



CAR-T Cell Therapies: How much for survival?

ECL Access to Medicines Task Force

by Théau Brigand, Anna Prokupkova and Guy Muller

What are CAR-T Cell Therapies?

A T-cell, or T lymphocyte, plays a central role in the immune system. T-cells can be distinguished from other lymphocytes by the presence of a T-cell antigen receptor on the cell surface that is responsible for recognising fragments of foreign antigens. An antigen is a molecule capable of stimulating an immune response, and is often produced by cancer or virus-infected cells. Once a cancer cell is recognised, the T-cell destroys it. With CAR T-cell therapies, T-cells will be subtracted from patient's blood and genetically modified to express a Chimeric Antigen Receptor (CAR), an engineered receptor capable to target specific cancer cells. Indeed, once a CAR is able to target a specific kind of antigen and tumour, the CAR DNA can be engineered and transferred to the T-cell through a virus. The T-cell will then produce the antigen receptor by itself to target the tumour.

An old concept with brand new ambitions

The concept of CAR-T therapies is not new. The first CAR was generated in 1986, but research only advanced in 2012, following the case of Emily Whitehead. After unsuccessful treatments and chemotherapies to cure Acute Lymphoblastic Leukaemia (ALL), Emily Whitehead, a 6-year old child at the time, became the first paediatric patient to be treated, and cured, with the CAR-T therapy. Despite two adult patients who had already achieved complete remission with CAR-T therapies in 2010-2011, Emily Whitehead's case benefited from a high media coverage, and her remission helped energise a new line of research.

Since 2012, the number of publications and research on CAR-T grew exponentially, from 16 in 2012 to more than 391 in 2017.¹ Currently, there is more than 200 ongoing clinical trials on CAR-T therapies, primarily to cure haematological cancers (lymphoma, leukaemia and myeloma), but also solid tumours (e.g. lung cancer, breast cancer, cervical cancer etc.).² CAR-T technology could also be potentially effective against HIV.



In addition, the renewed interest stimulated public funding. According to the NGO Knowledge Ecology International (KEI), the US National Institute for Health (NIH) invested more than 200 million dollars in CAR-T R&D between 1993 and 2017.³ By March 2017, 91% of CAR-T trials had an academic sponsor.⁴ Similarly, CAR-T therapies stirred private funding and investors' interest. Since 2012, there has been an explosion of commercial activity and CAR-T deals. A review by Nelson Biomedical "found a diversity of deals done in this space over the past years. Included are strategic partnerships, acquisition and licensing deals done between CAR-T companies, Big Pharma, smaller organisations, and academic institutions from 2012 through August 2016. Collectively these deals are worth at least \$2 billion in disclosed upfront payments and \$4 billion in additional milestone, royalty and other payments."⁵ In August 2017, Gilead Sciences bought Kite Pharma, one of the leaders on CAR T-cell therapies, for \$11.9 billion. In January 2018, Celgene made a \$9 billion deal with the acquisition of Juno Therapeutics Inc., with both companies being very advanced on CAR T-cell therapies development.⁶

1 PubMed. <https://www.ncbi.nlm.nih.gov/pubmed>

2 Hartmann J., Schüßler-Lenz M., Bondanza A., et.al. *Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts*. EMBO Molecular Medicine. 2017;9(9):1183-1197.

3 *Federal funding to organizations for projects related to chimeric antigen receptors*. <https://www.keionline.org/23838>

4 De Wilde S., Guchelaar HJ., Zandvliet ML., et.al. *Understanding clinical development of chimeric antigen receptor T cell therapies*. *Cytotherapy*. 2017 Jun;19(6):703-709

5 *CAR-T Deal Review*. Nelson Biomedical Report. www.nelsenbiomedical.com/app/uploads/2016/09/NelsenBiomedical_CAR-T_Deal_Review-2016.pdf

6 *With \$9 Billion Juno Deal, Celgene Doubles Down on Cancer*. Bloomberg. www.bloomberg.com/news/articles/2018-01-22/celgene-to-buy-juno-for-9-billion-signaling-cancer-aspirations



Are CAR T-cell technologies worth it?

The US Food and Drug Administration (FDA) approvals of the first two CAR-T therapies were based on strong clinical benefits data, despite the fact that the trials included small number of young lower risk patients. Novartis' Kymriah® was approved for Relapsed/Refractory B-cell ALL in children and young adults. The phase II study submitted to the FDA showed 82% of patients infused with the treatment achieved complete remission. For Relapsed/Refractory Diffuse Large B-cell Lymphoma (DLBCL), at month 3, the complete remission rate was 32%.⁷ As for Gilead's Yescarta®, out of 101 infused patients with DLBCL and other B-cell lymphomas, 51% achieved complete remission.⁸ Other approvals are under review; other trials underway.

However, CAR T-cell therapies pose serious safety risks to patients. Kymriah® and Yescarta® have the capacity to cause adverse events and toxicities such as cytokine release syndrome and neurologic toxicity (e.g. delirium, expressive aphasia, seizure etc.). The antigens used in the current CAR-T therapies are not restricted to tumour cells and target healthy tissues as well. Therefore, 'on-target/off-tumour' toxicity occurs throughout the treatment. Although such toxicity can be manageable, it can be lethal in some cases.

