX, VP Europe Oncology Medical Head, AstraZeneca

13:30 pm
Predicting the response to PD-1 immune checkpoint inhibitors
Vincent FERT, CEO and Co-founder of HalioDx.

13:40 pm
Evaluating the potential of second generation immunomodulator antibodies
Prof. Eric VIVIER, Professor of Immunology at Aix-Marseille University, Hospital Practitioner at AP-HM, Director of the Center of Immunology in Marseille-Luminy and Coordinator of the French immunology cluster Marseille Immunopole.

13:50 pm
Journalists' questions to members of the PIONEER team

14:20 pm
Coffee break

14:40 pm
Individual meetings with journalists
Opportunity to prolong discussions with members of the team until 16:00 pm.

Press contact

To organize your arrival and plan your interviews:

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The PIONEER Project

After targeted therapies at the end of the 90s, immunotherapy today improves the treatment of patients with non-small-cell lung cancer. In that respect, by restoring the ability of patients' T-cells to recognize and to kill cancer cells, the PD-1 immune checkpoint inhibitors lead to spectacular reduction in tumor volume and a significant lengthening of life expectancy in 20 to 25% of patients[2345].

Despite this progress, lung cancer remains the leading cause of cancer death worldwide (around 1.5 million deaths per year)[6]. Indeed, for reasons yet to be fully understood (molecular profile of the tumor, impact of the surrounding microenvironment, the patient's immune status…), the majority of patients with non-small-cell lung cancer see their cancer progress despite the anti-PD-1 treatment, and to date, no biomarker is able to identify this resistance in advance.

On the initiative of Marseille Immunopôle, Aix-Marseille University (AMU), Inserm and CNRS, five of their research (CIML, CRCM, CRO2) and technology (CIPHE, MI-mAbs) centers, Assistance Publique-Hôpitaux de Marseille (AP-HM), the Léon Bérard Center in Lyon (CLB), Toulouse Oncopole, the biotechnology company ImCheck Therapeutics, the two French leaders in immuno-oncology Innate Pharma (therapeutic) and HalioDx (diagnostic) and one of the worldwide leaders in the domain, the biopharmaceutical group AstraZeneca, have joined forces to take up the main current challenge of immuno-oncology: resistance to PD-1(L1) immune checkpoint inhibitors.

Winner of the 3rd University-Hospital Research in Health call for projects in the **"**Investments for the Future**"** program, this project, called PIONEER (**P**recision **I**mmuno-**O**ncology for advanced **N**on-Small Cell Lung Canc**e**r Pati**e**nts with PD-(L)1 ICI **R**esistance), is coordinated by Fabrice BARLESI, Professor of Medicine at AMU, Head of multidisciplinary oncology and therapeutic innovations department at AP-HM, Coordinator of the Marseille center for early clinical assays in cancer CLIP2 and co-founder of Marseille Immunopôle.

Conducted over a 5-year period, the project is articulated around 3 axes:

- A program of exploratory clinical trials to evaluate the efficacy and safety of new associations of immunomodulatory molecules that target simultaneously several immune checkpoints and cells implicated in the anti-tumoral immune response.
- The comparative analysis of biological samples taken from patients (blood and biopsy) to identify and validate predictive biomarkers for response to immunotherapy treatments and to develop associated diagnostic tests.

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[2] Nivolumab versus Docetaxel in Advanced Non-squamous Non-Small-Cell Lung Cancer, H. Borghae et al, N Engl J Med 2015; 373:1627-1639October 22, 2015, DOI: 10.1056/NEJMoa1507643

[3] Nivolumab versus Docetaxel in Advanced Non-squamous Non-Small-Cell Lung Cancer, J. Brahmer et al, N Engl J Med 2015; 373:123-135July 9, 2015, DOI: 10.1056/NEJMoa1504627;

[4] Pembrolizumab versus Docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomized controlled trial, RS Herbst et al, Lancet. 2016 Apr 9;387(10027):1540-50, DOI: 10.1016/S0140-6736(15)01281-7

[5] Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide program of the French Cooperative Thoracic Intergroup (IFCT), F. Barlesi et al, Lancet. 2016 Apr 2;387(10026):1415-1426, DOI: 10.1016/S0140-6736(16)00004-0

[6] Cancer fact sheet 2017, World Health Organization

- The validation of new generation immunomodulatory antibodies on *in vivo* models of the disease.

