PRESS KIT

OPPOSITION AGAINST THE EUROPEAN PATENT COVERING KYMRIAH®
ANTI-CANCER TREATMENTS: MÉDECINS DU MONDE – DOCTORS OF THE WORLD OPPOSES KYMRIAH® PATENT

The next generation of gene therapies used for treating cancer are now available on the market - with the first two CAR-T cell therapies priced at 320,000 and 350,000 euros. As was the case with hepatitis C drugs, these exorbitant prices reveal yet again the extent of the financialisation of the pharmaceutical market that puts profit ahead of medical treatment.

Seeking to condemn the abuses associated with these prices, enable governments to negotiate lower prices or organise the use of similar treatments and ensure universal access to optimum medical care in sustainable health systems, Médecins du Monde – Doctors of the World (MdM) and Public Eye have decided to oppose the patent of one of these two anti-cancer therapies, Novartis' Kymriah®.

In August 2018, two CAR-T therapies received marketing authorisation for Europe – Novartis’ Kymriah® (tisagenlecleucel) and Gilead Sciences’ Yescarta® (axicabtagene ciloleucel). Used to treat blood cancers by genetically modifying patients’ T-lymphocyte cells to recognise and attack cancer cells, these gene therapies bring significant hope to cancer sufferers, their families and health professionals. Indeed, for patients with particular life-threatening lymphomas, available clinical studies show estimated one-year survival rates are 40% for Kymriah® and 60% for Yescarta®.

But, at 320,000 or 350,000 euros per patient, the price of hope and highly personalised approach offered by this innovative medical technology is exorbitant.

Such prices can be justified neither by costs of production, nor investments in research and development, as these are largely supported by US and European public funds. As the World Health Organization noted in a recent report on the cost of cancer drugs, they appear to reflect solely the commercial interests of the pharmaceutical industry.
“In 2014, the price of sofosbuvir, a drug used to treat hepatitis C that cost 41,000 euros per patient, forced countries to ration access for a certain number of patients,” recalls Philippe de Botton, President of Médecins du Monde. “As for the price of new anti-cancer drugs, and in particular CAR-T therapies, they take the price issue to a whole new level. How much longer is it going to take the government to review the criteria regarding access to anti-cancer drugs?”

Currently used to treat rare and very specific types of cancer, CAR-T therapies are undergoing clinical trials for a range of other indications. In the future, health systems may adopt this therapeutic approach more widely. However, at these price levels, they won’t be able to ensure universal access to optimum medical care without compromising their financial viability.

MdM has decided to denounce these extortionate prices by opposing the patent of one of these therapies, Kymriah®. Patents protecting these therapies prevent competition, which also allows companies to set exorbitant prices. By accepting these monopolies, countries agree to high prices without ever calling them into question.

“CAR-T therapy patents include modified cells from actual patients, and it’s these cells that are being sold at a cost of over 300,000 euros”, comments Olivier Maguet, head of the Drug Prices and Health System Mission at MdM, “It’s legitimate to query the status of CAR-T therapy. Is it a drug? A medical procedure? The implications in terms of patents, the rights of companies and governments regarding production of the drug, and therefore its price, are considerable. These are some of the issues we want to bring to the public debate.”

By opposing the patent, MdM is seeking to alert governments and civil society to the prices of these drugs and the threat they pose, now and in the future, to access to medical treatment – an initiative already undertaken on two previous occasions when the organisation opposed sofosbuvir’s patent.
WHAT ARE CAR-T THERAPIES?

CAR-T (Chimeric antigen receptor T cells) therapies are genetic therapies for the treatment of cancer. T lymphocytes are subtracted from a patient's blood and genetically modified to express a receptor capable of identifying and targeting specific cancer cells.

This is a new and extremely personalised approach to cancer treatment. Car-T cells are a source of much hope for patients, families and health professionals as a treatment of certain refractory or relapsed cancers of the blood. In clinical trials, the estimated one-year survival rate of patients with certain life-threatening lymphomas varies between 40% and 60% for the two CAR-T therapies already available in Europe.

