

Triple-negative breast cancer

First patients included in an innovative and promising clinical trial, the result of 15 years of research at Institut Curie

Triple-negative breast cancers represent about 15% of cases, affect younger women more and remain difficult to treat. The new "Skyline" clinical trial, which has just opened as part of the RHU CASSIOPEIA Future Investment Program at Institut Curie, the 1st European center for breast cancer management, has a double objective: to evaluate the effectiveness of a new combination of two immunotherapies in combination with chemotherapy in women with triple-negative breast cancer and to better visualize the cancer and its possible metastases thanks to innovative imaging used for the first time in France. The first patients have just been included in this innovative and promising clinical study, co-developed by clinicians and researchers, which is part of the IHU project "Institute of Women's Cancers" founded by Institut Curie with PSL University and Inserm.

Called Skyline, this study will include 160 women with triple-negative breast cancer: 80 in the early phase (without metastases) and 80 being in a metastatic situation.

The diagnostic component uses an **innovative and unprecedented method in France: that of whole-body PET-scan imaging with a new radiotracer FAPI** (detecting cancer-associated fibroblasts overexpressing the FAP protein). All patients in the study will benefit from this new type of imaging examination for the detection and characterization of their disease.

"We hope that this new diagnostic tool will show a higher sensitivity than the classic PET scan and will make it possible to detect the presence of metastases and to more accurately assess the size of the tumor" emphasizes Dr. Fatima Mechta-Grigoriou, group leader of the "Stress and Cancer" team at Institut Curie and coordinator of the RHU CASSIOPEIA¹. FAPI is a radiotracer that detects a particular population of cells, FAP+ fibroblasts and very abundant and aggressive tumors that are involved in metastatic spread and resistance to immunotherapies. Resulting from the research that we have been conducting for 15 years at Institut Curie on these FAP+ fibroblasts, this new radiotracer is being used for the first time in France".

"The hope is obviously to show that this new imaging examination, which is non-invasive, better specifies the tumor extension, or even that it is predictive of the effectiveness of treatments in patients with triple-negative breast cancer", specifies Prof. François-Clément Bidard, medical oncologist at Institut Curie and lead researcher of the Skyline clinical trial².

The therapeutic component of the study, conducted in partnership with Roche and the Roche Institute, will **combine two immunotherapies intended to "unlock" the immune system by targeting 2 different, but complementary, mechanisms**, PD-L1 and TIGIT, by atezolizumab and tiragolumab, in addition to chemotherapy and before surgery (for patients without metastases). This is a Phase II trial that will evaluate, in all the patients in the study, the anti-tumor activity of this new treatment (response and survival).

"By freeing certain capacities of the immune system, immunotherapy is a proven treatment for metastatic diseases. However, many patients do not get a lasting benefit from it because cancer plays on many mechanisms of action to escape treatment, explains Prof. François-Clément Bidard. By combining these two immunotherapies, we hope to remove the brakes on the immune system and promote its anti-tumor action to obtain a therapeutic response and better survival."

The trial, opened at Institut Curie on both hospital sites, is coordinated in Paris by Dr. Florence Coussy, and in Saint-Cloud by Dr. Diana Bello-Roufai, both doctors of the Department of Medical Oncology.

The first results of Skyline are expected in 3 years and the full results within 5 years.

¹ Director of Advanced Research at Inserm, she is also the Deputy Director of the Cancer, Heterogeneity, Instability and Plasticity Unit (Inserm U830 / Institut Curie)

²He is also head of the Circulating Cancer Biomarkers Translational Research Group at Institut Curie and Professor at the University of Versailles Saint-Quentin-en-Yvelines / Paris-Saclay University.

- This clinical trial is a key step of the University Hospital Research Program in health **RHU CASSIOPEIA** coordinated at Institut Curie by **Dr. Fatima Mechta-Grigoriou**.

Obtained in 2021, this RHU CASSIOPEIA (ANR-21-RHUS-0002) receives assistance from the French State managed by the National Research Agency (ANR) under the Future Investment Program (PIA) France 2030.

In collaboration between Institut Curie, Roche and the Roche Institute, the CASSIOPEIA project, both fundamental and clinical, aims to better understand triple-negative breast cancers, in particular their heterogeneity in order to identify patients who could develop **treatment resistance**.

The teams will evaluate from **new methods for detecting metastases and early recurrences**.

The ambition is to **develop new therapies** targeting fibroblasts involved in resistance to immunotherapies, a very abundant cell type in aggressive tumors, and yet not yet targeted therapeutically.

Triple-negative breast cancers

Among the 61,000 new cases of breast cancer diagnosed each year in France, **triple-negative breast cancer affects about 15% of patients**,

Not sensitive to hormonal treatments, nor to targeted anti-HER2 therapies, it is one of the most aggressive and most **difficult to treat**.

It is **often diagnosed in younger women** (40% are under the age of 40), with a higher risk of early metastatic recurrence and a shorter overall survival compared to other subtypes of breast cancer.

The standard treatment is currently chemotherapy that can be combined with immunotherapy and followed by surgery for patients in the early phase (without metastases).

The most important challenges are:

- detection and mapping of cancer and its metastases,
- better prediction of the effectiveness and resistance to immunotherapy,
- development of new therapeutic options.

Source INCa 2023

Fibroblasts at the heart of a new clinical trial

The team led by **Dr. Fatima Mechta-Grigoriou**¹ has been interested for 15 years in a specific cell population: fibroblasts, cells present throughout the body at the level of connective tissues.

Activated by signals emitted in particular by tumor cells, the "cancer-associated fibroblasts" (CAF) constitute a very abundant population at the heart of tumors, mixing with tumor cells. They are very heterogeneous, and some particular types of fibroblasts are an important driver in the development of the disease, for example by promoting the spread of metastases and resistance to immunotherapies. Understanding the role and evolution of CAF during the disease and the specific targeting of deleterious fibroblasts is therefore essential to find new and more effective therapeutic approaches against cancers.

"Our work has shown that certain fibroblasts interact with immune cells and inhibit their anti-tumor action. In this case, the immune system no longer works and immunotherapy can no longer be effective," explains Dr. Fatima Mechta-Grigoriou.

The accumulation of these CAFs leads to a cascade of reactions which results in the inhibition of the anti-tumor activity of the immune system, and is associated with resistance in patients to antibodies which target the PD1 /PD-L1 signaling pathway, widely used in immunotherapy. These molecules, responsible for stimulating the immune system to attack cancer cells, are blocked by these CAFs.

"What is particularly gratifying is that thanks to work involving interdisciplinary teams of doctors, biologists, bioinformaticians and mathematicians, on complex issues, we have managed to obtain a result that is clinically adaptable, with, we hope, a real benefit for patients" concludes Dr. Fatima Mechta-Grigoriou.

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