

OVERCOME RESISTANCE TO ANTI-PD1(L1) IMMUNOTHERAPY: FIRST LUNG CANCER PATIENT ENROLLED IN THE PIONEER PROJECT'S CLINICAL TRIAL

- This randomized clinical trial is one of the pillars of the multifaceted undertaking that is The Pioneer Project, a major international research project that aims to understand, predict and overcome resistance to PD1(L1) immune checkpoint inhibitors (ICIs).
- Coupled to an analysis of predictive biomarkers of resistance, the multicentric umbrella trial includes 4 experimental arms that each combine the anti-PDL1 durvalumab (Imfinzi™, AstraZeneca) with one of four next generation ICIs.
- The trial's primary endpoint is the 12-week percentage of patients that will achieve complete response, partial response or maintain a stable disease under treatment.

MARSEILLE, France, December 20, 2019

The Pioneer Project, a major international Hospital-University Research (RHU) project that addresses the critical challenge of resistance to PD1(L1) inhibitors, today announced that a first patient has been included in its umbrella clinical trial designed to evaluate efficacy and safety of four original ICI combinations in patients with PD1(L1) inhibitor-resistant advanced non-small-cell lung cancer.

PD1(L1) inhibitors have led to a spectacular reduction in tumour volume and a significant lengthening of life expectancy in about 20% of NSCLC patients, and yet, lung cancer remains the leading cause of cancer deaths worldwide as most patients are or become resistant to these treatments. Still largely misunderstood, these mechanisms of resistance are highly complex and vary over time and space from one patient to another and within the same patient. To embrace such complexity, The Pioneer Project has designed an unprecedented multiparametric approach that should allow to better understand, predict and obviously overcome these resistances (Figure 1).

The study first interrogates a wide **panel of biomarkers**¹ that are potentially linked to and could predict the response to PD1(L1)-inhibitors and other ICIs: properties of the cancer cells themselves, density, identity and degree of anti-tumour activity of immune cells in the tumour, its invasive

¹ Monville F et al. Immunogram to decipher PD1/L1 ICI resistance: a proof of concept in advanced NSCLC patients of the PIONeer Project. SITC 2019.

margin and the bloodstream, and finally, identity of the microorganisms that live in the patient's gut (microbiota) which might influence the anti-tumour immune response, as recent studies suggest.

Second, the study is not limited to examining patients for whom PD1(L1)-inhibitors have been ineffective, but instead scrutinizes advanced lung cancer patients subjected to any of the existing PD1(L1) inhibitors prior to knowing their degree of response. Both progressors and non-progressors are therefore monitored before and throughout their treatment. Such an **agnostic approach** is more likely to uncover unbiased predictive biomarkers.

Third, the study includes a randomized clinical trial that addresses in parallel the effectiveness of **4 combination immunotherapies** with durvalumab (Imfinzi™, AstraZeneca) in early progressors (patients that progress between 6 and 18 weeks after the start of a PD1(L1)-inhibitor treatment). The 4 combinations were chosen to cover all possible tumour immune profiles: inflamed tumours (with large numbers of active immune cells within and around the tumour), immune excluded tumours (with a limited number and activity of immune cells in the tumour microenvironment) and immune deserts (absence of immune cells in and around the tumour).

Finally, the study also includes an exploratory program to uncover new pathways that might rescue immune checkpoint inhibitor resistance in pre-clinical settings.

