White Paper

Cell and Gene Therapy Hot Buttons Series

Part 1. Starting the CAR: An Introduction To Autologous CAR-T Therapy

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Summary

Cell and Gene Therapy (CAGT) activity has increased dramatically in recent decades, especially in Chimeric Antigen Receptor T-Cell (CAR-T) clinical trials and therapy registrations. The *IQVIA CAGT Hot Buttons* series covers basic concepts in CAGT for newcomers to this field.

In this whitepaper, we summarize the CAR-T regulatory status from Asia-Pacific markets, basics of CAR-T receptor structure and look at the common toxicities of currently available CAR-T therapies which have regulatory approval for hematological malignancies

Introduction

Chimeric Antigen Receptor T-Cell (CAR-T) therapy has been hailed as a game-changing cellular immunotherapy[1]. It has had rave reviews for the long-lasting impact it has had on treatment of B-Cell malignancies, especially for many people with Non-Hodgkin Lymphoma (NHL), B-Cell Acute Lymphoblastic Leukaemia (ALL) and multiple myeloma (MM). The US Food and Drug Administration (FDA) approved Kymriah® (tisagenlecleucel), the first commercially available adoptive T-Cell therapy, for selected B-Cell hematological malignancies in adults and children in 2017[2]. See Table 1 for more details.

By 2020, both Kymriah® and Yescarta® (axicabtagene ciloleucel) had Australian regulatory (Therapeutic Goods Administration (TGA)) approval. Both products have also begun entering Asian markets: Kymriah® is registered in Japan, Singapore and South Korea. Yescarta® was approved in China in June 2021 and was joined by Carteyva® (relmacabtagene autoleucel injection) in September 2021.[3]

By 2020, both Kymriah® and Yescarta® (axicabtagene ciloleucel) had Australian regulatory approval.

Table 1: FDA-Approved autologous CAR-T therapies registered in Asia-Pacific[4,5,6,7,8,9,10] (March 2022)

US REGISTERED NAME; FDA REMS REQUIRED?	INN	OTHER NAMES	SPONSOR	ASIA-PACIFIC APPROVAL STATUS	RECEPTOR CONSTRUCT	TARGET	INDICATION	USPI BLACK BOX
Abecma® Yes	idecabtagene vicleucel	bb2121	Celgene with Bristol-Myers Squibb	Japan	Lentiviral vector transduction of Anti-BCMA + CD3-zeta, 4-1BB	BCMA	Adult r/r MM	CRS NT HLH / MAS Prolonged cytopenia
Breyanzi® Yes	lisocabtagene maraleucel	JCAR017 LM	Juno with Bristol-Myers Squibb	Japan	Lentiviral vector-transduced FMC63 monoclonal antibody-derived scFv + IgG4 hinge + CD28, 4-1BB + CD3-zeta	CD19	r/r large B-Cell lymphoma including FL, excluding primary CNS lymphoma	CRS NT
Kymriah® Yes	tisagenlecleucel	CTL019, CART-19	Novartis	Australia, Japan, Singapore, South Korea	Lentiviral transduced CD3-zeta + CD8 hinge 4-1BB	CD19	Young (<25y) r/r B-Cell ALL Adult r/r DLBCL	CRS NT
Tecartus® Yes	brexucabtagene autoleucel	KTE-X19, Brexu-cel	KitePharma, Inc.	Nil	Gammaretroviral transduced CD3-zeta + CD28 Manufacture includes T-Cell enrichment	CD19	Adult r/r MCL Adult r/r B-Cell ALL	CRS NT
Yescarta® Yes	axicabtagene ciloleucel	KTE-C19, Axi-cel	Kite Pharma, Inc.	Australia, China, Japan	Gammaretroviral transduced CD3-zeta + CD28 Manufacture includes T-Cell enrichment	CD19	Selected Adult r/r DLBCL Adult r/r FL	CRS NT

