Radiotherapy, immunotherapy and DNA repair inhibitors: a winning combination towards the oncology of the future

The Institut Curie and Onxeo join forces in this ambitious project that will benefit cancer patients

Paris (France), Copenhagen (Denmark), January 31, 2017 – 08:30 am CET - Onxeo S.A. (Euronext Paris, Nasdaq Copenhagen: ONXEO), a biopharmaceutical company specializing in the development of innovative drugs for the treatment of orphan diseases, in particular in oncology, and the Institut Curie, a public-interest foundation heading one of Europe’s largest cancer research centers and two leading edge hospitals, join forces on World Cancer Day to launch a series of studies aimed at investigating the benefits of combining radiotherapy, DNA repair inhibitors and immunotherapy. This highly innovative combination would make it possible to reverse the disease in patients suffering from drug-resistant cancers.

As the birthplace of radiotherapy and the first French institute to build a large cancer immunotherapy center, the Institut Curie is naturally investing in this new and particularly promising field of clinical research.

In 2016, Onxeo, a French biopharmaceutical company specializing in the research and development of new treatments for orphan cancers, acquired AsiDNA™, a signal-interfering, DNA-repair-pathway inhibitor based on the DBait technology, which was notably discovered by the Institut Curie.

Both organizations are strengthening their partnership today to carry out an ambitious project.

A number of ongoing studies (more than 2001) that combine radiotherapy and immunotherapy are currently evaluating the effectiveness of this combination in the treatment of various metastatic or advanced cancers such as lung, esophagus, brain and prostate cancers, as well as melanoma, leukemia and sarcoma. As an example, recent trials have demonstrated the benefits of combining radiotherapy with ipilimumab (PD1-targeted immunotherapy) in metastatic melanoma: Increased survival and complete responses were observed in patients who received this double treatment.

Today the Institut Curie wants to add a new dimension to Marie Curie's most valuable legacy: radiotherapy. The institute located in Orsay specializes in the development of radiotherapy with the aim of developing new and particularly innovative combinations with immunotherapy.

Immunotherapy is undeniably a new weapon of choice against cancer. However, despite impressive results against some tumors, 80% of patients do not respond to these new therapeutic strategies, the most advanced of which are PD1 and PDL1 inhibitors.

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“Patients for whom new immunotherapies are ineffective generally suffer from types of cancer that have low-level DNA mutations and do not produce neo-epitopes. These small, cancer-specific molecules, which carry the mutation of a gene specific to the tumor cell, set the immune system on high alert and propel it to track down the dangerous cells,” explained Sebastian Amigorena, Director of the Immunotherapy Center at the Institut Curie.

The limitations in the efficiency of the new immunotherapies seem related to DNA alterations and, most likely, to the tumor’s capacity to repair its lesions, even if only in a residual way. Marie Dutreix, Research Director at the Institut Curie (Orsay site), is a renowned specialist in DNA repair mechanisms and the researcher behind a new class of very promising products, including the Dbait agents, which boost the effect of genotoxic treatments such as radiotherapy by diverting the enzymes meant to repair the DNA of cancer cells from their target, among other ways.

The combination of radiotherapy and Dbait agents has already shown very promising results in humans. The DRIM clinical study, performed in patients with skin metastases from melanoma, demonstrated that AsiDNA™ (the clinical form of Dbait) was well tolerated by patients when administered locally, with complete response rates (disappearance of tumor nodules) 4 times higher than those observed with radiotherapy alone.

Radiotherapy, DNA repair inhibitors and immunotherapy may become the winning combination
With Onxeo’s team, doctors and researchers from the Institut Curie will combine their expertise to evaluate the combination of immunotherapy with radiotherapy and AsiDNA.

Judith Greciet, CEO of Onxeo commented: “We are very pleased with this new program, which complements our ambitious development plan already in place and strengthens our collaboration with the Institut Curie. AsiDNA™ is a highly innovative new class of drugs that could ultimately result in a new cancer treatment paradigm.”

The combination of AsiDNA™ with radiotherapy and immunotherapy is a strong hope in the fight against cancer.
Concretely, this combination would work as a virtuous circle, each therapeutic approach contributing to the effectiveness of the others:

- Radiotherapy induces the death of tumor cells, which stimulates the expression of inflammatory response genes and, therefore, the immune system response;
- AsiDNA™ aims to amplify the effects of radiotherapy by preventing damaged tumor cells from repairing their DNA. It therefore increases the effectiveness of radiotherapy and the “immunogenic death of tumor cells”;
- Immunotherapy increases the ability of the immune system to recognize and destroy tumor cells.

