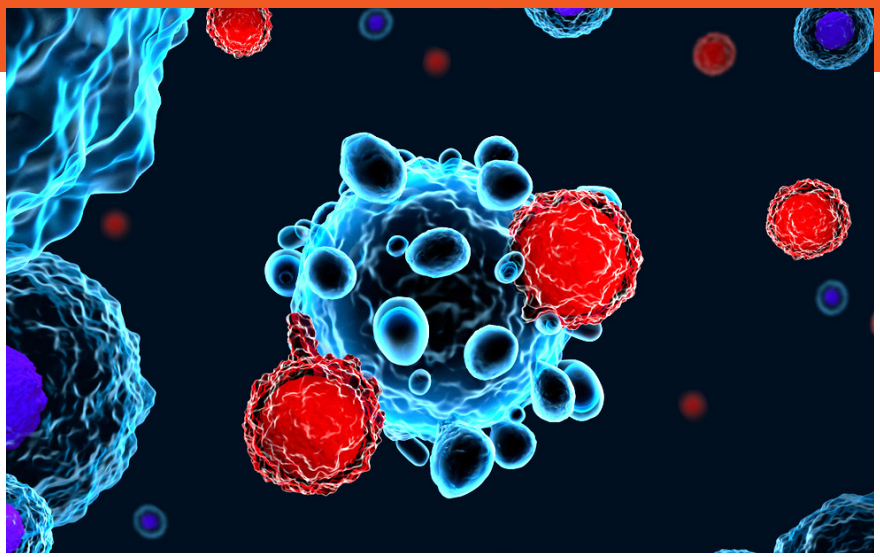

As High-Priced Immuno- & Gene Therapies Multiply, Who Pays and How?

Costing hundreds of thousands, even millions of USD per individual, a handful of immuno- and gene therapies have been developed to-date. But in fact it's no longer correct to talk of just "a handful" – usage expansion is already well underway and set to increase medium term.

So how can individuals be guaranteed access to such treatments? Who pays? Governments? Insurers? Reinsurers?

Discussions between all parties have begun in earnest. This article[1] aims to aid these discussions by outlining CAR T-cell gene therapies for cancer and by opening up the field to dialogue around financing solutions including new and innovative Life products.

Gene therapies

Gene therapies are essentially personalized medicines, developed for and tailored to an individual or small patient group for specific advanced cancers (currently representing a small area of oncology, but increasing), as well as for some rare diseases and genetic disorders. The treatment cost per-person, as shown in the examples below, goes far beyond conventional medicines.

CAR T-cell therapies - KYMRIAH® & YESCARTA®

At the end of 2017, the US Food and Drug Administration (FDA) approved the first two gene therapies for advanced-stage cancer patients using genetically modified human immune cells; CAR T-cell therapies (see box on following page). Both have now also been approved by the European Medicines Agency (EMA) and Health Canada. The costs reflect the sophisticated preparation which must also be produced individually for each patient, as well as high administration costs. It should be noted that, for example in Canada, the cost itself is a topic of discussion between governments and manufacturers.

> "With rapid expansion of CAR T-cell therapies and other gene therapies expected in the medium term, new challenges are set to emerge for manufacturers, healthcare providers and insurers, including the need for innovative financing approaches."
>
> Marc Archambault,
> CEO Life & Health, PartnerRe

CAR T-cell therapies

Chimeric antigen receptor T-cells (CAR T-cells) are complex, individually programmed, cell-based cancer "drugs" with the outstanding property that they can strengthen and persist in treated patients.

CAR T-cell therapy is one of the most important and effective new developments for treating certain cancers; the therapy is FDA-approved as the standard of care for some forms of refractory non-Hodgkin lymphoma and pediatric relapsed acute lymphoblastic leukemia (ALL), and is available through clinical trials for other forms of blood cancer. These therapies are already also being used "off label" and for cancers for which they weren't approved.

While the clinical development of CAR T-cell therapy is most advanced for lymphoma and leukemia, its use for solid tumors, such as prostate cancer, non-small cell lung cancer, sarcomas and multiple myeloma, is increasingly being investigated.[6,7]

What's the process?

CAR T-cell therapies are performed individually, in contrast to most cancer therapies which are similar from patient to patient with minimal variation depending on, for example, histology and stage of disease.