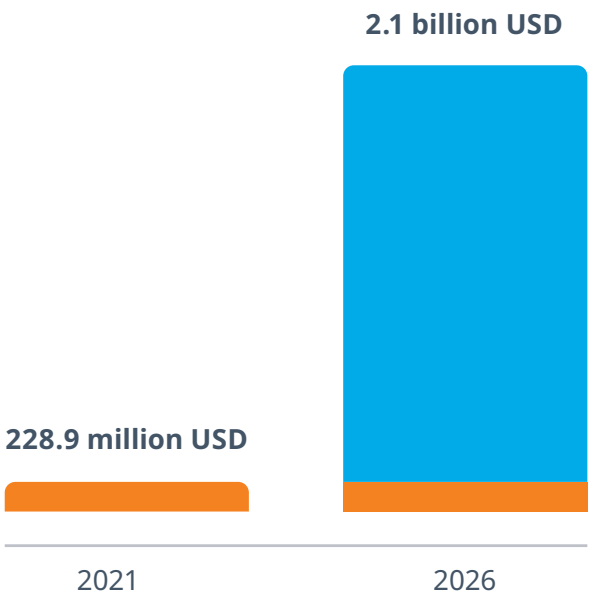
Abbreviations: ALL: Acute Lymphoblastic Leukemia; BCMA: B-Cell Maturation Antigen; CD19: Cluster of Differentiation 19; CNS: Central Nervous system; CRS: Cytokine Release Syndrome; DLBCL: Diffuse Large B-Cell Lymphoma; FL: Follicular lymphoma; HLH / MAS: Hemophagocytic Lymphohistiocytosis / Macrophage Activation Syndrome; INN: International Non-proprietary Name; MCL: Mantle Cell Lymphoma; MM: Multiple Myeloma; NT: Neurologic Toxicity; REMS: Risk Evaluation and Mitigation Strategy; r/r: relapsed / refractory; scFv: single chain variable Fragment; USPI: United States Package Insert.

CAR-T commercial context

The global market for CAR-T therapy is estimated to grow from 1.5 billion USD in 2021 to reach 7.6 billion USD by 2026, at a compound annual growth rate (CAGR) of 39.1% during 2021-2026[11]. Whilst the North American market for CAR-T therapy is estimated to grow from 751.5 million USD in 2021 to reach 3.5 billion USD by 2026, at a CAGR of 35.8% during 2021-2026, the Asia-Pacific market for CAR-T therapy is estimated to grow from 228.9 million USD in 2021 to reach 2.1 billion USD by 2026, at a CAGR of 56.0%.

The cost of CAR-T therapy will be one of the biggest challenges to expanding access. The marketed prices per single infusion vary between 350,000 USD (Yescarta®) and 475,000 USD (Kymriah®)[12]. The per-patient cost will exceed the 1 million USD threshold, since each therapy is individually made for the patient, a process which is currently associated with a high level of logistical, administrative, and medical effort, as described later in this publication.

Figure 1: Asia-Pacific CAR-T therapy market



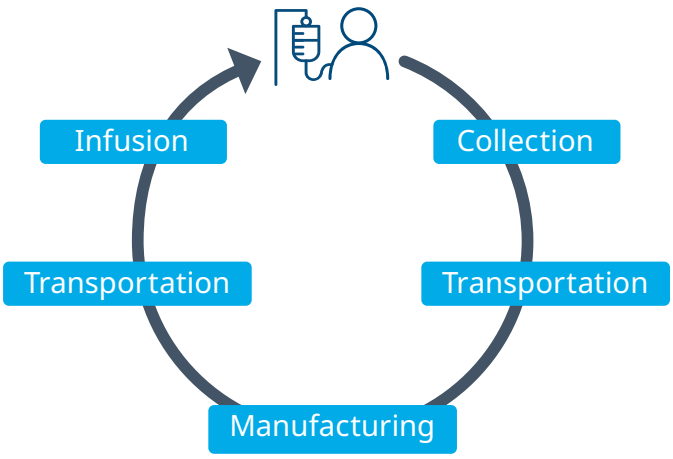
Market forecast to grow at a CAGR of 56%

The challenge of CAR-T logistics

In addition to marketing registrations, sponsors are actively expanding CAR-T manufacturing capabilities to try to address logistical bottlenecks. Notably, these bottlenecks are more patient-centered and individual-based rather than medical, life science or healthcare-associated.