PIONEER also seeks to:
- Elucidate the complex mechanisms of resistance to PD-1 inhibitor antibodies;
- Develop new therapeutic associations;
- Expand the set of immunomodulatory drugs in lung cancer;
- Open up new diagnostic and therapeutic options for these patients.

Key features

Management: Prof. Fabrice BARLESI (AMU, AP-HM)

Coordinator: Aix-Marseille University

Sponsor: Assistance Publique-Hôpitaux de Marseille

Design: Marseille Immunopôle

Total cost: 25,510,000 €

NRA funding: 8,502,000 €

Duration: 60 months

PIONEER

Aix-Marseille University (AMU)

AMU is the largest francophone university with 77,000 students, including 10,000 international students, 8,000 staff members and a budget of €750 million. Training, professional orientation and integration, research and knowledge translation are the pillars of this multidisciplinary and interdisciplinary establishment. AMU trainings team up with 130 research structures in connection with national agencies. In 2016, AMU and its partners (CNRS, Inserm, CEA, IRD, ECM, IEP, AP-HM) obtained the continuation of their Excellence Initiative (Idex), A*MIDEX, following assessment and proposition by an international jury.

Ever bolder research
A research-intensive university, AMU makes a significant contribution to the knowledge-based economy and the dissemination of knowledge, relating to disciplinary and interdisciplinary fundamental research. It is associated with large national players in research: CNRS, Inserm, IRD, EHESS, CEA, IFSTTAR, INRA... with whom it pursues a co-constructed scientific strategy. A strategic growth axis, AMU has set up five interdisciplinary and cross-sectorial research clusters (PR2i), to foster interaction between disciplines.

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Assistance Publique-Hôpitaux de Marseille (AP-HM)

With 4 hospitals and 3,400 beds, Assistance Publique-Hôpitaux de Marseille (AP-HM) is the third University Hospital Center in France. It is also the first employer in the region, with over 12,000 employees and almost 2,000 physicians. Its missions are treatment, teaching, research as well as prevention and health education. Its establishments offer a full range of medical specialities, from local health care to advanced treatments for rare and complex pathologies, for adults and children. Its medical and health care teams are committed to providing care that combines excellence with proximity, easily accessible to all.

www.ap-hm.fr
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Marseille Immunopole (MI)

The fruit of 40 years of research and innovation in immunology, the MI cluster is exclusively dedicated to the research and development of a new approach that is about to revolutionize the treatment of cancers and inflammatory diseases: immunotherapy. Over 2,000 researchers, clinicians and industrialists work hand in hand with academic and industrial partners from around the world to accelerate the development of immunotherapy antibodies and cellular therapies, to facilitate patients' access to these innovations and to position the metropolis at the forefront of world competition.

MI brings together a continuum of excellence that is unique in the world ranging from the discovery of targets to the clinical development of drug candidates: Aix-Marseille University, CNRS, Inserm, 10 of their research and technology centers, 3 of the Assistance Publique-Hôpitaux de Marseille, Institut Paoli-Calmettes, the Eurobiomed cluster and industrials including the two French leaders in immuno-oncology: Innate Pharma and HalioDx. Supported by all the actors and the stakeholders of regional innovation, the Public Investment Bank, the Commissariat-General for Investment and the departmental committee of the French Anti-Cancer League, MI is one of the 34 projects in the French Government's **"**Industry of the Future**"** program. The cluster's collaborative R&D projects are conducted by the University-Hospital federation MI-FHU that is labelled by the National Alliance for Life Sciences and Healthcare (AVIESAN).

www.marseille-immunopole.org
Twitter : @Immunopole
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Léon Bérard Center (CLB)

The CLB is one of the 20 French centers dedicated to cancer patients. It proposes on a single location all the necessary diagnostic tests, treatments and patient follow-up during and after the disease. The center is recognized as a regional, national and international center of reference for cancerology. It ensures a triple mission of treatment, research and teaching, with the permanent desire to improve the quality of and accessibility to treatment for cancer patients.