This data is encouraging as there are no treatment alternatives for the population concerned. However, studies have raised some significant concerns notably about long-term effects and the serious side effects observed.

There are two CAR-T therapies available in Europe today, Kymriah® (tisagenlecleucel) by Novartis and Yescarta® (axicabtagene ciloleucel)* by Gilead Sciences.

Our patent opposition concerns Kymriah®.

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1 https://www.has-sante.fr/portail/jcms/c_2970845/fr/car-t-cells-des-medicaments-prometteurs-que-la-has-reevaluera-pour-en-confirmer-le-potentiel
2 Tisagenlecleucel and Axicabtagene ciloleucel are the international nonproprietary names (INN)
CAR T-CELL THERAPY

1. Get blood with T-cells from patient
2. Insert gene for CAR
3. Create CAR T-cells that react to cancer cells
4. Grow many CAR T-cells
5. Inject CAR T-cells into patient
6. CAR T-cells attack cancer cells

Chimeric antigen receptor (CAR)
WHAT IS KYMRIAH®? WHAT KIND OF CANCER DOES IT TREAT?

Kymriah® was developed by the University of Pennsylvania and the pharmaceutical firm Novartis. It is the first CAR-T therapy in the world to obtain marketing approval for its first indication, Acute Lymphoblastic Leukaemia (ALL). This approval was issued by the FDA (Food and Drug Administration) in the United States in August 2017. The therapy also received marketing approval from the European Medicines Agency in August 2018.

The drug is approved in two indications:

- The treatment of paediatric and young adults up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse after a transplant of haematopoietic stem cells or in second or later relapse;

- The treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy.

The other CAR-T therapy currently available, Yescarta®, is indicated in the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of therapy.

1 https://www.fda.gov/media/106989/download
HOW MANY PEOPLE ARE CONCERNED BY THESE TREATMENTS?

Both treatments concern specific and rare blood cancers. In France, 50 patients a year are thought to be concerned by Kymriah® for acute lymphoblastic leukaemia.1

As for lymphoma covered by Yescarta® and Kymriah®3, the target population in France is estimated at between 400 and 600 people. Although these therapies don’t concern many people at the moment, a number of CAR-T therapies are currently being developed to treat other forms of cancer, especially multiple myeloma, cancers of the uterus, lung cancers, etc. Consequently, and despite the many uncertainties, CAR-T therapies look set to play an increasingly important role in the treatment of cancers.

HOW MUCH DO KYMRIAH® AND CAR-T TREATMENT COST?

In the United States, Kymriah® was approved with a list price of $475,000 per patient in its first indication, acute lymphoblastic leukaemia. An outcome-based contract was added to this price, with payment due only if the patient responds to the therapy by the end of the first month. In its second indication concerning lymphoma, the therapy was put on the market at $373,000 with no outcome-based requirements. This price was indexed to that of Yescarta® which was also put on the market at $373,000 with no outcome-based requirements in the same indication.

In Europe, the two therapies received marketing approval at the same time. Prices vary between €320,000 and €350,000 per patient.

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2 https://www.has-sante.fr/portal/upload/docs/application/pdf/2018-12/yescarta_pic_avis3_ct17214.pdf
HOW ARE THESE HIGH PRICES JUSTIFIED?

The companies use a number of arguments to explain these prices.

• They claim that production costs are high because it is expensive to produce personalised therapies. Due to a lack of transparency, it is difficult to obtain a precise estimate of production costs, but several very different amounts have been affirmed. In 2012, Dr Carl June, one of the principal researchers in CAR-T at Pennsylvania University, told the New York Times that production would cost about $20,000 per patient.\(^1\)

In 2017, analysts estimated the costs of producing Kymriah\(^2\) to be $200,000. These vastly different estimates demonstrate the total lack of transparency surrounding the real costs of production, and a probable over-estimation to justify the price.