The CAR-T therapy manufacturing starts with leukapheresis (see page 9 for more details), followed by (a possible international or inter-continental) transportation of the harvested cells under carefully-controlled cryogenic conditions to the pharmaceutical facility. After the cells have been modified and grown for use as an infusion, the cells are transported back to the patient, while keeping an uninterrupted cold chain and meeting strict quality control standards for pharmaceutical goods. Accordingly, there is a high demand for production facilities and on-site distribution logistics worldwide. The cooperation of pharmaceutical companies in the areas of production, logistics and sales is a decisive step for a functioning, well-organized supply chain. Companies can use existing strengths and processes here. A prominent example is BioNTech and Pfizer's partnership in the development, manufacture and commercialization of an mRNA vaccine during the COVID-19 pandemic.

Figure 2: The challenge of CAR-T logistics



Adapted from: https://www.susupport.com/logistic-solutions-car-t-cell-therapy/

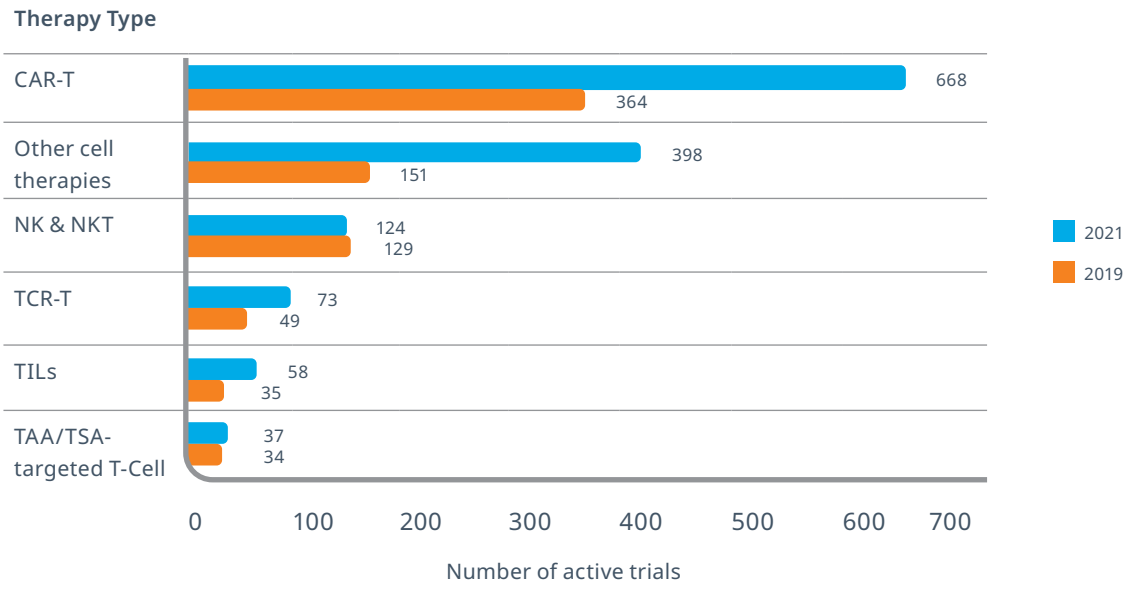
Australia and Japan are the two countries outside the EU and the USA that now have approval to manufacture Kymriah®. In October 2020, the Japanese regulator, the Ministry of Health, Labor and Welfare, granted approval for the first Asian production of CAR-T at the Foundation for Biomedical Research and Innovation (FBRI) in Kobe, Japan. In February 2021, the TGA approved Melbourne-based Cell Therapies as the first manufacturer of CAR-T products in Australia[13].

JW Therapeutics has set up the manufacture of Carteyva® in Suzhou, China. The Carteyva® manufacturing process was developed locally in China to boost CAR-T efficacy without worsening toxicity and facilitate domestic production of CAR-T therapies[3].

The expanding trial landscape

Clinical trial numbers are increasing steadily as refinements are made to CAR-T structure to enhance efficacy, and as targets and indications are expanded. In 2012, there were only 12 CAR-T clinical trials, but by June 2021, there were more than 600 active clinical trials globally, despite the impact of the COVID-19 pandemic[14].

