

# AXICABTAGENE CILOLEUCEL

## GENE THERAPY FOR NON-HODGKIN LYMPHOMA



On Wednesday, October 18, 2017, the Food and Drug Administration (FDA) approved a second anti-cancer gene therapy.

This gene therapy is based on the genetic modification of a line of a patient's immune cells in order to make them competent against the tumour.

The new treatment, employing Axicabtagene ciloleucel, is marketed under the trademark of Yescarta®, and manufactured by Kite Pharma. It was approved for the treatment of patients with refracting or relapsing non-Hodgkin B-cell lymphoma who previously had not responded to chemotherapy. [In the United States, more than 72,000 new cases of non-Hodgkin B-cell lymphoma are diagnosed each year, with a mortality of more than 20,000 people. In Spain, between 30 and 70 new cases per million inhabitants are diagnosed annually].

Axicabtagene ciloleucel turns a class of the patient's immune cells into veritable "living drugs" that destroy the tumour cells with extraordinary efficiency. This technology fits into the so-called "immunotherapy"<sup>(1)</sup>.

In the United States it is estimated that more than 3,500 patients are candidates for treatment using Axicabtagene ciloleucel (Yescarta®).

Axicabtagene ciloleucel is prepared to suit each individual. The cost of the treatment is \$373,000, and it is administered as a single intravenous infusion.

This treatment was developed within the scope of the US National Cancer Institute by Steven Rosenberg's team <sup>(2)</sup>. The final stages of research were financed by Kite Pharma, which, in return, received the royalties for its commercialization. The expectation generated by this gene therapy, developed by Kite Pharma, attracted the interest of multinational companies in this pharmaceutical laboratory. Finally, Gilead Sciences acquired the shares of Kite Pharma in August, 2017, at a cost of 11.9 billion dollars. The shares of Kite Pharma soared from an initial value of \$17, to \$67 quickly, recapitalizing up to \$170 million.

Kite Pharma was created by Arie Bellgedrum, former disciple, and later colleague, of Steven Rosenberg. Kite Pharma sponsored the National Cancer Institute's research, in return for the patent rights on this gene therapy.

This scenario raises two discrepant positions. On one hand, there are those who support public investment for private research arguing that, in this way, innovative treatments and vanguard therapies can be achieved. On the other hand, critics argue that taxpayers end up paying twice for the same drug; first, financing its research, carried out within the context of a public institution, and again acquiring the drug from a private company which also enjoys the full freedom, available in the United States, to set the market price of the therapy.

The National Institute of Health, a sister agency of the National Cancer Institute, has come to around 400 research agreements with pharmaceutical companies, granting hundreds of commercial licenses to private pharmaceutical companies.

These agreements take advantage of legislation approved by the US Congress three decades ago. This legislation has led to important advances: from the anti-cancer drug Paclitaxel <sup>(3)</sup>, to the anti-retroviral drug Prezista (Darunavir <sup>(4)</sup>), as well as two vaccines for cervical cancer, and a widely used test for the detection of HIV infection.

Yescarta® (Axicabtagene ciloleucel, or KTE-C19, to give its pre-clinical name) on its way to becoming one of the most lucrative drugs derived from government research, or, more precisely, from the government funding of private research, or from private financial support for government research.

According to Steven Rosenberg, forty-two-year-old director of the National Cancer Institute, these collaboration agreements between public agencies and private companies are essential for the development of innovative and complex therapeutic strategies.

As happens so many times, these important agreements arise from a personal relationship, in this case between Steven Rosenberg and Ari Beldegrun, both of Jewish origin.

Ari Beldegrun, who studied in Israel, where he did his initial clinical training, joined as a fellow of Steven Rosenberg's working group at the National Cancer Institute in 1985.

After completing his post-doctoral fellowship, he began practising as a surgeon in Los Angeles, California. He co-founded the biotechnology company Agensys, later sold for \$500 million. He also participated in the creation of another company, Cougar Biotechnology, which developed an important drug for prostate cancer, Zytiga® (Abiraterone acetate <sup>(5)</sup>). Cougar Biotechnology was acquired by the multinational Johnson & Johnson for a billion dollars in May 2009. A month later, Ari Beldegrun founded the company Kite Pharma, focussing his research on anti-cancer immunotherapy.

During that same month of June, a contractor from Florida, Eric Karlson, suffering from a non-Hodgkin lymphoma, became the first patient treated with what would become KTE-C19 gene therapy. Even though his non-Hodgkin's lymphoma was terminal, the patient is still alive and without a trace of malignant B-cells even today (2018). The National Cancer Institute did not patent KTE-C19; instead, it reached an agreement with Kite Pharma, whereby the laboratory would complete pre-clinical research, and conduct a clinical trial prior to the request for authorization by the US Food and Drug Administration.