The patient's own T lymphocytes (T-cells) are isolated by a process called leukapheresis. They are then activated and genetically engineered (via virus transfer) in a specialized laboratory to express an artificial T-cell receptor, through which they are programmed to target antigens present on the surface of tumors. The T-cells, modified by CAR gene transfer, are then transferred back intravenously to the pretreated patient via a single infusion of what is effectively a "living, individually tailored drug". When the CAR T-cells meet the antigens on the tumors, they are activated via the signal peptide, proliferate and become cytotoxic to cancer cells.

Making tumor cells visible to the immune system

Thus, a central problem of traditional cancer therapy seems to be at least partly solved: tumor cells that were previously "invisible" to the human immune system are made "visible" by an artificial receptor. CAR T-cells therefore combine the advantages of antibody-mediated and T-cell-mediated immunity. Once activated, the CAR-T cells proliferate and can persist in the patient for a certain time even after the disappearance of the tumor cells. This treatment therefore also seems to ensure a therapeutic effect in the event of a relapse.

Study basis for the FDA's approvals

The FDA approval of KYMRIAH® (Tisagenlecleucel) was based on a global pediatric registration study, ELIANA, which the manufacturer conducted in recent years at a total of 25 different centers in Europe, North America, Japan and Australia. In 52 out of 63 patients (83%), complete remission was achieved within three months of infusion.[8] No minimal residual disease (criterion indicating a possible relapse) could be detected in the successfully treated patients. These results are notable, since for patient groups treated conventionally with chemotherapy, radiation and stem cell transplants, typically less than 10% survive for 5 or more years.[9]

The FDA's approval of YESCARTA® was based on a similar response rate of 82% found in phase 2 of the ZUMA-1 study with 101 patients, for diffuse large B-cell lymphoma. Even at a median follow-up of 8.7 months after treatment, 39% of patients still had complete tumor remission.[4] Here too, treatment success compared to traditional methods stands out: when patients with refractory large cell B-cell lymphoma were treated with conventional therapies, the median survival duration was approximately 6 months.[5]

Side effects and unknowns

The study results are encouraging, but severe side effects, including death, have been observed for these CAR T-cell therapies. At present, at this early stage of implementation, not enough is known about the side effects and long-term results.

For example, in the first months after administration of the infusion in the pivotal studies, ELIANA and ZUMA- 1, an increased release of cytokines (cytokine release syndrome, CRS) was observed for KYMRIAH® (79%) and YESCARTA® (94%).[10,11] In most patients, the CRS symptoms were mild and flu-like, with fever and myalgia. However, if a very high concentration of inflammatory cytokines is released due to an overreaction of the immune system, this can lead to systemic cardio-vascular disorders or to multi-organ failure and death. In the studies, six fatal outcomes were reported due to CRS, despite the administration of steroids in 164 patients.[12] Furthermore, severe neurological side effects, such as encephalopathy, aphasia (speech disorder) and delirium, were observed in 31% (ELIANA) and 18% (ZUMA-1) of the treated patients.

The mechanism for these side effects is not yet fully understood. It is also unclear as to why some patients do not respond to the therapy. According to Nature Biotechnology, the dose used in the studies was not clearly correlated to the response rate, severity of CRS or other signals.[13]

It is also not yet known if these therapies are a definite cure or an extended remission.

Furthermore, CAR T-cells destroy all cells, healthy and diseased, that have the corresponding target; it is unclear as to whether this will cause further damage to the treated patient in the long term.

KYMRIAH® (Tisagenlecleucel), manufactured by Novartis, was approved by the FDA for patients under 25 years of age suffering from refractory lymphoblastic leukemia from B progenitor cells (ALL).

The National Cancer Institute estimates that every year in the US, about 3,100 patients aged 20 years and younger are diagnosed with ALL, which can be either B- or T-cell in origin, with B-cells being the most common. It is estimated that in about 15%-20% of patients, 300-600 patients a year, this cancer does not respond to initial conventional treatment or develops a recurrence.[2]

The cost for KYMRIAH® is approximately USD 475,000 per case.