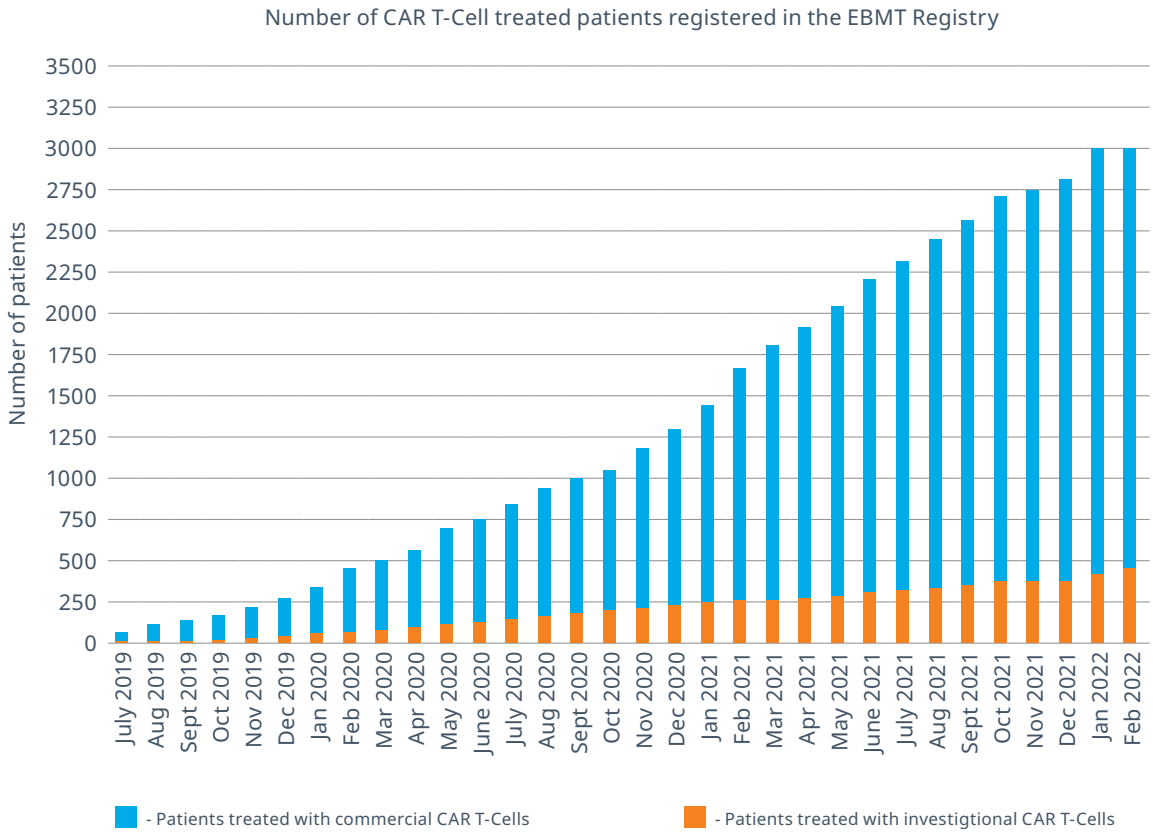
Figure 3: Global cell therapy clinical trial activity (as of April 2021)[14]



Patient monitoring programs

Regulators worldwide have moved to establish specific safety monitoring and mitigation programs for patients receiving CAGT products. For example, all European Union CAR-T recipients should be enrolled into the EBMT's Patient Registry for continued regulatory data reporting, whether they receive clinical trial products or registered products[3]. In the United States, all marketed CAR-T products are currently regulated by US FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) programs, under which sponsors are required to establish follow up safety protocols for their CAR-T recipients[4,5,6,7,8].

Figure 4: Number of CAR-T recipients entered in the EBMT Registry[15]



An evolving construction: Chimeric T-Cell receptors

There are two different types of CAR-T therapy: autologous and allogeneic. In autologous CAR-T therapy, a patient's own lymphocytes are used as starting material to manufacture their own unique drug. In allogeneic CAR-T therapy, the patient receives their infusion of genetically altered lymphocytes sourced from a different donor.

