EMPLOYER ACTION BRIEF

CAR T-cell Therapy - Preparing Employers to Derive Value from a Growing Pipeline of Effective but High-Cost Therapies

INTRODUCTION:

The last several years have seen significant growth in the number and utilization of specialty drugs. Cancer immunotherapy, in particular, has experienced growth in the number of available treatments, oftentimes offering a lifeline for otherwise terminal conditions. CAR T-cell therapy, immunotherapy approved for several types of cancer, is one of the new biologics that has entered the market. Although CAR T-cell therapy is currently approved by the Food and Drug Administration (FDA)to treat several rare cancers[1], there is reason to believe that the indications for this therapy will expand over the next several years, carrying significant implications for both patients and employers. This Action Brief will review what CAR T-cell therapy is, what the future of this treatment is likely to look like, and what this means in terms of value and cost.

WHAT'S INSIDE:

- What is CAR T-cell Therapy and how does it work?
- How is CAR T-cell Therapy currently being used?
- What do we know about outcomes of CAR T-cell Therapy?
- What does the future hold?
- What do we know about the economics and value proposition?
- What should employers be doing now and in the future?

GPBCH Greater Philadelphia Business Coalition On Health
"Building Bridges to Better Healthcare"

MBGH Midwest Business Group on Health

WHAT IS CAR T-CELL THERAPY & HOW DOES IT WORK?

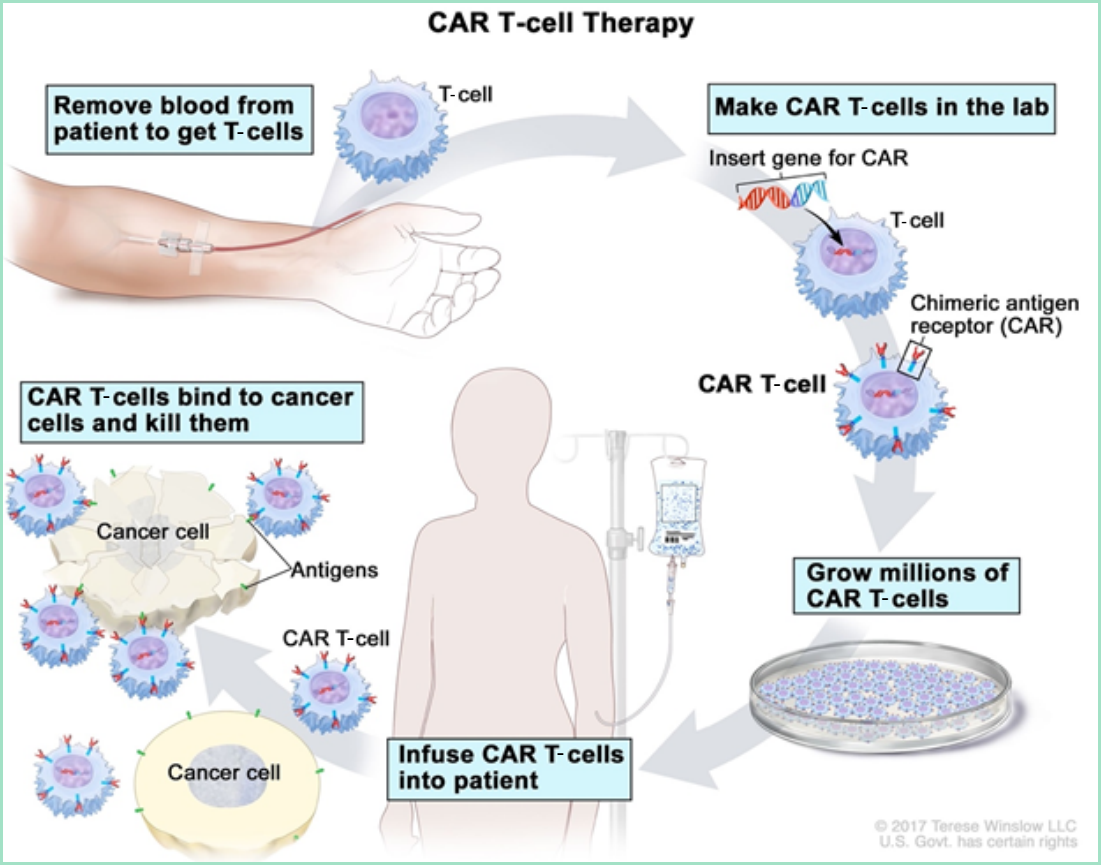
Our immune system knows how to recognize and attack foreign substances in the body, such as viruses and bacteria, to stop their proliferation and keep us safe. T-cells are one of our immune system's fighter cells[1]. They attach to viruses and bacteria using a protein called a receptor. Although T-cells are vital to our health and safety when it comes to foreign pathogens, they cannot recognize or fight off cancer cells as they originate in our bodies and are not foreign substances.

