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By

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PG/19/034

Hospital Management

Under the guidance of

Dr. Vinay Tripathi

Post-graduate Diploma in Hospital and Health Management

(2019-21)

IIHMR DELHI

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Date: 9th Aug 2021

TO WHOMSOEVER IT MAY CONCERN

This is to certify that **Ittu Kundan** has completed her internship in technical department at Mellalta Meets LLP, from **April 21st, 2020, to July 30th, 2021.**

She has worked on the project titled "**Impact of CAR-T Cell Therapy in Cancer Treatment"**. This project was aimed at *understanding the impact of marketed and emerging CAR-T Therapies as future treatment paradigm in cancer.*

During her internship, the candidate has demonstrated her self-motivation skills to learn new skills. Her performance exceeded our expectations, and she could complete the project on time.

We wish her all the best for her future endeavors.

Mridhu Verma

CEO

Mellalta Meets LLP

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This is to certify that **Dr. Ittu Kundan,** student of PGDM (Hospital & Health Management) from **International Institute of Health Management Research, New Delhi** has undergone internship training at **Mellalta Meets, Delhi** from **21/04/ 2021** to **30/07/2021.**

The Candidate has successfully carried out the study designated to him during internship training and her approach to the study has been sincere, scientific, and analytical. The Internship is in fulfillment of the course requirements. I wish her all success in all her future endeavors

Ms. Divya Aggarwal

Associate Dean, Academic and Student Affairs
IIHMR, New Delhi

Dr. Vinay Tripathi

Associate Professor

IIHMR, New Delhi

Certificate of Approval

The following dissertation titled **"Impact of CAR (Chimeric Antigen Receptor) T cell therapy in shifting the future paradigm of relapsed and refractory hematological cancer."** is hereby approved as a certified study in management carried out and presented in a manner satisfactorily to warrant its acceptance as a prerequisite for the award of **PGDHM (Hospital &Health Management)** for which it has been submitted. It is understood that by this approval the undersigned do not necessarily endorse or approve any statement made, opinion expressed or conclusion drawn therein but approve the dissertation only for the purpose it is submitted

Dissertation Examination Committee for evaluation of dissertation.

Name

Signature

Certificate from Dissertation Approval Commitee

INTERNATIONAL INSTITUTE OF HEALTH MANAGEMENT RESEARCH, NEW DELHI

CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled "**TITLE-Impact of CAR (Chimeric Antigen Receptor) T cell therapy in shifting the future paradigm of relapsed and refractory hematological cancer." a**nd submitted by **Dr. Ittu Kundan** Enrollment No. **PG/19/034** under the supervision of **Dr. Vinay Tripathi** for award of **PGDM (Hospital & Health Management)** of the Institute carried out during the period from 2019 to 2021 embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other Institute or other similar institution of higher learning.

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1. ABSTRACT

Cancer is one of the major causes of death all over the world. Several therapies have been developed for the treatment of cancer. However, there is still a huge unmet need for the management of the relapsed and refractory cases of cancer. The currently available treatments still lack in efficacy and there is continuous search for new therapeutic options with better treatment outcomes to improve the overall condition of the patients. Chimeric antigen receptor (CAR) T cell therapy has emerged as a breakthrough in cancer immunotherapy over the past decade. Outstanding results in hematologic malignancies and encouraging preclinical anticancer activity against a wide range of solid tumors have made CAR T cells one of the most promising fields for cancer therapies. This therapy has paved the way for a potential paradigm shift in the way refractory or relapsed cancers are treated. CAR T cell therapy is also being explored in solid tumours. Recently, fast track designation was granted to CAR-T therapy for the treatment of Thyroid Cancer. Also, research around the efficacy of the CAR-T cells in Brain tumor is currently underway. With cell and gene therapies emerging as innovative treatment options for many cancers and other rare diseases, there are currently thousands of cell and gene therapies in the development and commercialization pipeline. As a result, the FDA is preparing for the wave of experimental therapies, and by 2025, the FDA may approve 10 to 20 new cell and gene therapy products a year.

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Ittu kundan

3.TABLE OF CONTENTS	
a)	Introduction
b)	Objective
c)	Methodology
d)	Results
e)	Limitation
f)	Conclusion
g)	References

4. LIST OF FIGURES		
Fig.1	**Page no. 16**	**Schematic representation of chimeric antigen receptor (CAR) structure.**
Fig.2	**Page no.18**	**CAR-T Cell Therapy**
Fig.3	**Page no.19**	**Difference between Autologous Vs. Allogenic CAR-T Therapies**
Fig.4	**Page no.20**	**Generation of CARs**
Fig.5	**Page no.21**	**Evolution of CAR generations**

6.LIST OF TABLES		
Tab.1	**Page no.23**	**CAR-T: Marketed Products**
Tab.2	**Page no.27**	**Phase III Studies of the Marketed CAR-T Products submitted to gain Approval.**
Tab.3	**Page no.28**	**Emerging CAR-T Therapies in the last-stages of Development**
Tab.4	**Page no.28**	**Ongoing Clinical Trials of the CAR-T drugs in Pre-registeratio Phase and Phase3 Clinical development and are expected to be launched in next few years**