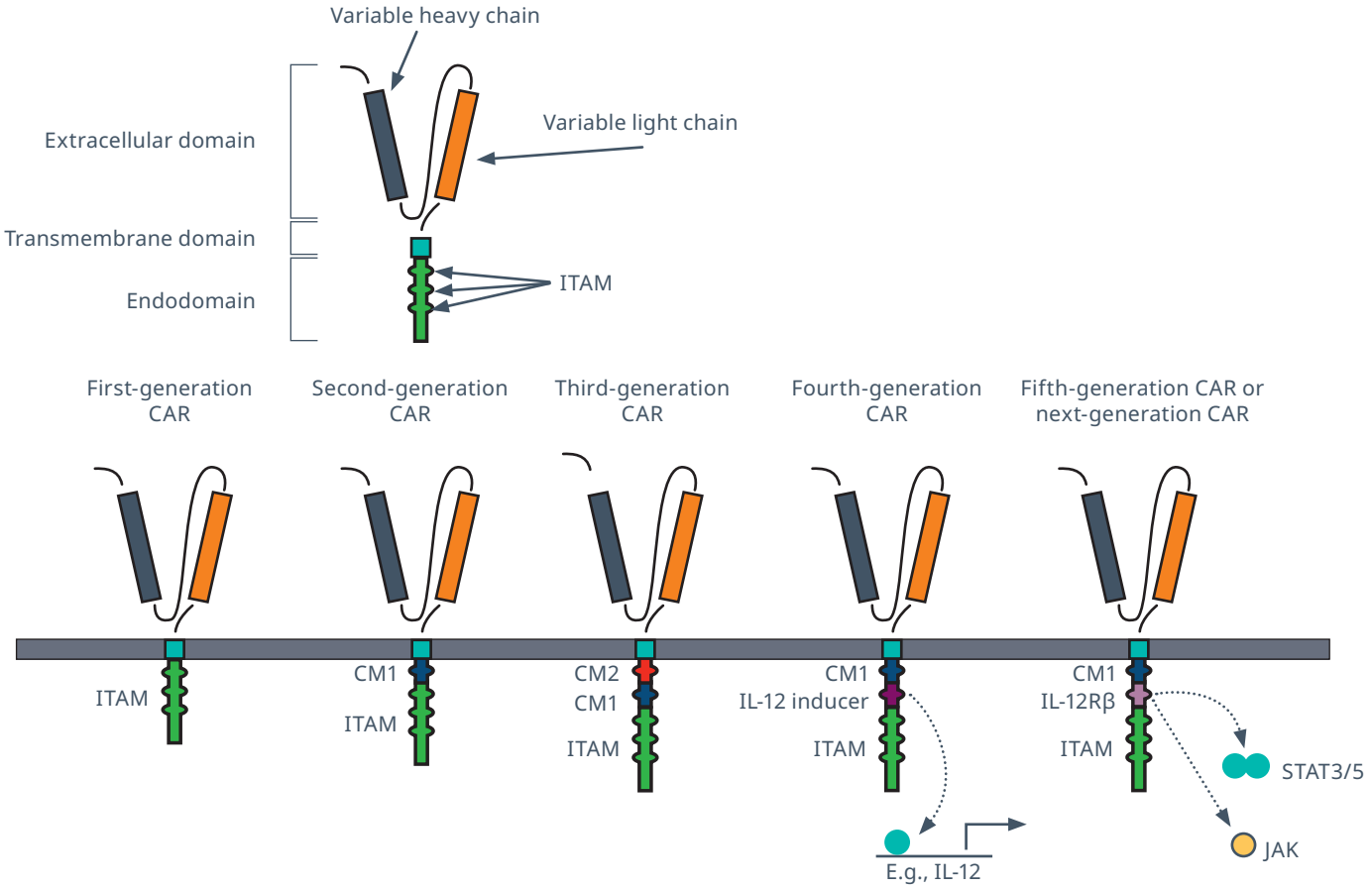
CAR-T therapy has the advantages of both specificity and direct immune activation because of the T-Cell receptor structure.

CAR-T lymphocytes have synthetic receptor structures that are created in a manufacturing laboratory. The synthetic receptors consist of extracellular specific antigen-binding domains and intracellular signaling domains linked by hinges and transmembrane constructs. The receptor structures are encoded by murine genes that have been moved into lymphocytes'

cell nuclei in the manufacturing laboratory (transduction).

There are currently five CAR-T receptor generations. The generations are classified by the intracellular receptor domain structure. Recent developments have been based on the second generation, which includes costimulatory signaling to activate the CAR-T-Cell. The first generation of CAR-T receptors did not include costimulatory internal signaling and these cells had inadequate efficacy.