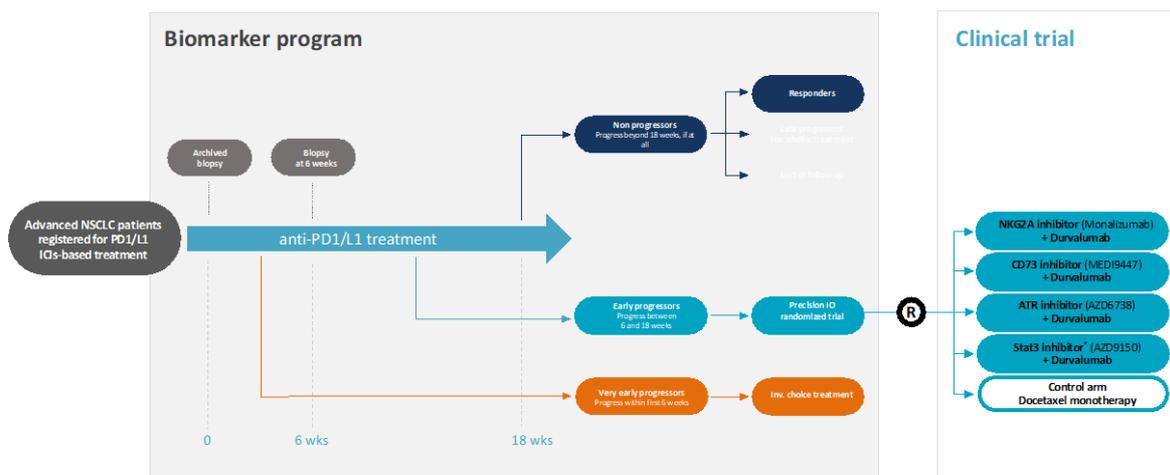


Figure 1. PIONeer clinical research flowchart

Patients with advanced NSCLC registered to receive one of the available PD1(L1)-inhibitors and for whom a tumour biopsy prior to treatment is available can enter the biomarker program of The Pioneer Project. Throughout the PD-1(L1)-inhibitor treatment and regardless of their response, tumour biopsies and stool samples (at 0 and 6 weeks), as well as blood and plasma samples (at 0, 3, 6, 9, 12, 15 and 18 weeks) are collected. Early progressors (patients that progress between 6 and 18 weeks of treatment) can then enter the Pioneer clinical trial and will receive either a control Docetaxel monotherapy, or a combination therapy of durvalumab (Imfinzi™, AstraZeneca) with one of 4 next generation ICIs that cover the range of possible tumour immune profiles. The treatment of very early progressors (that progress before 6 weeks) and late progressors (after 18 weeks) is left at the investigator's discretion.

"It is by approaching resistance to immune checkpoint inhibitors simultaneously on several fronts and with all the artillery available to us that we hope to shed light on the path to resolve this major issue. The awaited inclusion of a first patient in the clinical trial is most certainly a key milestone in the progression of our endeavour", said Fabrice BARLESI, Coordinator of The Pioneer Project, Professor at Aix-Marseille University, Head of the 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 the French immunology cluster Marseille Immunopôle. "I would like to emphasize the incredible act of altruism of our patients, especially given that only an estimated 50% of those that enter the biomarker program will benefit from the combination treatments offered in The Pioneer Project's clinical trial. We are grateful for the commitment of our patients which today has taken us a major step ahead in the advancement of this study".

"The Pioneer Project embodies an original approach to clinical research in immuno-oncology: it is to my knowledge the very first study that addresses resistance to immunotherapy from an agnostic perspective, searching for predictive biomarkers from the start and throughout treatment with anti-PD-1(L1) immune checkpoint inhibitors, and browses through different combination options to overcome resistance. Our expectations are obviously very high, we are aiming for life-changing solutions for our patients" reminded Solange PETERS, President-elect of the European Society for Medical Oncology (ESMO), Head of the Medical Oncology Service at the Vaud University Hospital Center in Lausanne, Switzerland, and member of The Pioneer Project's SAB.

THE PIONEER PROJECT RHU

The Pioneer Project is a 5-year research project that takes up the main current challenge of Immuno-Oncology (IO): resistances to PD1(L1) ICIs.

On the initiative of Marseille Immunopôle (MI), Aix-Marseille University (AMU), Inserm, CNRS, 4 research & technology centers (CIML, CRCM, CIPHE, MImAbs), Assistance Publique-Hôpitaux de Marseille (AP-HM), the Paoli-Calmettes Institute, the Léon-Bérard Center, Toulouse Oncopole, ImCheck Therapeutics, the two French leaders in IO, Innate Pharma (therapeutics) and HalioDx (diagnostics) and one of the worldwide leaders in the field, the biopharmaceutical group AstraZeneca, have joined forces to better understand, predict and overcome these resistances in non-small-cell lung cancer, the deadliest of all cancers worldwide.

Winner of the 3rd University-Hospital Research in Health call for projects in the "Investments for the Future program", the Pioneer Project 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 MI. The project gathers over 100 scientists across 3 different countries, 8 research labs, and 11 hospitals, all committed to the scientific, medical and human adventure that it represents. Today, the project has recruited 86 patients to its biomarker program and one patient to the Pioneer clinical trial.

More information: <https://marseille-immunopole.org/en/the-pioneer-project/>





THE PIONEER COLLECTIVE

Aix-Marseille Université (RHU coordinator)

Aix-Marseille Université (AMU) is the largest French-speaking university in the world, hosting 78,000 students and nearly 8,000 staff. The university owns its architectural heritage. It has 5 large campuses meeting international standards and is spread over 9 major cities in 4 French departments.