6. LIST OF ABBREVIATIONS

- ACT- Adoptive Cell Transfer
- ALL- Acute Lymphoblastic Leukemia
- DLBCL- Diffuse large B-cell lymphoma
- EMA- European Medicines Agency
- FDA- Food and Drug Administration
- HLA- Human leukocyte antigen
- IGRT- Image guided radiation therapy
- PMBCL- Primary mediastinal large B-cell lymphoma
- TAAs- Tumor-associated antigens
- TCRs- T-cell receptors
- TRUCK- T-cells redirected for universal cytokine killing
- 3D-CRT- Three-dimensional conformal radiation therapy

7. TEXT

7.1.Introduction

Hematological cancers are one of the main causes of death in the world. Over time, various conventional cytotoxic methodologies have been created for neoplastic diseases. Albeit, due to the restricted effectiveness of these approaches as per the heterogeneity of disease cells, there is a consistent quest for therapeutic approaches with improved result.
The immune system is the body's defense against infection and cancer. It is made up of billions of cells that are divided into several different types.
Lymphocytes, a subtype of white blood cells, comprise a major portion of the immune system. There are three types of lymphocytes:

- B lymphocytes (B cells) make antibodies to fight infection.
- T lymphocytes (T cells) have several functions, including helping B lymphocytes to make antibodies to fight infection, and directly killing infected cells in the body.
- Natural killer cells also attack infected cells and eliminate viruses.

Immunotherapy

- It is a type of treatment that utilizes the body's own immune system to fight cancer.
- Improves the body's ability to detect and kill cancer cells.
- Is based on the concept that immune cells or antibodies can recognize and kill cancer cells.

Immune cells or antibodies can be produced in the laboratory under tightly controlled conditions and then given to patients to treat cancer. Several types of immunotherapies are either approved for use or are under study in clinical trials to determine their effectiveness in treating various types of cancer.
The development and impact of cancer treatments in the past decade is the fruit of decades of research. Immunotherapy, unlike traditional treatments, tries to use, modify, and boost the body's defenses to attack and remove tumor cells. Cancer immunotherapy is currently the most studied field in clinical trials around the world[1].
The term "cancer immunotherapy" encompasses a broad range of therapeutic options, including monoclonal antibodies, immune checkpoint inhibitors, vaccines, oncolytic viruses, cytokines, adjuvant immunotherapy and adoptive immunotherapy with T cell and natural killer (NK) cell transfers.

Adoptive T cell transfer (ACT) is a new area of transfusion medicine which involves the infusion of lymphocytes to mediate antitumor, antiviral, or anti-inflammatory effects. Three forms of ACT are being developed for cancer therapy; these include tumor-infiltrating lymphocytes (TILs), T cell receptor (TCR) T cells, and CAR T cells. Out of these three, CAR-T cells are the most developed ACTs, with more than 700 clinical trials underway worldwide investigating their use for treatment of blood cancers and, to a lesser extent, solid tumors. Adoptive T-cell therapy (ACT) was designed to treat metastatic cancer with a patient's own T-cells, and it has been shown throughout time by manipulating, expanding, and reinfusing T-cells ex vivo. Rosenberg in 1980, was the first to report a unique approach for producing huge numbers of autologous lymphoid cells capable of lysing fresh, non-cultured, primary, and metastatic cancer cells.

CAR-T Cell Therapy is the form of Adoptive Cell Transfer (ACT) that has progressed the most in clinical trials. It is a significant step forward in customized cancer treatment. It entails genetically altering a patient's autologous T-cells to express a CAR specific for a tumor antigen, followed by ex vivo cell multiplication and re-infusion. CARs are fusion proteins of a selected single-chain fragment variable from a specific monoclonal antibody and one or more T-cell receptor intracellular signaling domains. This T-cell genetic modification may occur either via viral-based gene transfer methods or nonviral methods, such as DNA-based transposons, CRISPR/Cas9 technology or direct transfer of in vitro transcribed-mRNA by electroporation. Chimeric antigen receptor (CAR)-T cell therapy has been revolutionary as it has produced remarkably effective and durable clinical responses. CARs are engineered synthetic receptors that function to redirect lymphocytes, most commonly T cells, to recognize and eliminate cells expressing a specific target antigen. CAR binding to target antigens expressed on the cell surface is independent from the MHC receptor resulting in vigorous T cell activation and powerful anti-tumor responses. CARs are made up of an antibody-derived single-chain variable region (scFv) for antigen recognition and binding, a membrane-spanning domain, and an intracellular signaling domain that are designed to recognize specific cancer-associated antigens. Endogenous TCRs have an intracellular CD3ζ domain which initiates downstream killing pathways on receptor activation, in a process known as signal. TCR interaction is not enough to activate T-cell signaling in normal physiology; costimulatory molecules on the T-cell must also be activated, a process known as signal. Cross-linking between the TCR and costimulatory receptors occurs because of this co-stimulation, resulting in T-cell activation.