Figure 5: Progress in receptor structure from first to fifth generation CAR-T constructs[16]



The most successful tumor target candidate for CAR-T therapy has been CD19, which is present on all B lymphocytes, but there has also been significant progress with targeting the B-Cell maturation antigen (BCMA) on the surface of mature B lymphocytes.

Notably, CAR-T therapy results have historically been less impressive for treatment of solid tumors, for three key reasons[13]:

1. No universal solid tumor target
2. Solid tumor target antigen location
3. Tumor microenvironment hostility to infused T-Cells, e.g., tissue hypoxia

From patient to patient – the CAR-T process

Preparation for CAR-T therapy manufacture starts with leukapheresis. In this process, the blood collected from the body is separated into components to extract the lymphocytes. The rest of the blood is returned to the circulation. The process will ensure that a sufficient number of lymphocytes is harvested to be modified in the manufacturing laboratory.

Some patients with aggressive malignancies, e.g., B-ALL, require disease control with bridging chemotherapy after leukapheresis and while waiting 3-4 weeks for their autologous CAR-T product[18].

For the best chance of CAR-T success in hematological malignancy treatment, the recipient's own lymphocyte numbers should be reduced shortly before the CAR-T infusion, a process known as lymphodepletion (LD)[18].

LD is the administration of chemotherapy to provide a favorable environment for the infused CAR-T-Cells.

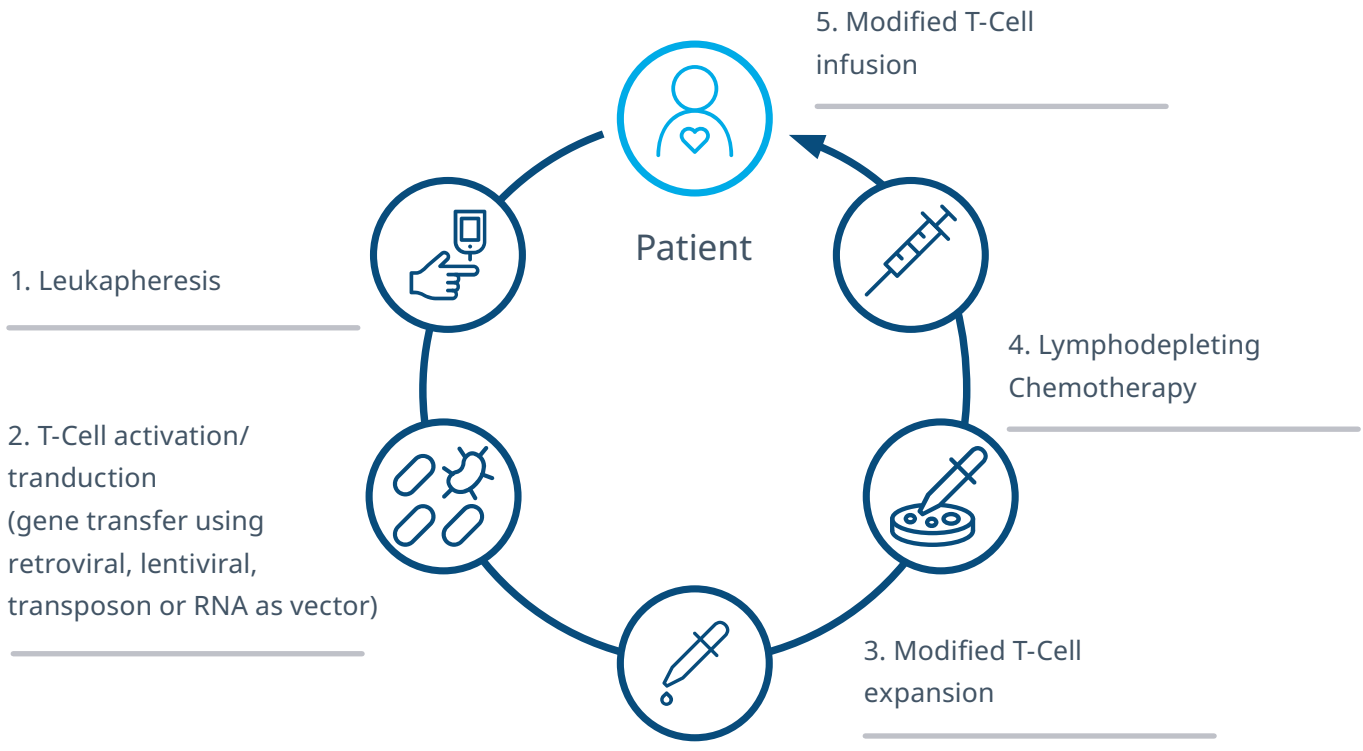
The chemotherapy removes the regulatory and immunosuppressive components of the immune system. The most commonly used LD agent is fludarabine. Although LD enhances the efficacy of infused CAR-T-Cells, it is associated with higher rates of Cytokine Release Syndrome (CRS) and infections.