Nevertheless, there exist no treatment alternatives for patients with ALL and DLBCL, and CAR T-cell therapies have generated tremendous excitement and hope among physicians and patients... but at what price?

⁷ Novartis presents results from first global registration trial of CTL019 in pediatric and young adult patients with r/r B-ALL. Novartis. <https://www.novartis.com/news/media-releases/novartis-presents-results-first-global-registration-trial-ctl019-pediatric-and>

⁸ Kite's Yescarta™ (Axicabtagene Ciloleucel) Becomes First CAR T Therapy Approved by the FDA. Gilead. <http://www.gilead.com/news/press-releases/2017/10/kites-yescarta-axicabtagene-ciloleucel-becomes-first-car-t-therapy-approved-by-the-fda-for-the-treatment-of-adult-patients-with-relapsed-or-refractory-large-bcell-lymphoma-after-two-or-more-lines-of-systemic-therapy>.

CAR-T therapies: the pricing issue!

Novartis' Kymriah® was approved by the FDA in August 2017 with a list price of \$475,000. The company introduced an outcomes-based contract, with a payment due only in case the patient responds to Kymriah by the end of the first month.⁹ However, CAR T-cell therapy is a living drug and a short-term response to the treatment is quite common. Unfortunately, this does not mean the treatment will actually work in the long-term.



Gilead/Kite's Yescarta® which was approved two months after Kymriah® was priced at \$373,000 with no outcomes related condition. Both Gilead and Novartis justified these prices with the 'value based pricing' model which builds the price on the value of the treatment generated by the patient outcomes (such as clinical benefits, response rate, toxicity, safety, adverse events and quality of life indicators) and the cost to the society (e.g. treatment cost, cost of therapeutic alternatives and illness burden). As Kymriah® and Yescarta® enable complete remission for patients with no treatment alternatives, the high value they bring is undisputable. In March 2017, the National Institute for Health and Care Excellence (NICE), the Health Technology Assessment (HTA) body of the UK, analysed the cost-effectiveness of CAR-Ts and concluded that a \$649,000 price tag would still be justifiable for young patients with ALL.

Value based pricing is praised by pharma-companies, but it comes with societal concerns. Marie-Paule Kieny, the WHO Assistant Director-General for Health Systems and Innovation, addressed value-based pricing as 'very dangerous'. "What's the value of life? This structure is good for luxury goods because you have a choice...if I'm sick with cancer, what's the choice? We think value-based pricing is not feasible for products that are indispensable." she stated. Moreover, many factors influence the results of the analysis, such as the set of relevant patient outcomes, the clinical and quality data available, data used to estimate costs, the choice and price of comparator, and the target population. Regrettably, most of the data used for the assessment remain confidential and thus hidden from a proper public scrutiny.

⁹ How to cover Novartis' \$475K CAR-T drug Kymriah? A 'new payment model' is the only way, Express Scripts says. FiercePharma. www.fiercepharma.com/financials/car-t-and-other-gene-therapies-need-new-payment-model-says-express-scripts

Controversies over CAR-T prices

Even though there are currently no CAR-T therapies available on the European market, their price is already connected to number of controversies. The first issue is the price in itself. Even if cost-effective, the US prices are too high.¹⁰ It will be a challenge (if not impossible) for European payers to ensure access to the CAR-T-cell therapies for all patients under the current functioning of healthcare systems. According to David Mitchell (Patients for Affordable Drugs), Kymriah® should cost no more than \$160 000.¹¹ Secondly, other controversies are connected to explanations used by pharmaceutical industry to justify the high prices, mainly associated with the production cost and public involvement in R&D. After Emily Whitehead's remission, the public sector heavily invested in CAR-T development, hence the research was and still is fuelled by public spending. Unfortunately, this was not reflected in the price. According to Novartis, the company paid more than one billion US dollars to bring Kymriah® to the market. However, the Patients for Affordable Drugs NGO has calculated that solely the NIH poured \$200 million into research to develop CAR-T therapies.¹² In April 2018, KEI filed a lawsuit against the NIH to challenge an exclusive license of patents on CAR-T treatment awarded to Gilead Sciences. The non-profit argued that CAR-T was a taxpayer-funded health technology and the decision to licence patents to Gilead neglected public involvement and the need for affordable medicines.¹³

The third controversy is linked to the real cost of the product. As the new technology is based on the patient's own immune system, CAR-T therapies are personalised and thus expensive to produce. However, there are many different cost estimates which tend to grow over time. In 2012 Dr. June, a major contributor to the use of CAR-Ts in cancer care, said to the New York Times that producing engineered T-cells would cost about \$20,000 per patient.¹⁴ In 2015, Kite CFO Cynthia Butitta, said that their financial models set a base case price at \$150,000 per treatment.¹⁵ In 2017, Novartis' cost for Kymriah® treatment was reportedly around \$200,000.¹⁶

The last two controversies underline the clear lack of transparency. R&D investments and production costs are mainly based on partial information and estimates.