CAR T-cell therapy is personalized cancer immunotherapy. CAR T-cells are made from naturally occurring T-cells that are gathered from a patient's blood[1,2]. These T-cells are altered in a lab, and a receptor is added to them that helps them recognize and attack cancer cells. Once the cells are altered and grown in a lab, they are placed back into the patient's body through an IV line[2]. Although the receptor added to the T-cells is the same, each CAR T-cell therapy is individual to the patient's immune system.

HOW IS CAR T-CELL THERAPY CURRENTLY BEING USED?

Immunotherapy is the newest addition to the mainstays of cancer treatment which have traditionally relied on surgery, radiation, and chemotherapy. CAR T-cell therapy is viewed as one of the breakthrough successes in cancer immunotherapy treatment. Currently, four different CAR T-cell therapies have received FDA approval for several types of blood cancers. Yescarta (axicabtagene ciloleucel) is approved to treat adult patients with diffuse large B-cell lymphoma (DLBCL). Kymriah (tisagenlecleucel) is approved for the treatment of DLBCL in adult patients, as well as acute lymphoblastic leukemia (ALL) in children and young adults up to 25 years). Tecartus (brexucabtagene) received FDA approval for the treatment of adults with mantle cell lymphoma (MCL)[1]. Most recently, Abecma (idecabtagene vicleucel) was approved for use in adult patients with multiple myeloma[4].

Because CAR T-cell therapy is a relatively new treatment, carrying higher costs and less robust safety profiles (see below), it is not currently used as a first line therapy[5]. Instead, it is used when traditional therapies, such as chemotherapy and radiation, have failed to cure the patient of their cancer. CAR T-cell therapy is used to treat patients with severe blood cancer who could not achieve complete remission or for patients whose cancers came back after a period of remission. This is termed refractory or relapsed cancer.



Source: CAR T-Cell Therapy. *National Cancer Institute*[3].

WHAT DO WE KNOW ABOUT OUTCOMES OF CAR T-CELL THERAPY?

A series of clinical trials with CAR T-cell therapy showed huge remission rates for several rare blood cancers, leading to the FDA approval of Yescarta, Kymriah, Tecartus, and Abecma (see Table 1). The trials found that of the patients with severe blood cancer who have relapsed or refractory lymphoma, about 40% to 60% were able to achieve a complete remission with CAR T-cell therapy at the time of follow up, meaning all the signs and symptoms of the cancer had disappeared[6,8]. The figure is even higher for relapsed or refractory leukemia, with 60% to 80% of patients achieving initial complete remission[6]. In the newly approved therapy for multiple myeloma, over a third of the patients achieved a complete response to therapy[7]. Although this is an incredible figure and provides hope to people who were otherwise out of options, remission, and even complete remission, is not synonymous with a cure. It means that all signs and symptoms of the cancer have disappeared at the time of follow-up; it does not guarantee that the cancer will not come back. Over the course of the study, many of the patients who initially achieved remission did relapse. However, the response to CAR T-cell therapy proved durable for many patients. Clinical trials for both Kymriah and Yescarta found that roughly 40% of patients had an ongoing response over two years after the treatment[6].

Severe toxicities have been reported from the use of CAR T-cell therapy. The most common toxicities include cytokine release syndrome (CRS) and immune effector cell-associated cytotoxicity syndrome (ICANS)[5]. CRS is a systemic inflammatory response caused by the activation of the body's immune cells. CRS is a fairly common response and completely reversible, usually presenting as fever, malaise, and myalgias. Although it is generally mild, CRS can progress into organ failure if left untreated[5,9]. ICANS presents as neurologic symptoms such as confusion, but more severe cases can cause seizures, coma, and motor weakness. Like CRS, ICANS is entirely reversible, and most patients have a self-limited course[5]. Although most cases are mild and resolve with supportive care alone, it is important to note that serious complications from CAR T-cell therapy can occur, and so CAR T-cell therapy is only administered in the inpatient setting. Even though CAR T-cell therapy is a one-time infusion, patients may remain in the hospital for a period of several weeks to monitor response to treatment and side effects[10]. Additionally, as with any cancer, period monitoring is necessary to assess for disease progression.