Because of the increased infection risks from the underlying disease, previous treatments and preparation for infusion, patients may also require preventive treatment with antiviral and antifungal medications.

Each center has protocols in place for planning the timing of their infusions e.g., LD is usually not started until after the manufactured product has been received at the treatment location.

After administration, the genetically altered T-Cells start multiplying (expanding) and killing cells bearing the target antigen, without needing additional signaling from the host's immune system[18,19] .

Figure 6: Autologous CAR-T therapy manufacture and administration[20]



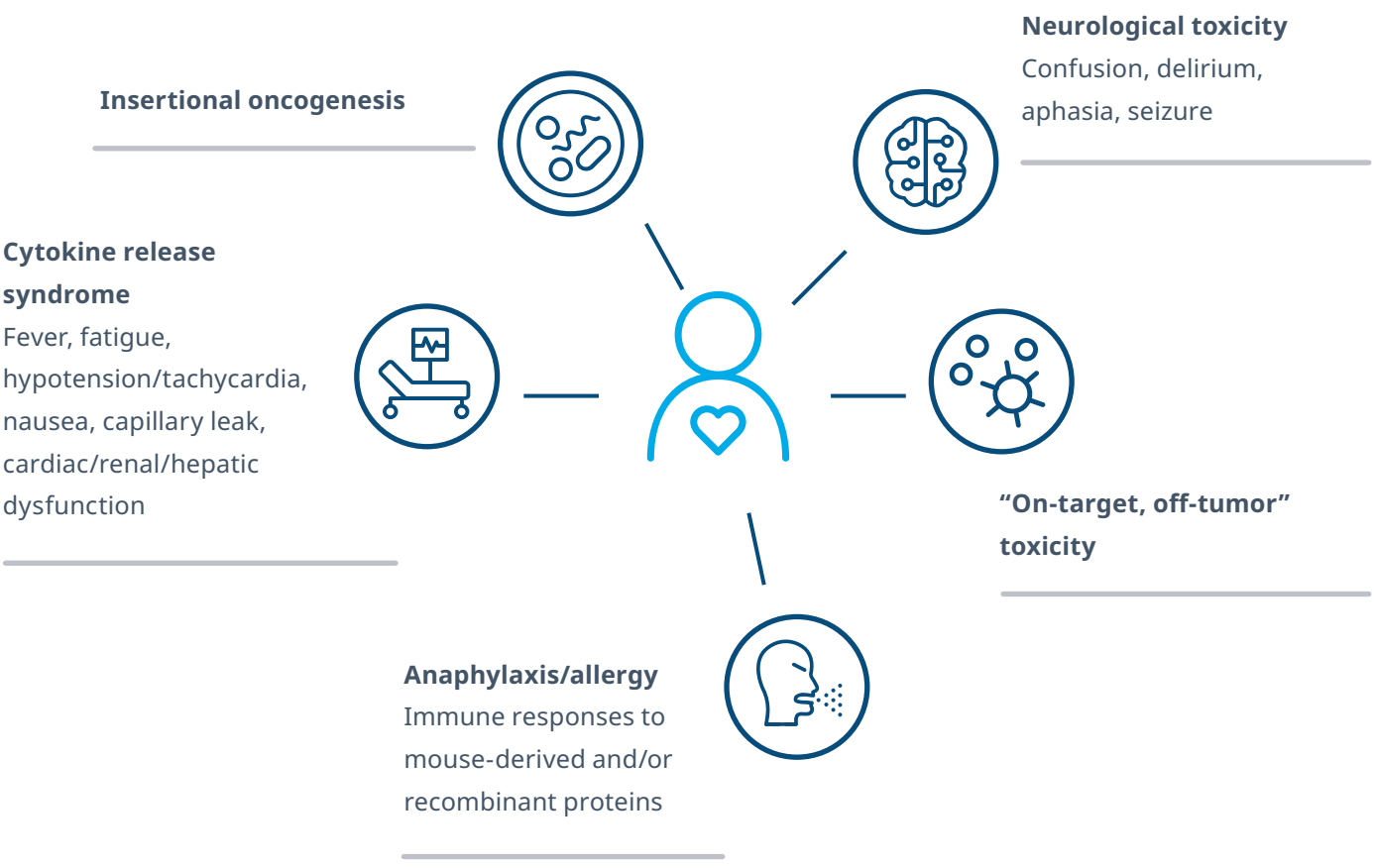
CAR-T therapy safety considerations

Any intravenous infusion carries a risk of an immediate infusion reaction or an allergic reaction and CAR-T therapy is no exception. To limit this, pre-medication is required immediately before CAR-T infusion. Standard pre-medications include acetaminophen and an antihistamine, but not corticosteroids, due to the risk of impaired efficacy of the infused T-Cells[18].

Autologous CAR-T therapies targeting CD19 have toxicities in common with each other. The most frequently reported toxicity is CRS. Rates vary widely between adults and children and between patients with different malignancies and CRS is reported to occur in 30-100%[18].

Other toxicities include Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS), hypogammaglobulinemia and prolonged cytopenia. CAR-T toxicities are considered "on-target, off-tumor" if they are directly linked to damage of normal cells displaying the target antigen.

Figure 7: Potential CAR-T therapy-specific toxicities[21]



Clinical trial sites should be trained to anticipate potential adverse reactions and their typical onset times and presentation. This is essential to guide appropriate toxicity management. Additionally, CAR-T recipients require close and regular follow up and may be required to enroll in local regulatory registries.

The question that also arises at a regulatory authority level is to what extent risk management plans (RMPs) should be applied during the approval process. RMPs provide substantial information on a medicine's safety profile, describe the activities of the marketing authorization holder to further characterize the safety