YESCARTA® was approved by the FDA shortly after for KitePharma. This works according to the same principle as KYMRIAH® and can be used in adult patients with refractory or recurrent large cell B-cell lymphoma[3,4] (the most common aggressive Non- Hodgkin's lymphoma).

The number of potential YESCARTA® therapy candidates in the US is significantly higher than for KYMRIAH®, at around 7,500 patients per year.[5] The cost is approximately USD 373,000 per case.

USD 0.5 million

Approximate cost per person for CAR T-cell therapy

Gene therapies for cancers and rare diseases set to increase

It's already the case that the two approved CAR T-cell therapies are being subsequently approved for other cancers and patient subsets.

Looking forward. As shown in **figure 1**, the number of clinical trials for CAR T-cell therapies has increased almost exponentially: at the end of 2017, a total of 300 CAR T-cell studies were registered worldwide, although the majority are still in phases 1 and 2.[12,14] In 2017 alone, 87 further studies were added.

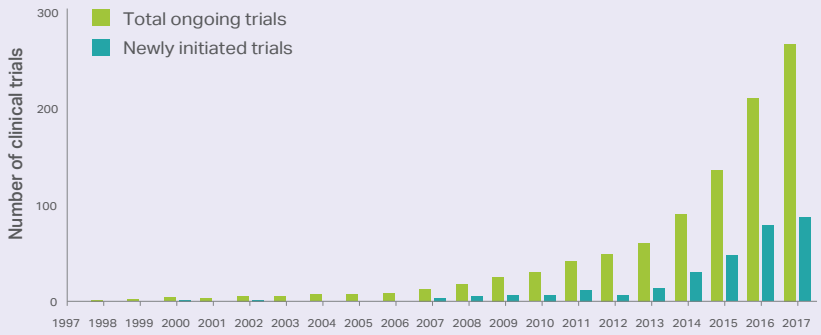

Figure 1: Development of worldwide CAR T-cell clinical trials since 1997, annually initiated and running total of ongoing trials. Source: [12,14]

The pharmaceutical industry is investing heavily in the development of new CAR T-cell therapies; for example, Glaxo-Smith-Kline (GSK), Novartis and Gilead have a combined investment reaching double-digit billion USD amounts.[15] New cost-intensive CAR T-cell therapies are therefore likely to be approved for the treatment of other cancers in the medium term.

A similar trend is observed in gene therapies for rare diseases which impact 3.5–5.9% of the global population.[16,17]

Financing considerations

Spreading the payment. The high cost of gene therapies is often made as a one-off payment and/or due within a short time period. Based on this aspect alone, the increasing use of these therapies can represent a severe financial balance sheet threat to healthcare providers and/or insurers. To help overcome this issue, some pharmaceuticals accept payment in installments (e.g. over 5 years).

Savings potential. It's important to note here that although the costs of these therapies are exceptionally high, if a therapy is a genuine cure, it could, in some cases such as hemophilia, represent a saving compared to ongoing treatment costs.

Rebating unsuccessful treatments. At the same time, it should be considered that gene therapies (in contrast to conventional therapies) cannot be stopped or reversed if they prove to be ineffective or associated with severe side effects (of which currently too little is known), so the risk of accumulating ongoing treatment costs in fact remains, and indeed total costs could be compounded by the need to return to conventional treatments and to treat any resulting severe side effects from the therapy.

Rebating unsuccessful therapy costs is one solution to this, as is provided, for example, by the manufacturers of YESCARTA®. Such outcome-based models require pre-agreement between manufacturers, healthcare providers and/or insurers regarding the criteria for success and failure, and how severe side effects (caused by therapy) and rebates are to be handled.

Immunotherapy: Cancer treatments that help the body's immune system to find and fight cancer cells.

Gene therapy: A treatment that works by inserting (beneficial) genes into cells to treat a variety of diseases including some cancers (e.g. CAR T-cell therapies) and congenital diseases.

CAR T-cell therapy: A treatment in which a patient's T-cells (a type of immune system cell) are genetically altered so that they will find and fight cancer cells.

Contact us

Whatever financing approaches prove the most workable and sustainable for the future, innovative life products and reinsurance are well positioned to play a key role.

At PartnerRe we are excited to be involved in discussions shaping future risk solutions for gene therapies. Please contact us if you would like to discuss this topic with us.

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