T cells, as promising effector cells for adoptive cell therapy, could detect transformed cells through the specific recognition between T-cell receptors (TCRs) and peptide/human leukocyte antigen (peptide/HLA) complexes. These peptides are derived from tumor-associated antigens (TAAs) which are mutant proteins or over-expressed proteins exist in malignant cells. An increasing number of TAAs have been identified by T-cell epitope cloning, together with advanced genomic, transcriptomic, and proteomic technologies. Among these TAAs, melanocyte differentiation antigen glycoprotein 100 (gp100) is of particular interest because it is over-expressed in melanoma (>90%) and highly immunogenic[2]. The TCR α and β chains from the gp100-reactive T-cell clones have been isolated and subsequently used to transduce patients' lymphocytes, which induced a 19% objective tumor regression rate in 16 treated patients with melanoma. Despite of its clinical efficacy, further development of adoptive therapy based on transgenic TCR has been limited due to the difficulty in TCR acquisition and the potential danger of TCR mispairing.

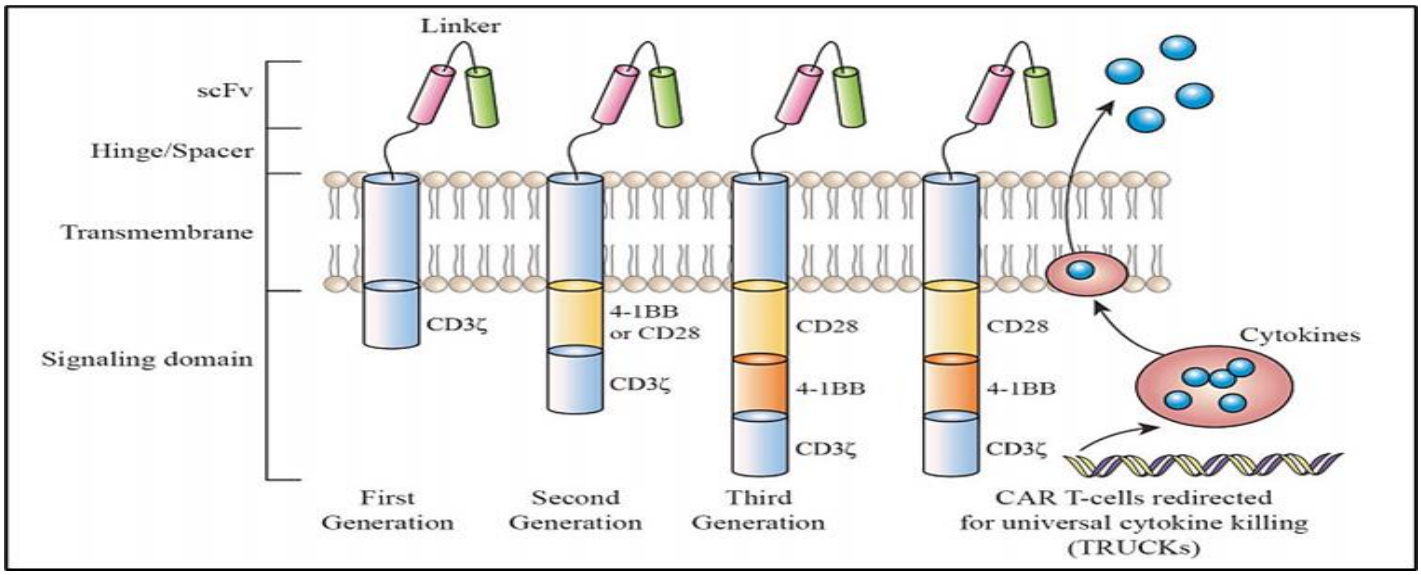


Fig 1. Schematic representation of chimeric antigen receptor (CAR) structure.

As shown in the above figure, the extracellular domain of the CAR consists of the antigen binding moiety and a spacer. These antigen binding moieties could be:

- A scFv (single-chain fragment variable), derived from antibodies.
- A human Fab fragment, selected from phage display libraries.
- Nature ligands that engage their cognate receptor

More specifically, the scFv is a variable monoclonal antibody fragment, derived from mouse monoclonal antibodies (mAbs), humanized Abs or fully human Abs and it is responsible for recognizing and binding to tumor-associated antigens (TAAs), expressed on the tumor cell surface. The simplest form of spacer is the hinge region of IgG1 and is sufficient for most scFv-based constructs. A spacer is the connection between the antigen binding domain and the transmembrane domain (TM). This TM domain relates to an intracellular signaling moiety. The most stable receptor is the CD28 TM. The most common component of the intracellular domain is CD3ζ, shown to deliver the first signal for T-cell activation and function. Concomitant co-stimulatory signals (CD28 or 4-1BB) are needed as the second signal, critical for increased secretion of cytokines (IL-2) and the in vivo expansion and persistence of T-cell. The intracellular signaling domain has been extensively evaluated both pre-clinically and clinically and can greatly affect the functional activity of CARs. CARs recognize unprocessed antigens, as well as carbohydrate and glycolipid structures, typically expressed on the cell surface of a tumor cell, without the requirement of antigen presentation through the MHC.