The continuum of research-treatment is a strength of the CLB. It welcomes over 30,000 patients every year in hospitalization, consultation or for an examination and 6,000 new tumors are diagnosed. The CLB has technical facilities for examinations and treatment (operating room, radiotherapy center, medical imaging departments, anatomy and pathological cytology and nuclear medicine…).

1,700 people (including 200 physicians, 400 researchers, 600 carers) work at the CLB in the sectors of treatment, research, teaching and "support" functions.

www.centreleonberard.fr
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University Institute of Cancer Toulouse (IUCT) Oncopole

The IUCT (University Institute of Cancer Toulouse) Oncopole comprises the Claudius Regaud Institute (cancer research center, Toulouse) and several oncology teams of the CHU Toulouse. 1500 employees mobilize their know-how to provide the best possible treatment. By grouping together, the two structures propose a complete and innovative range of public health care spread across three sites (Oncopole, Purpan and Rangueil-Larrey).

The Institute is located at the heart of the campus grouping together private and public stakeholders involved in the fight against cancer. It has three missions: treatment, research, teaching. The IUCT Oncopole welcomes 10,000 new patients per year for the following specialities: hematology, cancers found in women, ENT cancers, skin cancers, certain sarcomas, urology (medical and innovative surgery).

The critical state-of-the-art technology necessary for the diagnosis, treatment and research in cancerology are provided on the site. The establishment is equipped with the platforms required for the development of personalized treatments: molecular biology, oncogenetics, phases I, II and III clinical research. To promote the continuum of research, the CRCT building adjoins the Institute.

www.iuct-oncopole.fr
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CIML

Founded in 1976, the Marseille-Luminy Immunology Center is an internationally recognized research institute. The CIML is also a visionary center in terms of organization, which, from its inception, has developed specific practices and customs to foster the creativity and risk-taking of its researchers.

From worm to human, from molecule to the whole organism, physiological to pathological, the CIML addresses, on various models and scales, all areas of contemporary immunology: the genesis of different cell populations, their mode of action and differentiation, their implication in cancers, infectious and inflammatory diseases and the mechanisms of cell death.

Founding member of the cluster Marseille Immunopole (MI), the CIML is a Joint Research Center of the CNRS, Inserm and Aix-Marseille University. Directed by Professor Eric Vivier, it consists of 14 research teams and a staff of 200 persons.

www.ciml.univ-mrs.fr
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CRCM

Created in 2008, the Marseille Cancer Research Center (CRCM) includes the four major stakeholders in research in PACA: Inserm, CNRS, Aix-Marseille University and the Paoli-Calmettes Institute. With 250 staff members divided into 17 teams, the CRCM implements innovative research programs in cancer, the most fundamental aspects of clinical research in humans.

The priority scientific and medical activities are, on the one hand, the decoding of molecular bases of oncogenesis and tumor dissemination, and on the other hand, the discovery and implementation of therapeutic innovations in the treatment of breast and pancreatic cancers and hematologic malignancies.

The CRCM is one of the founding members of the cluster Marseille Immunopole.

www.crcm.marseille.inserm.fr
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CIPHE

Founding member of the cluster Marseille Immunopole (MI), the Center for Immunophenomics contributes to the development of the first functional encyclopedia of mouse genes associated with immune response. Its mission is at the heart of a global project of the International Mouse Phenotyping Consortium (IMPC): to understand the implication of our genes in major diseases.

To accelerate the generation of animal models, to follow the evolution of their biological and clinical parameters and to evaluate the functioning of their immune system, in normal and pathological situation, CIPHE leans on a high-throughput synthetic biology unit, a clinical and biological examinations center and a high security BSL-3 laboratory, unique in Europe. The data and the models from the platform are made freely available to academic laboratories and accessible, on a contractual basis, to industry.

With the Mouse Clinic Institute in Strasbourg-Illkirch and the transgenesis and archiving center in Orléans-Villejuif, CIPHE has created PHENOMIN, a unique national interface that facilitates the creation, archiving and distribution of human diseases.