Its University Foundation A*Midex, which supports the IDEX, contributes to the development of a multidisciplinary and interdisciplinary centre of world-class higher education and research. Known as an "intensive research university", the university boasts 120 research structures linked to the major national organizations.

AMU places interdisciplinarity at the heart of its strategy and training program. It has set up Interdisciplinary and Intersectoral Research Poles (PR2I), Territorial Innovation Poles (PIT), and access for economic actors to labelled technological platforms. The Aix-Marseille City of Innovation and Knowledge (CISAM) and 13 institutes strengthen the ties between research and education.

A responsible and committed university, Aix-Marseille Université encourages the values of living together in harmony and makes its anti-discrimination and CSR policy a priority – something for which it has been distinguished in international rankings.

Widely open to the world since its creation (10,000 international students and more than 40 diplomas in international partnership), the university has been awarded the European Commission's call for projects to build "CIVIS, a European Civic University" with 7 European partners, contributing to the major societal challenges facing Africa and the Mediterranean in particular.

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Assistance Publique-Hôpitaux de Marseille (clinical trial sponsor)

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 specialties, 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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Inserm

Founded in 1964, Inserm is a public scientific and technological institute which operates under the joint authority of the French Ministries of Health and Research. The institute is dedicated to biomedical research and human health, and is involved in the entire range of activities from the laboratory to the patient’s bedside. It also partners with the most prestigious research institutions in the world that are committed to scientific challenges and progress in these fields.

www.inserm.fr
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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 1,100 research and service units. With 22 Nobel laureates and 13 Fields prize winners, CNRS has a long tradition of excellence.

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Marseille Immunopole (project initiator)

The French immunology cluster is exclusively dedicated to the research and development of the two weapons poised to revolutionize the treatment of cancer and inflammatory diseases: immunotherapy antibodies and cell therapies. At the crossroads of talents, technologies and application fields, more than 2,000 researchers, clinicians, engineers and industrials are working together to accelerate the development and facilitate patients’ access to these innovations and position the metropolis at the heart of global competition.

MI brings together a unique continuum of excellence ranging from targets discovery to the clinical development of drug candidates: Aix-Marseille University (AMU), CNRS, Inserm, 10 research & technology centers, 3 hospitals of **Assistance Publique-Hôpitaux de Marseille (AP-HM)**, the **Paoli-Calmettes Institute**, Eurobiomed, biotechs and industrials, first and foremost, the French leaders of immuno-oncology Innate Pharma and HalioDx.

Supported by the public authorities and innovation actors of the territory, the Departmental Committee of the French League against Cancer, the Public Investment Bank and the Commissariat General for Investment, MI is part of the 34 projects of the industry for the future program of the French Government. The collaborative R&D projects of the cluster are led by MI-FHU, a University-





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Hospital Federation labelled by the French National Alliance for Life and Health Sciences (AVIESAN). The headquarters of MI are located at the Timone Hospital (AP-HM).

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Paoli-Calmettes Institute

Certified by the French National Authority for Health (HAS) and member of the French Federation of Comprehensive Cancer Centers UNICANCER, the Paoli-Calmettes Institute (IPC) brings together 1,800 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 2018 alone, the IPC carried out over 101,200 medical consultations and received over 11,080 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 IPC is entitled to receiving donations and legacies.

www.institutpaolicalmettes.fr

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Léon Bérard Center

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 37,000 patients every year in hospitalization, consultation or for an examination and 11,000 new cancer cases 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...).

1,800 people (including 200 physicians, 500 researchers, 600 careers) 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 Oncopole

The IUCT 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 specialties: 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 & 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 in the field. 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 Dr. Philippe Pierre, it consists of 16 research teams and a staff of more than 200 persons.

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CRCM

Created in 2008, the Marseille Cancer Research Center (CRCM) includes the four major stakeholders in research in South Region Provence-Alpes-Côte d'Azur: Inserm, CNRS, Aix-Marseille University and the Paoli-Calmettes Institute. With 400 staff members divided into 19 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 for breast & pancreatic cancers and hematologic malignancies.

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

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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-Ilkirsch 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.



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MI-mAbs

MI-mAbs is the French demonstrator of immunotherapy antibodies. By converting the most promising targets from academia, start-ups and industry into drug candidates and developing cutting-edge immuno-technologies, **it** allows research institutions, public technology transfer offices and biotech companies to de-risk the development of next generation immunotherapies against cancer and inflammatory diseases, keeping one step ahead of the competition.