On the basis of discussions with a number of researchers working on the development of CAR-T therapies, we estimate the real cost of production to be between €20,000 and €60,000.

• The companies also claim to have made heavy investments in research & development.

In 2017, Novartis maintained that it had spent more than one billion US dollars putting Kymriah\(^3\) on the market. In 2019, this figure was up to US$1.6 billion.\(^4\)

However, according to the NGO Knowledge Ecology International (KEI), almost US$200 million of public money was invested in the development of CAR-Ts in the United States alone, especially during the first and riskiest phases.\(^5\)

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5. https://www.keionline.org/23838
KEI also reports that Carl June, having developed Kymriah® with Novartis, puts the cost of the clinical trials at about US$150,000 per patient. Yet the clinical trials on Kymriah® were conducted with a very small number of people: 167, of whom 115 received the therapy. On this basis, the cost of the clinical trials would be US$25 million at most, a far cry from the billions announced.

Again, a lack of transparency, this time with regard to research & development, prevents any reliable estimates being made of the real amounts spent on this technology and the proportion of public money invested in the research.

• The companies also justify their prices according to the economic and medical value of the treatment, using a system known as “value-based pricing.” This pricing strategy aims to link the price of the treatment to its therapeutic outcomes, and, by implication, the savings or wealth that it can produce for the health system and society. While real investments in R&D are being increasingly challenged as a justification for high prices, including by public decision-makers, this value-based pricing model is the new paradigm used by pharma-companies to justify their prices.

This medico-economic approach raises a number of questions. Firstly, given the lack of transparency, this approach is based entirely on data supplied by the manufacturers. Secondly, it normalises high prices, gives them a semblance of objectivity, but is in fact founded on a very individual approach and takes very little account of the economic and budgetary context of states and health systems. And last but not least, it puts a price on a patient’s life.
THE PRICE OF KYMRIAH®:
FINANCIALISATION OF THE PHARMACEUTICAL MARKET

In a recent report on the pricing of cancer medicines and the impact of these prices on access to care, the World Health Organization concluded that the costs of R&D and production seems to bear little or no relation to how pharmaceutical companies set the prices of cancer medicines. On the contrary, WHO notes that prices are set according to the commercial and financial objectives of pharma companies, with a focus on extracting the maximum amount that a countries and health systems are willing to pay.

For CAR-T therapies, this economic and financial approach would explain the high prices. In 2012, Emily Whitehead was cured by a CAR-T therapy invented by Dr Carl June. Emily Whitehead’s case marked the launch of research into this therapeutic approach. Just four years later, Nelsen Biomedical identified up to US$4 billion in funding deals for different CAR-T developments, some of which were between the University of Pennsylvania and Novartis for the development of Kymriah. In August 2017, Gilead Sciences bought out Kite-Pharma, a company at the cutting-edge of CAR-T development, for 12 billion dollars.

In January 2018, Celgene announced the acquisition of Juno Therapeutics for 9 billion dollars - both of these companies were spearheading genic therapies. A year later, Bristol-Myers Squibb (BMS) announced a £74 billion deal to buy out Celgene.

Financial investments in CAR-T therapies have now reached tens of billions of dollars - for a health technology that has only been around for 7 years. These are not investments in research & development; they are stock exchange transactions aimed at making large profits. Indeed, the prices of medicines in general, and the price of CAR-T therapies in particular, are major leverage for achieving the returns on investment sought.

1 https://www.nelsenbiomedical.com/market-reports/#car-t-deal-review/
3 https://www.celgene.com/newsroom/cellular-immunotherapies/celgene-corporation-to-acquire-juno-therapeutics-inc/
4 https://lexpansion.lexpress.fr/actualites/actualite-economique/rachat-de-la-biotech-celgene-par-bms-mega-fusion-a-74-milliards-de-dollars_2055780.html
IN WHAT WAY ARE THESE PRICES A THREAT FOR THE HEALTH SYSTEM?