Table 1. Summary of Sample CAR T-Cell Therapy Clinical Outcomes

Table 1	Yescarta[1] (Non-Hodgkin's lymphona	Kymriah[2] (Non-Hodgkin's lymphoma)	Kymriah[2] (Acute lympho-blastic leukemia)	Abecma[3] (Multiple Myeloma)
Overall response to therapy	82%	61.8%	Not Reported	73%
Complete remission	64%	39.5%	85.5%	33%
6-month Progression free survival	Not Reported	38.7%	52.4%*	Not Reported

Table 1 Notes:
Clinical outcome of CAR T-cell therapy measured in percent of patients who had an overall response to treatment, complete remission, and 12-month progression free survival. Figures are drawn from studies reporting clinical outcomes of real-world patients or, if there are none available, from clinical trials.

1. Clinical outcomes from 275 patients who received Yescarta for large B-cell lymphoma, with a median follow-up of 12.9 months from the time of CAR T-cell infusion[11].

2. Clinical outcomes from a real-world setting, with data gathered from a cellular therapy registry. Study reported outcomes from 255 pediatric and young adults patients with acute lymphoblastic leukemia (ALL), as well as 155 adult patients with non-Hodgkin's lymphoma (NHL) who received Kymriah. Data reported from 73 centers, with a median follow-up time of 13.4 months for ALL, and 11.9 months for NHL[12].

3. Data from 128 patients who received Abecma® in a phase 2 clinical trial[7].

*Figure represents 12-month event-free survival, as reported for ALL patients receiving Kymriah.

WHAT DOES THE FUTURE HOLD?

CAR T-cell therapy is regarded as a breakthrough in cancer immunotherapy. Although it is currently FDA approved for treating several rare blood cancers, there is ongoing research into many other indications.

Moving beyond blood cancers, researchers are looking into using CAR T-cell therapy to treat many solid tumors. Researchers have to overcome barriers for using CAR T-cell therapy in solid tumors that are not present in blood cancers, such as delivering the therapy to the tumor site and overcoming the tumor's defense systems[13]. Despite these challenges, there are currently dozens of clinical trials underway that are looking at the efficacy of CAR T-cell therapy in the treatment of brain and central nervous system cancers, liver cancers, and ovarian cancers, among many others[14,15](see Table 2). Cancers with some of the highest lifetime risk in the United States' population, such as breast, prostate, and colorectal, are also being investigated for treatment with CAR T-cell therapy. Because CAR T-cell therapy is a relatively new treatment, many of these trials for solid tumor indications are in the early stages[13]. However, as these trials progress, we may begin to see the expansion of CAR T-cell therapy to a larger pool of patients.

Table 2: Number of registered trials for CAR T-cell therapy (as of March, 2021)

Malignancy	Recruiting	Ongoing Trials – Recruitment Complete	Completed Trials
Brain/CNS	29	5	6
Hepatocellular	10	2	2
Ovarian	10	2	2
Lung	9	1	1
Pancreatic	6	1	3

*Data from clinicaltrials.gov, using search term 'CAR T-cell therapy'.

WHAT DO WE KNOW ABOUT THE ECONOMICS & VALUE PROPOSITION?

Although the efficacy of CAR T-cell therapy in blood cancers has been well established through clinical trials, the economic value of this therapy can be harder to define. Because CAR T-cell

therapy is a new specialized therapy, it carries high costs of treatment. The current cost for an infusion of Yescarta is $373,000, and that of Kymriah is $473,000[15]. These costs do not include the cost of the inpatient hospitalization, which is required to receive the infusion or the cost of managing side effects such as CRS. The impact of this treatment on an individual organization's budget is hard to determine as the likelihood of encountering a case of rare blood cancer in an employee pool is difficult to predict.

Although long-term follow-up data on many patients is not yet available, models and projections of currently available data can provide insight into the value of the therapy. The cost of treatment can be weighed against the life-years gained by the patient to objectively gauge the value of the treatment[17]. To account for the adverse effects, disability from disease, and other factors that may diminish the quality-of-life post-treatment, the life-years gained are multiplied by a utility index creating a value called a quality-adjusted life year, or QALY[17] The cost of the treatment is divided by the QALYs gained to arrive at an incremental cost per QALY.

