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PRESS RELEASE

Human papillomavirus (HPV)-induced cancers:

First patient enrolled in Phase I/IIa clinical trial for Lenti-HPV-07, the TheraVectys' therapeutic vaccine candidate against oropharyngeal and cervical cancers

TheraVectys, a biotechnology company that designs and develops lentiviral vector-based vaccines and immunotherapies against infectious agents and cancers, announces that the first patient has been enrolled in the Phase I/IIa clinical trial evaluating the onco-therapeutic vaccine Lenti-HPV-07 for the treatment of human papillomavirus (HPV)-induced cancers.

This study will include 36 patients in a dose-escalation protocol conducted at several cancer centers in the United States. Selection and inclusion of these patients are already underway.

The Lenti-HPV-07 vaccine is based on the lentiviral vector technology platform developed by **Pasteur-TheraVectys Joint Laboratory and pioneered by TheraVectysfor for nearly 20 years.** The highly promising preclinical studies results on the Lenti-HPV-07 vaccine candidate, published in September 2023 in **EMBO Molecular Medicine** (1) and in June 2024 in **NPJ Vaccines** (2), showed that after a single intramuscular injection the vaccine was able to induce a strong cellular immune response against the E6 and E7 antigens of HPV16 and HPV18, resulting in:

- complete elimination of HPV-induced tumors in 100% of individuals, regardless of tumor size,
- a very long-lasting immune memory, notably based on anti-tumor cytotoxic $CD8^+$ T cells, essential for avoiding relapses, which are responsible for a large proportion of deaths,
- profound remodeling of the tumor microenvironment,
- elimination of metastases in 100% of individuals, and
- a strong synergy of Lenti-HPV-07, even at a sub-optimal dose, with treatments such as anti-PD1[1] antibodies.

Aims and methodology of the human trial

The open-label Phase I/IIa trial will evaluate the safety of ascending doses of Lenti-HPV-07, determine its immunogenicity profile and assess the preliminary efficacy through the Objective Response Rate. It will include two groups of patients with oropharyngeal or cervical cancers induced by HPV-16 or HPV-18, all of whom will be clinically and immunologically followed for one year. Group A will consist of patients with recurrent/metastatic cancers who have not responded to multiple lines of treatment, including immunotherapies. These patients will receive two intramuscular injections of Lenti-HPV-07, one month apart. Group B will be composed of patients with newly diagnosed, treatment-naïve, locally advanced cancers. Patients in Group B will receive a single intramuscular injection of Lenti-HPV-07.

[1] Immune checkpoint inhibitors; PD1 = programmed cell death protein-1

The trial comprises 2 parts: a dose escalation and dose expansion.
In the dose escalation portion participants are enrolled successively to receive increasing doses of Lenti-HPV-07. Safety will be carefully monitored after each dose and before proceeding to enrolment at a higher dose. Enrolment and dose escalation in each arm A and B will be conducted independently. In each arm, when 18 participants will have received Lenti-HPV-07 treatment in the dose-escalation portion and the safety results will be satisfying, a dose-expansion portion of the trial will be open to treat 18 additional patients at the Optimal Biological Dose**. In total, 72 patients with HPV$^+$ cancer will be enrolled in this Phase I/IIa clinical trial.**

In terms of safety, TheraVectys has already completed a Phase I clinical trial on a therapeutic HIV-1 vaccine based on an integrative lentiviral vector. Over a 5-year follow-up, this clinical trial revealed no notable side effects or genotoxicity. The ongoing Lenti-HPV-07 clinical trial uses a non-integrative lentiviral vector, which reinforces the safety of the approach.

It should be noted that since group B patients are newly diagnosed and untreated, their immune systems will not have been affected by other chemo- or radiotherapy treatments. These patients will receive standard care, often including anti-PD1 treatments, one month after treatment with Lenti-HPV-07. TheraVectys has shown in animal models that the Lenti-HPV-07 vaccine acts synergistically with treatments such as anti-PD1, increasing the efficacy of anti-PD1 immunotherapy alone by a factor of 4 (1, 2).

Professor Christian Bréchot, Medical Director of TheraVectys commented: "*The inclusion of the first patient in the Phase I/IIa trial represents a key milestone for TheraVectys. It is the achievement of more than 2.5 years of preparation, from first interaction with the FDA, production of the vaccine, performance of the preclinical studies, review and approval by the regulatory authorities till sites preparation. The careful selection of adequate partners and the development of a cooperative relationship have been key in successfully building the project.*"

Pierre Charneau, head of the Pasteur-TheraVectys Joint Laboratory and founder of TheraVectys, said*: "With the launch of this study, we are proud to bring our product to a new phase of its development. We expect the preliminary results on safety and immunogenicity a couple of months after all patients in one group will have received their last injection."*

HPV causes almost all cervical cancers, as well as many oropharyngeal and anogenital cancers. The preventive HPV vaccines currently available essentially induce HPV-neutralizing antibodies and thus prevent infection, but have no effect on chronic HPV infections or established tumors.

In comparison to Lenti-HPV-07, the immunotherapeutic potential of mRNA-based vaccine technology has only been shown to be effective against very small HPV-related tumors, with early relapse in almost 50% of treated animals (3). In contrast, in the preclinical study conducted by Pasteur-TheraVectys Joint Laboratory, Lenti-HPV-07 immunotherapy was active against large tumors, which are notoriously more difficult to control, demonstrating the superior efficacy of the lentiviral vector-based vaccine platform.

A recent publication of a cross-sectional comparison of the most relevant vaccine strategies tested to date in preclinical anti-HPV immuno-oncotherapy showed that lentiviral vector-based approaches were the most effective at eliminating tumors, while providing the longest-lasting memory (4).

About lentiviral vector technology

TheraVectys is Institut Pasteur's exclusive licensee for all human and animal vaccine applications of lentiviral vectors worldwide. Thanks to its interaction with dendritic cells, this

technology stimulates the body's natural immune defenses, particularly T cells, more effectively than other vaccine strategies.
The technology is based on the natural attraction of lentiviral vectors for dendritic cells and on their ability to induce directly in these cells a sufficiently long-lasting and highly effective endogenous antigenic presentation of the antigens encoded by the vector. Dendritic cells programmed in this way play a key and unique role in the development of T cell responses, the main effectors against tumor cells.

About TheraVectys

TheraVectys Biotech, specialist in immunotherapy, is based on more than 20 years of research on lentiviral vectors and brings an innovative technology to the field of vaccinology.
Research is carried out in the Pasteur-TheraVectys Joint Laboratory under the scientific direction of **Pierre CHARNEAU**, inventor and pioneer of lentiviral technology, and **Laleh MAJLESSI**, Director of Research in Immunology.
Christian BRECHOT, the former General Director of Institut Pasteur and INSERM, is the Medical Director of TheraVectys.
Estelle BESSON, Director of Clinical Operations, coordinated and supervised the preparatory work required to obtain FDA approval, including production of the vaccine, regulatory preclinical studies, preparation of the IND filing, selection and implementation of the clinical trial in collaboration with TheraVectys' partners.

The biotech's work is based on a proprietary platform for delivering cytotoxic T-cell vaccines in response to critical unmet medical needs. The technology used is at a clinical stage.

TheraVectys' technology and its worldwide license area address a broad spectrum of infectious diseases, cancers and viral cancers, positioning it at the origin of a genuine revolution in the field of vaccination.
Our aim: To make profound improvements to global health.
Our approach: Strategic industrial partnerships to take our vaccine candidates from proof of concept to clinical trials and marketing.

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