Clinical trials combining radiotherapy and immunotherapy have already demonstrated the efficacy of this combination. This new, triple combination could help reach a new stage in the fight against cancer.

The Institut Curie’s research teams working on DNA repair and immuno-oncology enjoy a worldwide recognition. As for Onxeo, the company specializes in the development of drugs, with a proven know-how that has helped the company to market 3 products already.

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2 In December 2016, Dr. Marie Dutreix received the prestigious Guy Lazorthes Award from the French Academy of Sciences for her highly innovative work on the DNA repair mechanism of cancel cells.

2 Le Tourneau et al. 2016; First-in-human phase I study of the DNA-repair inhibitor DT01 in combination with radiotherapy in patients with skin metastases from melanoma; British Journal of Cancer 114, 1199-1205
In addition, to boost the development of and research on this innovative therapeutic combination, the Institut Curie will welcome a renowned addition: Professor Head of department of Radiation Oncology at the Radboud University Medical Center in Nijmegen (Netherlands) and Professor at Radboud University. He will head the Department of Radiotherapy at the Institut Curie, starting from March 2017, and will bring his preclinical and clinical expertise to this project in order to validate this new therapeutic approach, for the benefit of patients.

“The combination of AsiDNA with radiotherapy and immunotherapy could be a groundbreaking innovation with a great potential for development,” he concludes.

For more information

**Radiation therapy** is a major asset against cancer: About two-thirds of patients receive this treatment, which has been shown to be effective against localized tumors while showing good tolerance. For 20 years, the techniques have evolved considerably: They have adapted to the characteristics of the tumor and reduced the side effects. The combination of radiotherapy and chemotherapy drugs has further improved its effectiveness. However, these improvements do not make it possible to defeat all tumors.

**Immunotherapy**, which involves stimulating the body’s natural defenses to destroy cancer cells, is a major hope for people affected by cancer. Dramatic progress in recent years has completely changed the situation, especially for patients with advanced cancers. Building on the rise of immunotherapy, the Institut Curie opens this year a Center for Cancer Immunotherapy with the aim of bringing researchers, doctors and patients together in one place to facilitate interactions and accelerate the shift from basic research to medicine.

**AsiDNA™** is an inhibitor of tumor DNA repair with an original mechanism of action. It simulates the signals sent by damaged DNA from tumor cells to recruit restorative enzymes. These enzymes then go to AsiDNA™ instead of repairing the DNA of the tumor cells, which, continuing to replicate with damaged DNA, die. AsiDNA™ and its unique mechanism of action have been developed by four centers of excellence from the French public research, led by the Institut Curie. It represents a potential new treatment option for patients suffering from various types of cancer.

**About Institut Curie**

A leading player in the fight against cancer, **Institut Curie** brings together an internationally-renowned research centre and an advanced hospital group that provides care for all types of cancer – including the rarest forms. Founded in 1909 by Nobel laureate Marie Curie, Institut Curie comprises three sites (Paris, Saint-Cloud and Orsay), where more than 3,300 members of staff are dedicated to achieving three objectives: hospital care; scientific research; and the sharing of knowledge and the preserving of legacy.

As a private charitable foundation since 1921 that is recognised as serving the public interest, Institut Curie is supported by donations and grants. This support is used to fund discoveries that will improve treatment and the quality of life of cancer patients.

For more information: [www.curie.fr/en](http://www.curie.fr/en)

**About Onxeo**

Onxeo is a biotechnology company developing innovative drugs for the treatment of orphan diseases in oncology, driven by high therapeutic demand in one of the fastest growing segments of the pharmaceutical industry. Onxeo’s objective is to become a major international player in the field of rare cancers. Its growth strategy is founded on the development of innovative, effective, and safe drugs based on breakthrough technologies that can make a real difference in the treatment of orphan oncology diseases and considerably improve the quality of life of patients affected by rare and aggressive cancers. Onxeo’s comprehensive portfolio features a broad orphan oncology pipeline, with four independent programs in various stages of clinical development, including Beleodaq®, Onxeo’s first product approved in the United States in an orphan cancer indication. The Company is headquartered in Paris, France and has approximately 50 employees. Onxeo is listed on Euronext in Paris, France (Ticker: ONXEO, ISIN Code: FR0010095596) and Nasdaq Copenhagen, Denmark (Ticker: ONXEO).

Pour plus d’information : [www.onxeo.com](http://www.onxeo.com).
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