In 2009, some immunotherapies were not patented because it was considered very unlikely that they would become effective treatments.

One major problem with Axicabtagene ciloleucel (and with other gene therapies) is the side effects that sometimes compromise the survival of the patients. The most severe iatrogenic signs and symptoms include: high fever, hypotension and syncope, pulmonary congestion and severe neurological problems. This scenario, an undesired extension of the treatment's own pharmacological mechanism (massive destruction of the tumour tissue), may require the patient to be placed in Intensive Care. During the

pivotal study that led to the approval of this gene therapy, two patients died. The management of adverse reactions to gene therapy is complex.

Due to the risks associated with gene therapy, both Axicabtagene ciloleucel (Yescarta®) and the first recently commercialized gene therapy, Kimriah® (Tisagenlecleucel [6]), are being introduced into the pharmaceutical market very gradually. Their use, at present, is restricted to a very limited number of hospitals, and *only* in the United States.

In the case of Yescarta® (Axicabtagene ciloleucel), it can only be administered in 15 specialized medical centres, *all* in the United States. It is expected that at the end of 2018, the number of hospitals with teams trained specifically to manage this type of treatment will increase to seventy or ninety.

The pharmaceutical industry competes to develop new forms of immunotherapy. The first anti-cancer treatment based on the modification of the patient's T-cells to make them competent in the fight against the tumour, was authorized in August 2017, for acute lymphoblastic leukaemia. This first gene therapy was marketed as Kimriah® (Tisagenlecleucel) by the Swiss multinational, Novartis AG. The cost of treatment with Kimriah® is \$475,000. This laboratory assumes the cost of treatment if the patient's response does not meet expectations. In addition, Novartis AG hopes to expand the use of Kimriah® (Tisagenlecleucel) to other types of haematological cancers. The extension of these uses should result in a decrease in the price of the therapy.

For the time being, Kite Pharma also plans to apply for the authorization of Yescarta® (Axicabtagene ciloleucel) for non-Hodgkin's lymphoma in its early stages, but does not foresee a reduction the cost of its therapy.

Over the next few years, this anti-cancer immunotherapy will lead to a significant number of new gene therapies.

The Food and Drug Administration has approved this kind of therapy via accelerated authorization procedures <sup>(7)</sup> due to the urgent need for treatment for patients with terminal cancer.

Kite Pharma and Novartis AG aspire to develop gene therapies for solid tumours which represent approximately 90% of deaths due to cancer.

Before becoming known as Yescarta®, this gene therapy, developed in its final stages by Kite Pharma was known by other names, such as Axi-cel, Axicabtagene ciloleucel (which has ended up settling down); and KTE-C19 (pre-clinical designation).

The study that led to the approval of Yescarta® involved 111 patients in 22 hospitals; 101 patients received Yescarta®. All patients suffered from one of the following three diseases: B-cell lymphoma, mediastinal B-cell lymphoma, or transformed follicular lymphoma.

Initially, 54% achieved complete remissions, that is, their tumour "disappeared". Another 28% of patients showed partial remissions, meaning that the tumours had retracted, and their activity (determined by the activity of specific "markers") decreased. After 6 months of treatment, 80% of the 101 patients who received Axicabtagene ciloleucel were still alive.

After 8.7 months, 39% of the 101 patients still maintained the complete resolution; and 5% partial remissions.

The study was conducted in two North American hospitals: Dana-Farber Cancer Institute, and Brigham and Women's Cancer Center, both in Boston, Massachusetts. To get an idea of the situation, some patients joined the study from the hospices where they received only palliative care.

The treatment requires the removal of millions of T-cells from the patient. These cells are frozen and sent to the laboratory (Kite Pharma). There, they are genetically reprogrammed by "teaching" them to attack B cells that have become malignant ("non-Hodgkin B-cell lymphoma"). The genetically modified T-cells (designated as CAR-T, Chimeric Antigen Receptor-T-cells) are frozen again, forwarded to the hospital, where, once thawed, the patient receives a single infusion. The preparation times of this individualized therapy have been optimized up to 17 days. The reduction of this time interval is a priority because it is terminally ill.

The laboratory's T-cell processing centre (Kite Pharma), located in El Segundo, California, is adapted to prepare individualized treatments for 4,000 or 5,000 patients each year. Likewise, the laboratory plans to shortly apply for the authorization of Axicabtagene ciloleucel (Yescarta®) in the European Union.

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Zaragoza, May, 2, 2018

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