Therefore, the first steps should be taken towards making the price understandable, if not acceptable, and ensure more transparency in pricing of CAR-T therapies.

¹¹ *Drugs Don't Work If People Can't Afford Them: The High Price of Tisagenlecleucel*. Health Affairs. <https://www.healthaffairs.org/doi/10.1377/hblog20180205.292531/full/>

¹² *Taxpayers and U.S. Patients Pay Twice for Kite's New Car-T Drug*. Patients for Affordable Drugs. www.patientsforaffordabledrugs.org/2017/10/18/taxpayers-and-us-patients-pay-twice-for-kites-new-car-t-drug/

¹³ *KEI sues NIH over license of CD30 CAR T patents to Gilead*, Knowledge Ecology International. <https://www.keionline.org/27669>

Nonprofit sues over NIH licensing of cancer tech to Gilead. Reuters. <https://www.reuters.com/article/health-nih/nonprofit-sues-over-nih-licensing-of-cancer-tech-to-gilead-idUSL1N1RXIYY>

¹⁴ *In Girl's Last Hope, Altered Immune Cells Beat Leukaemia*. The New York Times. www.nytimes.com/2012/12/10/health/a-breakthrough-against-leukemia-using-altered-t-cells.html

¹⁵ *Kite CEO plans to learn from Gilead's pricing playbook*. Reuters. www.reuters.com/article/us-healthcare-kite-pharma/kite-ceo-plans-to-learn-from-gileads-pricing-playbook-idUSKBN0KO2EF20150115

¹⁶ *Profit on \$475,000 Novartis cancer drug could be a while coming*. Reuters. www.reuters.com/article/us-novartis-fda-price/profit-on-475000-novartis-cancer-drug-could-be-a-while-coming-idUSKCN1BB2EA

CAR-T therapies in Europe: How to meet the challenge?



Both Yescarta® and Kymriah® were classified as advanced therapies (ATMPs) subjected to the centralised authorisation procedure and their sponsors have submitted the marketing authorisation application to the European Medicines Agency (EMA) on 31 July and 6 November 2017,¹⁷ respectively. Both therapies have been awarded the accelerated assessment scheme for therapies of major therapeutic advantage in areas of high unmet medical need (PRIME). However, due to the drug's complexity, the Committee for Medicinal Products for Human Use (CHMP) decided revert back to the standard timetable of Yescarta's assessment in December 2017. To approve a complex ATMP at the EMA can take more than a year. We can assume that the first CAR-T shall be approved for the European market by the end of 2018.¹⁸ In the meantime, the EMA laid out recommendations for improving the use of patient registries to support the benefit-risk evaluation CAR-Ts, especially for post-authorisation data monitoring.¹⁹

The greater problem, however, will arrive after CAR-Ts are approved by the EMA and enter the HTA review stage and the pricing and reimbursement debate between the pharmaceutical company and payers. This price-setting negotiation is dependent on the institutional framework of each Member State and it is likely to continue for more than a year after the EMA market approval. Having in mind that CAR-T therapies are paediatric orphan designated medicines, treating life-threatening diseases where there exist no treatment alternatives, with very high price tag, we can expect a lengthy, highly politicised debate influenced by the public pressure for timely access to CAR-Ts due to the enormous therapeutic value clashing with the budgetary constraints connected to the need for sustainability in European healthcare spending.

¹⁷ Committee for medicinal products for human use (CHMP). *Minutes of the meeting on 11-14 December 2017*. European Medicines Agency. www.ema.europa.eu/docs/en_GB/document_library/Minutes/2018/02/WC500243632.pdf

¹⁸ *Initial (Full) Marketing Authorisation application assessment timetables Advanced therapy medicinal product (ATMP)*. European Medicines Agency. www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500198885.pdf

¹⁹ *Report on CAR T-cell therapy Registries. Workshop 9 February 2018*. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2018/05/WC500249247.pdf

ECL Access to Medicines Task Force Strategy



Established in 2016, the ECL Access to Medicines Task Force aims to make cancer medicines available for all cancer patients in Europe by insisting on accessibility, sustainability of the healthcare system and transparency in drug pricing. The Task Force strongly believes in the power of dialogue. We urge all stakeholders to push for innovative improved treatments, improving both clinical outcomes and the quality of life of cancer patients. Currently, 25 national/regional cancer societies, representing over 450 million Europeans, have signed the Task Force's Declaration of Intent.

To ensure timely and equal access to CAR T-cell therapies, the Task Force urges national governments to:



1. Push for transparency in pricing, starting with intergovernmental knowledge-sharing between European payers.



2. Acknowledge the importance and measure the extent of public investment in the R&D of medicines to avoid paying twice or thrice.



3. Support and implement strong European collaboration in Health Technology Assessment (HTA) which would improve timely access to high value medicines for all patients in Europe.



4. Participate in initiatives aspiring toward joint price negotiations (BENELUXA, Valletta Declaration) to increase payers' bargaining power in the pricing and reimbursement negotiations with the pharmaceutical industry.

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