The cost per QALY can be used as a decision-making tool regarding whether or not to fund a therapy. The U.S. has an accepted threshold of roughly $50,000- $100,000/QALY, and higher costs are often considered in the face of newly emerging therapies. A survey of cancer physicians found an acceptable value to be $150,000/QALY, and the World Health Organization (WHO) recommends a threshold grounded in the country's GDP, placing the U.S. threshold at $180,000/QALY[16].

In the case of a new treatment like CAR T-cell therapy, where lifelong data is not available, models are created based on different assumptions of patient survival. Kymriah and Yescarta studies used 20%, 30%, and 40% long term progression-free survival to estimate costs, with a higher progression-free survival leading to lower overall costs. In three economic studies performed assessing Kymriah for B-ALL in children, the calculated cost ranged from $43,000- $64,600 per QALY gained[16,18]. Of the nine economic models evaluating Yescarta for LBCL, the costs per QALY gained ranged from $58,000-$230,000, with all but two scenarios producing values under $168,000/QALY[16]. Children have the largest number of potential life-years to gain if they achieve complete remission, leading to the lower overall costs per life-year. For adult indications, the average age of patients receiving CAR T-cell therapy in clinical trials was 56 to 58 years old; however, the treatment is indicated for adults over 25 years old[16]. Younger patients would have a larger amount of life years gained, reducing the overall cost per QALY.

Based on the majority of currently available models, the cost of treatment with CAR T-cell therapy compared to the life years gained lies within a reasonable threshold based on gross domestic product, assuming there is a 30-40% long term progression free survival rate[16,18]. However, longer follow up data is needed for more accurate economic modeling. Additionally, the budget impact on an individual employer is difficult to determine, as most employers will likely never encounter an employee who develops a rare blood cancer for which CAR T-cell therapy is indicated. However, with the likely expansion of indications in the near future, more employers will encounter the potential need for CAR T-cell therapy amongst their workforce and thus should be aware of the values and costs of therapy.

WHAT SHOULD EMPLOYERS BE DOING NOW AND IN THE FUTURE?

With the probable expansion of CAR T-cell therapy over the coming years, more employers will see the use of this treatment within their workforce.

Employers can utilize the following strategies so that the price of therapy does not become a burden.

- Review your stop-loss coverage. Ensuring that you have adequate stop-loss insurance coverage can protect you from unpredictable or catastrophic claims. Reviewing your exposure with your consultants and carriers can help you assess your level of liability and adjust your coverage to meet your needs.
- Review cost-sharing strategies and economic burden on the employee. Cost-sharing by way of co-pay or co-insurance is a standard method used to alleviate some of the cost burdens from the purchaser and payer. However, co-insurance may still make these drugs unaffordable to many patients who could benefit.
- Utilize a tiered drug plan, in which more traditional lower cost therapies are prioritized and used as a first line treatment before trialing the high-cost alternatives. Ensure that your carriers have a qualified professional (e.g., oncologist) making coverage decisions and reviewing prior authorization requests.
- Consider amortized drug plans. ·Amortization of high-cost drugs spreads out the payment for the therapy over a period of time, making an employer less vulnerable to a large one-time payment[19].
- Discuss a value-based pricing system with your consultants and payers, where the cost of the drug is grounded in patient outcomes. Value-based pricing would tie payment for the drug to pre-specified clinical milestones, allowing for only partial payment or no payment based on sub-optimal results[20].
- Engage in local employer advocacy groups. Business coalitions and local advocacy groups work to protect employers from unfavorable policies (e.g., mandated coverage) and promote cost control measures such as value-based pricing.

Although paying for high-cost pharmaceuticals is likely to remain an issue for patients, employers, and insurers, utilizing some of the above strategies can help improve appropriate use and mitigate the cost burden on employers. Cost-sharing, value-based pricing, and a tiered formulary can help to offset the costs of the therapy, while stop-loss coverage and favorable policies can help protect employers from catastrophic expenses. Engaging in immediate cost reduction strategies alongside long-term policy advocacy can prove to be the best strategy for a sustainable pricing structure in the future.

ACKNOWLEDGEMENTS

This brief was prepared by Diana Koval, a third-year IPPE student at the Jefferson College of Pharmacy, during a rotation at GPBCH. Dr. Michael Kolodziej provided input as clinical oncology and managed care expert.

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