Located in the historical birthplace of Marseille Immunopôle (MI), the **MI-mAbs**' building homes a fully integrated suite of platforms covering all steps leading to preclinical proof-of-concept. All R&D projects are managed in an industrial mindset by a multi-disciplinary team of experts specifically dedicated to antibody engineering, biochemistry, immunohistochemistry, bioproduction and immunopharmacology. **MI-mAbs** has also established and continues to set up strategic scientific and technological partnerships both with academia and industry, notably with CIPHE, the IPC and the CRCM.

Winner of the 2011 "Investments for the Future" in the "pre-industrial demonstrators" category, MI-mAbs was founded by Aix-Marseille University and its subsidiary Protisvalor subsidiary, the CNRS, Inserm, the Paoli-Calmettes Institute, the French leader of immuno-oncology Innate Pharma and Sanofi, one of the world leaders in healthcare. MI-mAbs is a founding member of the French immunology cluster MI.

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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. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide.

In France, AstraZeneca currently has more than 150 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 (pediatric oncology) and MultiSarc (sarcoma).



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Innate Pharma

Innate Pharma S.A. is a commercial stage oncology-focused biotech company dedicated to improving treatment and clinical outcomes for patients through therapeutic antibodies that harness the immune system to fight cancer.

Innate Pharma's commercial-stage product, Lumoxiti, in-licensed from AstraZeneca in the US, EU and Switzerland, was approved by the FDA in September 2018. Lumoxiti is a first-in class specialty oncology product for hairy cell leukemia. Innate Pharma's broad pipeline of antibodies includes several potentially first-in-class clinical and preclinical candidates in cancers with high unmet medical need.

Innate has been a pioneer in the understanding of natural killer cell biology and has expanded its expertise in the tumor microenvironment and tumor-antigens, as well as antibody engineering. This innovative approach has resulted in a diversified proprietary portfolio and major alliances with leaders in the biopharmaceutical industry including Bristol-Myers Squibb Novo Nordisk A/S, Sanofi, and a multi-products collaboration with AstraZeneca.

Based in Marseille, France, Innate Pharma is listed on Euronext Paris and Nasdaq in the US.

Learn more about Innate Pharma at 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 sophisticated algorithm and 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. HaliuDx collaborates with renowned international clinical groups to support clinical utility and ensure rigorous performance validation of its assays in selected cancer indications.

HaliuDx has an experienced team of more than 165 employees, CLIA-certified laboratories and compliant facilities in Europe and in the US to develop, manufacture, register and market in vitro diagnostic (IVD) products. HaliuDx executes biomarker studies and companion diagnostic assay development in conformity with regulations and in partnership with biopharmaceutical companies. Based in Marseille, France and Richmond, Virginia, USA, the company has co-founded the French immunology cluster Marseille Immunopôle (MI).

For more information: www.haliudx.com, www.immunoscore-colon.com, @HaliuDx
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ImCheck Therapeutics

ImCheck Therapeutics is designing and developing a new generation of immunotherapy antibodies positioned at the crossroads of two high-potential immunological fields: $\gamma\delta$ T cells and an original super-family of immunomodulators, butyrophilins.

Due to their mechanism of action, and notably their ability to simultaneously modulate innate and adaptive immunity, ImCheck's "first-in-class" antibodies may be able to overcome resistance to the first-generation of immune checkpoint inhibitors and to treat other serious, invalidating pathologies such as autoimmune diseases.

Starting in 2020, the company's first drug candidate, an anti-BTN3 antibody, should begin phase I assessment in oncology.

Co-founder of the Marseille Immunopole cluster, ImCheck benefits from support from Prof. Daniel Olive (INSERM, CNRS, Paoli-Calmettes Institute, Aix-Marseille University), a worldwide reference in $\gamma\delta$ T cells and butyrophilins, from the experience of an expert management team and from the commitment of leading European investors.

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National Research Agency (ANR)

The French National Research Agency (ANR) is the funding agency for project-based research in France. A public body under the authority of the French Ministry for Research, the agency's mission is to fund and promote basic and applied research, technical innovation and technology transfer, as well as partnerships between research teams in the public and private sectors, on national, European and international levels.





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ANR is also the main operator of Investments for the Future programs (PIA 1, 2 and 3) in the field of higher education and research for which it oversees project selection, funding and monitoring. ANR is ISO 9001 certified for all its processes associated with “project selection”.

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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