profile during post-marketing (pharmacovigilance activities) and explain the measures that are taken in order to prevent or minimize the medicine's risks in patients (risk minimization measures).

Risk management for CAR-T therapies is described in the next issue of the IQVIA CAGT Hot Buttons series: Part 2: Autologous CAR-T Risk Management.

Future directions

Research is active on receptor structure modifications to enhance targeting efficacy, e.g., overcoming resistance mechanisms and enhancing persistence. The aim is to do this without creating additional toxicity [18,21]. Future research includes studying the ability to control the effector action of the infused T-Cells e.g., "suicide switches", and improving early detection and management of CRS and ICANS[19].

The use of "off the shelf" allogeneic CAR-T products, nonviral vectors for transduction and semi-automation all have potential to simplify CAR-T processing and to improve wider market access to these therapies.

Conclusion

Clinically, CAR-T recipients not only need sufficient functional reserves to tolerate leukapheresis, but also to wait for manufacture and the infusion itself. Then they may face additional hazards before and after infusion. Careful candidate selection is essential.

Selection continues with regard to choosing staff to administer CAR-T therapy in the clinical trial context. They should be thoroughly trained in both the use of this treatment and Good Clinical Practice according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP). Site staff should be prepared to anticipate, manage and record all adverse events. Successful patient management includes careful and thorough documentation of all safety data[22].

Experienced trial sites, Contract Research Organizations (CROs) and logistics partners understand the need for effective planning, documentation, and communication in order to navigate the notorious complexity of these trials. Heightened regulatory and scientific scrutiny is inevitable in this field, so the old adage "if it's not documented, it's not done" rings truer than ever.

CAR-T therapy is rightly receiving a great deal of public attention, as it has led to incredible therapeutic successes in some clinical applications for cancer patients with advanced tumor disease. A sophisticated and highly-organized approach to clinical trial implementation is vital to bringing this game-changing cellular immunotherapy to life whilst ensuring patient safety.

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