Supported by the program “Investment for the Future” and a member of the European network INFRAFRONTIER, CIPHE is a services unit of Inserm (US012), CNRS (UMS3367) and Aix-Marseille University (AMU). It has a headcount of 40 persons consisting mostly of researchers, engineers and technicians.

www.ciphe.marseille.inserm.fr
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MI-mAbs

Launched at the end of 2012, the immunotechnology center MI-mAbs is a pre-industrial demonstrator that aims to accelerate the development of new antibodies against cancers and inflammatory diseases.

Open to therapeutic targets of academic research and industry, MI-mAbs determines their expression profile, generates specific antibodies, characterizes their mechanism of action and evaluates their efficacy and safety in *in vivo* models mimicking human diseases and on biological samples from patients. By validating the therapeutic potential of these new antibodies, MI-mAbs allows industrials to immediately focus their efforts on the most promising drug candidates.

Winner of the 2011 “Investments for the Future” in the “pre-industrial demonstrators” category, MI-mAbs was founded by Aix-Marseille University, which also ensures its administation through its Protisvalor subsidiary, CNRS, Inserm, Paoli-Calmettes Institute, three of their research centers (CIML, CRCM and Ciphe), biopharmaceutical companies Innate Pharma and Sanofi, one of the world leaders in healthcare. It has the support of the DRRT PACA, the PACA Region, the County Council 13, the city of Marseille, Aix-Marseille Provence Metropolis and Committee 13 of the French League Against Cancer. Founding member of Marseille Immunopole, MI-mAbs is located at the center of the Marseille-Luminy MI-Biopark. It is directed by Professor François Romagné and has a headcount of 28 persons.

www.mimabs.org
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AstraZeneca

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialization of prescription medicines, primarily for the treatment of diseases in three therapy areas: oncology, cardiovascular & metabolic diseases & respiratory. The Company also is selectively active in the areas of autoimmunity, neuroscience and infection. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide.
In France, AstraZeneca currently has 137 clinical development programs in oncology and concluded numerous partnerships in basic and translational research with academia. AstraZeneca France participates in three major initiatives in precision medicine: SAFIR 02 (lung and breast cancers); AcSé ESMART (paediatric oncology) and MultiSarc (sarcoma).

www.astrazeneca.fr
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Innate Pharma

Innate Pharma S.A., a clinical-stage biotechnology company, designs and develops first-in-class therapeutic antibodies that harness the innate immune system to improve cancer treatments. Innate Pharma specializes in immuno-oncology, a new therapeutic field that is changing cancer treatment by mobilizing the power of the body's immune system to recognize and kill cancer cells. The Company's portfolio comprises four «first-in-class» therapeutic antibodies in clinical stage, preclinical candidates and innovative technologies with the potential to address a large number of cancer indications with high unmet medical needs.

Innate Pharma has pioneered the discovery and development of checkpoint inhibitors (IPCI or checkpoint inhibitors) to activate the innate immune system, with unique expertise in the biology of NK cells. This has resulted in major alliances with leaders in the biopharmaceutical industry including AstraZeneca, Bristol-Myers Squibb, Novo Nordisk A/S and Sanofi. The Company is building its foundations to become a fully-integrated biopharmaceutical company in immuno-oncology. Based in Marseille, Innate Pharma has more than 170 employees and is listed on Euronext Paris.

www.innate-pharma.com
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HalioDx

The immune response to cancer diagnostics

HalioDx is an immuno-oncology diagnostic company providing oncologists with first-in-class Immune-based diagnostic products and services to guide cancer care and contribute to precision medicine in the era of immuno- oncology and combination therapies.

Immunoscore® proprietary technology, pioneered by Jérôme GALON at the Cordeliers Research Center, Paris, France, integrates immunohistochemistry combined with advanced imaging analysis enabling extraction of spatially-organized tissue molecular information. Immunoscore® is a platform for many cancers, as immune response to tumor is a key hallmark of disease progression. HalioDx collaborates with renowned international clinical groups to support clinical utility and ensure rigorous performance validation of its assays in selected cancer indications. HalioDx develops also assays such as Halioseek™ and Immunosign® to help stratifying patients for immunotherapies.