The unprecedented success of anti-CD19 CAR-T cell therapy against B cell malignancies resulted in its approval by the US Food and Drug Administration (FDA) in 2017. Life-threatening CAR-T cell-associated toxicities, limited efficacy against solid tumors, inhibition and resistance in B cell malignancies, antigen escape, limited persistence, poor trafficking and tumor infiltration, and the immunosuppressive microenvironment are all major limitations that must be addressed. In addition, the workforce must adapt to meet the needs of this growing and evolving field by developing educational programs to train a workforce. Many approaches including combining CAR-T cell therapy with other anticancer therapies or employing innovative CAR engineering strategies to improve anti-tumor efficacy, expand clinical efficacy, and limit toxicities have been proposed.

Recent dramatic clinical responses in studies with gene-modified T-cells expressing chimeric antigen receptors (CARs) in malignant B-cell tumors have generated great excitement and have become the first genetically engineered cell-based therapy to receive approval from the US Food and Drug Administration. This therapy has paved the way for a potential paradigm shift in the way refractory or relapsed cancers are treated. CAR T cell therapy is also being explored in solid tumors. Recently, fast track designation was granted to CAR-T therapy for the treatment of Thyroid Cancer. Also, research around the efficacy of the CAR-T cells in Brain tumor is currently underway. With cell and gene therapies emerging as innovative treatment options for many cancers and other rare diseases, there are currently thousands of cell and gene therapies in the development and commercialization pipeline. As a result, the FDA is preparing for the wave of experimental therapies, and by 2025, the FDA may approve 10 to 20 new cell and gene therapy products a year.

7.1.1. CAR-T Cell Therapy

According to the National Institute of Cancer, CAR-T Cell Therapy (Also called chimeric antigen receptor T-cell therapy) is a type of immunotherapy in which a patient's T cells (a type of immune system cell) are changed in the laboratory so they will attack cancer cells. T cells are taken from a patient's blood. Then the gene for a special receptor that binds to a certain protein on the patient's cancer cells is added to the T cells in the laboratory. The special receptor is called a chimeric antigen receptor (CAR). Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion. CAR T-cell therapy is used to treat certain blood cancers, and it is being studied in the treatment of other types of cancer.

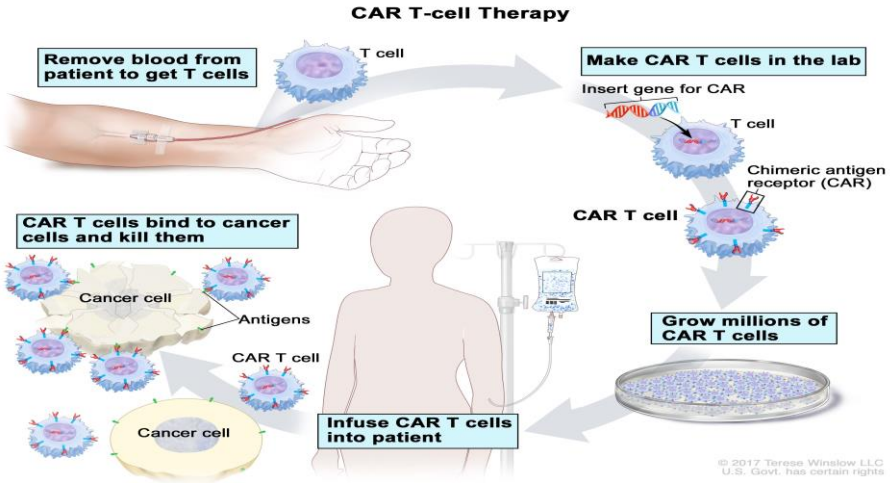


Fig 2: CAR-T Cell Therapy

7.1.2 Sources of CAR-T Cells

Currently, there are two main sources of T cells that can be engineered into CAR T cells: those derived from a patient (autologous) and those derived from a healthy donor (allogeneic). In both cases, viral vector transduction, either Ɣ-retroviral vector or lentiviral vector, are most used to insert DNA constructs into the T cell genome which transforms the normal T cells into CAR T cells. More recently, genome editing tools such as CRISPR/Cas9 have also been used to achieve this genetic integration.

Autologous CAR-T cell therapies have generated impressive clinical results with complete remission rates in B-acute lymphoblastic leukemia in over >80% of patients5. However, some key pain points with autologous cells like cost, complex logistics, reliability, and the potential of serious side effects warrants consideration and are current roadblocks to more expansive use of the therapy.