In 2014, new hepatitis C therapies arrived in Europe at prices ranging from €40,000 to €50,000 for 12 weeks of treatment. Given these prices and the number of people concerned, countries have had to introduce the rationing of access to care, selecting patients according to their state of health. With these therapies, and in an unprecedented manner, price as a barrier to care has become a major issue, including in the wealthiest countries.

Similarly, the prices of cancer treatments are increasing constantly. Immunotherapies for cancer cost several tens of thousands of euros per year and per person. CAR-T therapies are on a whole other price scale, costing between €320,000 and €350,000 per person. And cancers concern many more people than hepatitis: almost 3.7 million cancers are diagnosed in Europe each year.

States and health systems have not been able to maintain universal access to treatment for hepatitis C. For how long will it be possible to ensure universal access to the best cancer treatment?

WHAT IS PATENT OPPOSITION?

The purpose of these many research deals and company buyouts is to develop CAR-T therapies and/or obtain patents.

A patent is a form of intellectual property right that protects a technical innovation. A patent guarantees its owner a complete monopoly for a maximum duration of 20 years. These monopolies, which prevent any form of competition, are what enable pharma companies to demand such high prices for medicines.

In the European Patent Convention, an invention must satisfy three patentability criteria:

- Novelty: an invention is considered new if it is not already known.
- The invention must involve an inventive step: the invention must not obviously derive from the prior state of the art.
- The invention must be considered “susceptible of industrial application”.

Patent opposition is an administrative proceeding which allows any person to challenge the validity of a patent with the office that delivered it, with a view to obtaining its annulment. A patent opposition can be based on the claim that one or several patentability conditions have not been met by the invention. In the case of medicines, patent oppositions can permit the production of generic versions or affordable copies.

Patent oppositions have been used on numerous occasions to defend access to medicines at affordable prices. Médecins du Monde – Doctors of the World (MdM) has already organised two patent oppositions against sofosbuvir, a treatment for hepatitis C. These two oppositions obliged Gilead Sciences to modify the patents on sofosbuvir and helped draw attention to the abuse of intellectual property, monopolies and pricing.
ON WHAT IS THE PATENT OPPOSITION TO KYMRIAH® BASED?

For Kymriah®, during the initial procedures for validating the first patent, the European Patent Office noted that certain claims did not involve an inventive step and were already known in the state of the art.

When the request was examined, the company amended its claims, strengthening its arguments concerning the inventive nature of the technology. They were then accepted by the European Patents Office.

However, it would appear that the inventive nature claims may still be considered abusive.

MdM is basing its opposition on this lack of an inventive step.

WHY IS MDM OPPOSING THE PATENT FOR KYMRIAH®?

MdM defends access to the best possible care for all provided by a sustainable healthcare system and so campaigns for access to quality treatments at reasonable prices. It is on these grounds that we are opposing the patent for Kymriah® today.

The excessively-high price of this medicine is a barrier to accessing care and a threat to the sustainability of health systems. By demonstrating the abusive nature of the patent on this CART therapy, MdM is seeking to provide states and payers with legal arguments for demanding lower prices.

This opposition is also another opportunity to demonstrate the non-compliance with patentability criteria and the abuse of monopolies. MdM has already demonstrated this with its patent opposition to sofosbuvir. We intend to do the same for cancer therapies. If monopolies permit companies to demand overly high prices for supposedly innovative medicines, we must challenge them. And the signatories to the European Patent Convention must require the European Patents Office to impose stricter compliance with patentability criteria.

Lastly, this patent opposition also seeks to challenge the notion of CART therapies as legal objects. Today, these therapies are considered medicines in Europe. Yet the procedure is managed essentially by hospitals and could therefore be considered a medical procedure. These two qualifications could have important consequences with regard to the reach of intellectual property rights - and therefore on the possibility for hospitals and treatment centres to produce their own copies of the CART therapies, publically and at a lower cost.
PRESS CONTACT