HalioDx has an experienced team of more than 130 employees, a CLIA laboratory and compliant facilities to develop, manufacture, register and market *in vitro* diagnostic (IVD) products and perform patient sample testing in a GCP/GCLP compliant environment. HalioDx executes biomarker studies and companion diagnostic assay development in conformity with regulations and in partnership with biopharmaceutical companies. The company co-founded the European immunology cluster Marseille Immunopôle (MI).

www.haliodx.com, **www.immunoscore-colon.com** and **www.halioseek.com** and follow the company on Twitter **@HalioDx**

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ImCheck Therapeutics

A spin-off of the CRCM., Marseille's Cancer Research Center (IPC, CNRS, Inserm, AMU), ImCheck Therapeutics is a privately-held French biotech company pioneering the next generation of immune checkpoint modulators with a highly-differentiated & diversified portfolio of first-in-class therapeutic antibodies in cancers and auto-immunity.

Founded in 2015 by Daniel Olive, a worldwide recognized leader in innate immunity & co-signaling molecules, Professor of Immunology at Aix-Marseille University & Institut Paoli-Calmettes and Head of the immune monitoring program for early-stage oncology clinical trials at IPC, the company has secured worldwide exclusive IP rights for its pipeline from Inserm Transfert and SATT-SE.

With a precision medicine-based translational approach and several established academic collaborations with renowned institutions, ImCheck is uniquely positioned to develop theragnostic candidates for precision & personalized medicine in cancers and auto-immunity diseases. To date, ImCheck is developing two first-in-class immunomodulator antibodies and is advancing several discovery programs on undisclosed targets, all playing a defined immune-modulating role in both innate and adaptive immunity.

The company is based within the Institut Paoli-Calmettes in Marseille and is engaged in an active recruitment dynamic.

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Inserm

The Inserm is the French National Institute of Health and Medical Research institution. Ranked as the number one academic research institution in biomedical research in the European Union, Inserm operates under the dual auspices of the Ministry of Health and the Ministry of Research. It was created in 1964 as a successor to the French National Institute of Health.

www.inserm.fr
presse&inserm.fr

CNRS

Founded in 1939, the Centre National de la Recherche Scientifique (National Center for Scientific Research) is a public organization under the responsibility of the French Ministry of Education and Research. It produces knowledge and makes it available to serve society. With nearly 33,000 employees, distribution throughout France, CNRS produces science in all

fields of knowledge, relying on more than 1100 research and service units. With 20 Nobel laureates and 12 Fields prize winners, CNRS has a long tradition of excellence.

www.cnrs.fr
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Institut Paoli Calmettes

Certified by the French National Authority for Health (HAS) and member of the French Certified by the French National Authority for Health (HAS) and member of the French Federation of Comprehensive Cancer Centers UNICANCER, The Institut Paoli Calmettes (IPC) brings together 1,407 researchers, medical and non-medical staff, committed to an integrated approach to the understanding and treatment of cancers, which includes research, medical care and support, teaching and training. In 2014 alone, the IPC carried out over 78 970 medical consultations and received over 8 650 new patients. Healthcare at the IPC is provided at the rates established by the French Social Security with no overrun fees. Governed by articles L6162-1 through -13 of the Public Health Code, the Institut Paoli Calmettes is entitled to receiving donations and legacies.

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National Research Agency (ANR)

The French National Research Agency (ANR) provides funding for project -based resea
Employing a method based on competitive peer reviews that complies with international standards, ANR attaches great importance to providing the scientific community with instruments and conditions that promote creativity and openness, and stimulate new ideas and partnerships, particularly between the public and private sectors. The agency notably offers a funding instrument specifically dedicated to the Young Researchers. Its activity also contributes to enhancing the competitiveness and the influence of French research in Europe and across the world.

More than 11,000 research projects were financed by ANR since its creation in 2005.

www.anr.fr
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PIA (Investments for the Future Program)

Launched in 2009 by the French Government and steered by the General Investment Commission (CGI), **the "Investments for the Future program" are strategic initiatives which aim to boost French competitiveness by investing in research, higher education and vocational training, in industry and SMEs, in sustainable development and in expanding sectors such as digital technology, biotechnology and nuclear energy.**

www.gouvernement.fr/investissements-d-avenir-cgi
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