7.1.2.1. Autologous CAR-T Therapy

In 2017, the U.S. FDA approved the first two CAR-T cell therapies: Novartis' Kymriah® for treatment of acute lymphoblastic leukemia (ALL) and Gilead subsidiary Kite Pharma's Yescarta for certain types of large B-cell lymphomas, a type of non-Hodgkin lymphoma. These autologous therapies are patient-specific where the therapeutic CAR-T cells are created from a patient's own cells.

Briefly, a patient's T cells are collected via leukapheresis and subsequently transported to a manufacturing facility for ex vivo genetic modification. First, the leukapheresis material undergoes enrichment of target T cells using positive selection of CD4 and CD8 markers. Then the T cells undergo activation and viral transduction with CARs targeted against a specific tumor antigen (i.e., CD-19)[5]. The transduced cells are culture-expanded, formulated, and cryopreserved. This final formulated CAR-T product is then shipped back to the treatment center, thawed, and administered to the patient via infusion as a single dose. This complex manufacturing process is compounded by a time-sensitive logistical matrix with many stakeholders and points of potential failure. These

and other factors are challenges to be overcome with autologous CAR-T therapies.

7.1.2.2. Allogenic CAR-T Therapy

There are several advantages to using allogeneic CAR-T cells including reduced cost of goods, a more simplified supply chain and better characterization/ quality testing of the start and end products, which are common issues associated with autologous CAR-T cells. However, allogeneic CAR T cells may cause life-threatening graft-versus-host disease and may be rapidly eliminated by the host immune system[5]. The development of next-generation allogeneic CAR T cells to address these issues is still an active area of research.

	Time	Cost	Quality Control	Availability
Autologous CAR-T Therapies	Autologous CAR-T therapies have a long lead-time since it utilizes a patient's own cells for the manufacturing process and can take 2-4 weeks.	The cost of patient-specific CAR-T therapies are high and the logistics are very complex making it a challenge for widespread use.	The variability of the starting cell population makes it difficult to control parameters during the manufacturing process and perform tests to ensure product quality.	The patient's cells can impact the success of the CAR-T manufacturing. This can mean manufacturing failures that result in a patient not being able to receive treatment.
Allogeneic CAR-T Therapies	Allogeneic cell therapies can be made in advance of when they are needed, which means treatment is available to patients "on demand".	Because the therapy can be used for many patients, the cost of goods is considerably reduced compared to single-patient autologous therapy. The manufacturing is scalable.	Advanced manufacturing allows allogeneic therapies to be properly tested to maintain CQAs to ensure product efficacy and safety.	The inventory of a pre-manufactured cell therapy product can more readily managed and stored in centers globally to ensure that patients have access to the therapeutic when needed.

Fig 3: Difference between Autologous Vs. Allogenic CAR-T Therapies

7.1.3. CARS Generations

Since the initial development of CARs in 1989, CAR T-cells can be divided into four generations, according to the structure of the intracellular domain.

- **First generation:** First generation CARs comprised of the ζ (zeta) chain of complex TCR/CD3 (CD3ζ).
- **Second generation:** Second generation CARs are characterized by the dual signal for T-cell activation: one triggered by the antigen recognition and another produced by a co-stimulatory molecule, such as CD28/B7, which promotes the IL-2 synthesis to complete the activation of T-cells and avoid apoptosis.

- **Third generation:** Third generation CARs combine sequences of co-stimulatory signals, such as OX40 (CD134), CD28, 4-1BB (CD137), CD27, DAP10 or other molecules, in combination with CD3ζ. The combination of multiple co-stimulatory signals may enhance CAR T-cell function via increased cytokine production, T-cell proliferation and killing in the setting of recursive exposure to antigen. However, these treatments have failed to improve the patients' outcomes relative to those with second generation CARs (small number of cases studied). More studies are needed to explore the safety and efficacy of third generation CARs.
- **Fourth Generation CARs:** Additionally, further optimized design of CARs, such as CAR T-cells redirected for universal cytokine killing (TRUCK) has also been suggested by many researchers. TRUCK cells produce and then release a transgenic product, such as IL-12 or IFN-γ. IL-12 can activate innate immune responses against tumor cells, invisible to CAR T-cells, while IFN-γ can contribute to the antigen-independent destruction of tumor cells through IFN-γR, which is expressed in the tumor stroma.
- **Fifth Generation CARs:** The fifth generation of CARs, based on the second generation, uses gene editing to inactivate the TRAC gene, leading to the removal of the TCR alpha and beta chains.

Table 1: CARs Generations: Snapshot

Properties	1st Generation	2nd Generation	3rd Generation	4th Generation CAR-T
Alias names	CARs	Armored CARs	Armored CARs	TRUCKS (CAR T-cells redirected for universal cytokine killing)
Co-Stimulatory (Additional signaling) domain	Absent	One	Two or more	One
Safety	Normal	Better	Ambiguous	Ambiguous
Structure	ScFv + spacer+ signaling domain as CD3-zeta	ScFv + spacer+ CD28/ OX40 (CD134)/ 4-1BB (CD137)/ DAP10/ ICOS/ Lck+ CD3-zeta	ScFv + spacer+ CD3z-CD28-41BB/ CD3z-CD28-OX40+ CD3-zeta	ScFv + spacer + CD28+ CD3-zeta+ NFAT (nuclear factor of the activated T cell) responsive expression cassette encoding transgenic IL-12

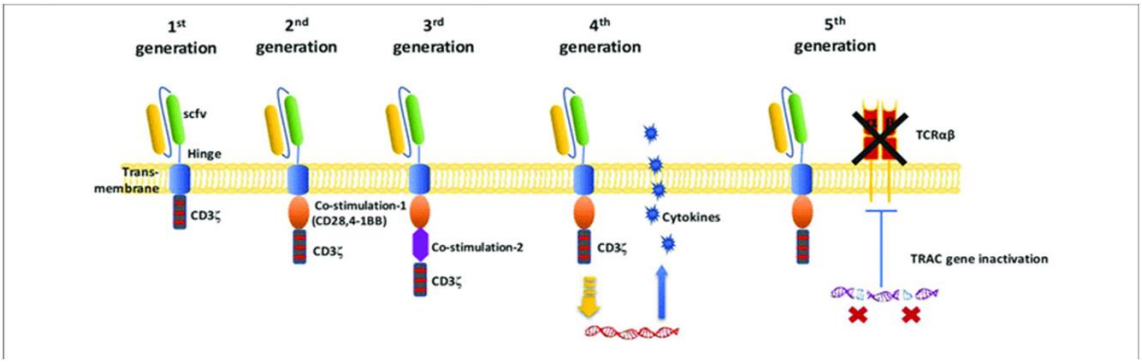


Fig 4: Generation of CARs

7.1.4. Evolution of CAR Designs

Kuwana et al. (1987) reported the first proof of principle of combining antibody-type antigen specificity with T-cell signaling by fusing the TCR constant region to the variable regions of a bacterial antigen-recognizing antibody. Single-chain variable fragments (scFvs), composed of the variable heavy (VH) and light (VL) chains of a monoclonal antibody (mAb) separated by a flexible linker, are still commonly used as the extracellular antigen-sensing domain of CARs. The first reports of tumor-targeting CARs demonstrated that an scFv recognizing antigens such as human epidermal growth factor receptor 2 (HER2), fused to the CD3z signaling domain can elicit tumor-specific cytotoxicity, but T cells expressing these ‘‘first-generation’’ CARs that included only the CD3z chain for T-cell signaling generally failed to elicit potent antitumor effects[3].

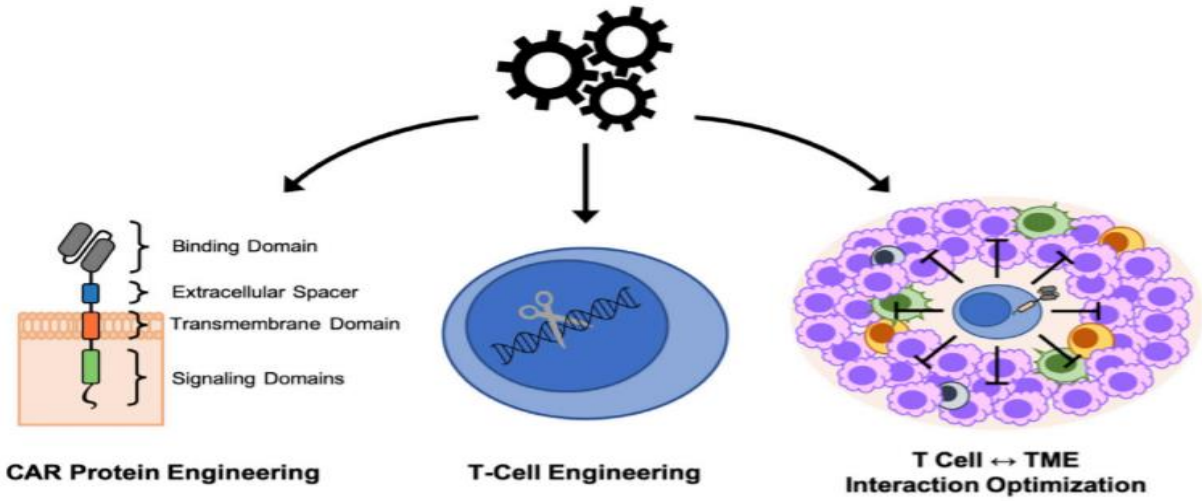


Fig 5: Evolution of CAR Design

7.2 Objective

- To understand the current scenario of the CAR-T therapies and how massively they have impacted the current hematological cancer treatment space
- To understand the Phase III CAR T-cell therapies that have transformative potential as a new type of cancer treatment

7.3 Methodology

➢ Secondary research was conducted to obtain accurate and precise information. The latest data and status of CAR-T therapy / drugs have been identified through various relevant database searches such as, Clinicaltrial.gov.in, ICRTP, PubMed, conference publications such as -ASH 2020, ASCO 2020, and ESMO 2020.

➢ Additionally, the company’s website was referenced for CAR-T pipeline therapies, CAR-T technologies descriptions, company presentations, annual reports, press releases and quarterly reports. In addition, the US FDA website and the EMA website were used to identify granular information of the marketed products such as registration studies, indications, efficacy, side effects, etc.

➢ Data were also retrieved using relevant MeSH terms such as **“Phase III” or “marketed CAR-T cell**

therapy", **"CAR-T therapy**", "**CAR-T marketed drugs**", "**CAR-T emerging drugs**", "**CAR-T approved by the FDA**", **"T Therapy**", **"Current Cancer Treatment vs CAR-T**"; **"Relapsed / Refractory Cancer**."

- **INCLUSION CRITERIA**- Only USFDA and EMA marketed CAR-T therapies and Phase 3 CAR-T therapies were considered. Note that recent 2019-2021 publications were used to extract the information.

- **EXCLUSION CRITERIA**- Phase 2 drugs, Phase1 drugs, Preclinical drug, terminated drugs, withdrawn drugs were excluded. The articles published prior to 2019 has not been considered.

7.4 Results

FDA has approved the following Five CAR-T cell Therapies for the treatment of Lymphoid Cancers-

7.4.1.CAR-T MARKETED THERAPIES

Tab 1.CAR-T: Marketed Products

Drug Name	Alias Name	Year of Approval	Location	Indication	Route of Administration
Tisagenlecleucel-t	KYMRIAH	·2017- ALL ·2018-DLBCL	Marketed (US, EU, Switzerland, Canada)	·Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) ·Relapsed or refractory acute lymphoblastic leukemia (ALL)	Injectable
Lisocabtagene maraleucel	BREYANZI	2021	Marketed (US)	Diffuse large B cell lymphoma (DLBCL), High-grade B-cell lymphoma ·Primary mediastinal large B-cell lymphoma ·Follicular lymphoma grade 3B	injectable
Brexucabtagene autoleucel	TECARTUS	2020	Marketed (US)	Relapsed or refractory mantle cell lymphoma.	Injectable
Idecabtagene vicleucel	ABECMA	2021	Marketed (US)	Relapsed or refractory multiple myeloma	Injectable
Axicabtagene ciloleucel	YESCARTA	2017	Marketed (US, EU)	·Relapsed/ Refractory Diffuse large B-cell lymphoma (DLBCL) ·Primary mediastinal B-cell lymphoma ·High grade B-cell lymphoma ·DLBCL that results from follicular lymphoma. ·Follicular lymphoma	Injectable

7.4.1.1.Kymriah: Novartis

Product Description

Kymriah (tisagenlecleucel) is a prescription cancer treatment approved for the use in patients up to 25 years old who have Acute Lymphoblastic Leukemia (ALL) that is either relapsing (went into remission, then came back) or refractory (did not go into remission with other leukemia treatments). It is made from your own white blood cells. Kymriah is a CD19-directed genetically modified autologous T cell immunotherapy comprised of autologous T cells that are genetically modified using a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signaling domains for 4-1BB (CD137) and CD3 zeta. It involves the reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal cells. Upon binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the Kymriah cells.
Kymriah is a first-of-its-kind treatment approach that fills an important unmet need for children and young adults with this serious disease.

Regulatory Milestones

- On Jan 28,2020, Novartis declared the reimbursement of Kymriah in eligible pediatric and young adult patients up to 25 years of age with acute lymphoblastic leukemia (ALL), which was announced in 2019. On August 30, 2017, the FDA approved tisagenlecleucel for treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory in second or later relapse.
- September 2018: Novartis received Health Canada approval of its CAR-T cell therapy, Kymriah (tisagenlecleucel) following a Priority Review for use in pediatric and young adult patients 3 to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) who are refractory, have relapsed after allogenic stem cell transplant (SCT) or are otherwise ineligible for SCT, or have experienced second or later relapse; and for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
- August 2018: Novartis received European Commission approval of its CAR-T cell therapy, Kymriah (tisagenlecleucel) for the treatment of pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse; and for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
- May 2018: Kymriah (tisagenlecleucel), first-in-class CAR-T therapy from Novartis, received second FDA approval to treat appropriate r/r patients with large B-cell lymphoma.
- August 2017: Novartis announced the regulatory approval of Kymriah (tisagenlecleucel) in patients up to 25 years old who have Acute Lymphoblastic Leukemia (ALL) that is either relapsing (went into remission,

then came back) or refractory (did not go into remission with other leukemia treatments), in US by the US Food and Drug Administration (USFDA).

Research & Development

Clinical Studies

The safety and efficacy of Kymriah were demonstrated in one multicenter clinical trial of 63 pediatric and young adult patients with relapsed or refractory B-cell precursor ALL. The overall remission rate within three months of treatment was 83 percent. The treatment with Kymriah has the potential to cause severe side effects. It carries a boxed warning for cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR T-cells causing high fever and flu-like symptoms, and for neurological events. Both CRS and neurological events can be life-threatening. Other severe side effects of Kymriah include serious infections, low blood pressure (hypotension), acute kidney injury, fever, and decreased oxygen (hypoxia). Most symptoms appear within one to 22 days following infusion of Kymriah. Since the CD19 antigen is also present on normal B-cells, and Kymriah also destroyed those normal B cells that produce antibodies, there may be an increased risk of infections for a prolonged period.
The most common (>20%) adverse reactions in the ELIANA trial are cytokine release syndrome (CRS), hypogammaglobulinemia, infections-pathogen unspecified, pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury and delirium. In the study, 49% of patients treated with Kymriah experienced grade 3 or 4 CRS, an on-target effect of the treatment that may occur when the engineered cells become activated in the patient's body. CRS was managed globally using prior site education and implementation of the CRS treatment algorithm. Within eight weeks of treatment, 18% of patients experienced grade 3 or 4 neurologic events. There were no incidents of cerebral edema. The most common neurologic events were encephalopathy (34%), headache (37%), delirium (21%), anxiety (13%) and tremor (9%).

7.4.1.2. Yescarta: Kite Pharma (Gilead Sciences)

Product Description

Yescarta (also known as axicabtagene ciloleucel; KTE-C19) is an intravenously infused CD19-directed genetically modified autologous T-cell immunotherapy. A patient’s own T-cells were harvested and genetically modified ex vivo by retroviral transduction to prepare Yescarta. This was done to express a chimeric antigen receptor (CAR) compromising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains.
Yescarta binds to CD19-expressing cancer cells and normal B cells. The studies have demonstrated that following anti-CD19 CAR T-cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.
Yescarta which was developed by Kite Pharma (acquired by Gilead Sciences on October 3, 2017) received the marketing authorization by the USFDA as the first chimeric antigen receptor T-cell therapy for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Regulatory Milestones

- April 2021: Axicabtagene ciloleucel was launched for B-cell lymphoma and Diffuse large B cell lymphoma in Canada.
- August 2018: Kite, a Gilead Company has been granted Marketing Authorization from the European Commission (EC) for Yescarta (axicabtagene ciloleucel) as a treatment for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy. The Marketing Authorization approves axicabtagene ciloleucel for use in the 28 countries of the European Union, Norway, Iceland, and Liechtenstein.
- October 2017: USFDA granted approval to Yescarta for the treatment of patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
- May 2017: the company announced that the USFDA has accepted for priority review the Biologics License Application (BLA) for axicabtagene ciloleucel. The submission followed positive data demonstrated with a single infusion of axicabtagene ciloleucel in the ZUMA-1 Phase II trial in patients with refractory aggressive NHL.
- April 2016: Axicabtagene ciloleucel was granted orphan designation for Primary mediastinal B-cell lymphoma (PMBCL) and Follicular lymphoma (FL) by the USFDA.
- December 2015: the USFDA granted breakthrough therapy designation for refractory, aggressive NHL.
- April 2014: Axicabtagene ciloleucel was granted orphan designation for Diffuse large B-cell lymphoma (DLBCL) by the USFDA.

7.4.1.3. Tecartus: Kite Pharma (Gilead Sciences)

Product Description

Brexucabtagene autoleucel (Tecartus), an autologous CD19 CAR-T cell therapy, developed by Gilead (Kite Pharma before acquisition) is the first and only approved chimeric antigen receptor (CAR) T cell therapy for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). Tecartus uses the XLP manufacturing process that includes T cell enrichment, a necessary step in certain B-cell malignancies in which circulating lymphoblasts are a common feature. The approval of Tecartus is supported by data from the ongoing, single arm, open-label ZUMA-2 pivotal trial. The study enrolled 74 adult patients with relapsed or refractory MCL who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody therapy and a Bruton tyrosine kinase inhibitor (ibrutinib or acalabrutinib).
Tecartus has been launched only in the U.S. On April 2020, the U.S. Food and Drug Administration (FDA) has granted accelerated approval to Tecartus (brexucabtagene autoleucel). The approval of this one-time therapy follows a priority review and FDA Breakthrough Therapy Designation and is based on results of ZUMA-2.

7.4.1.4. Breyanzi: Bristol-Myers Squibb

Product Description

Lisocabtagene maraleucel (Breyanzi) developed by Bristol-Myers Squibb (Celgene before acquisition (before acquisition Juno Therapeutics)), using its chimeric antigen receptor (CAR) modified T-cells technology is a CD19-directed chimeric antigen receptor (CAR) T cell immunotherapy, for the treatment of hematological cancers. It is genetically modified patient-derived CD19-specific CAR T-cells, delivered through lenti-viral vector expressing an EGFRt. It consists of autologous T cells that are genetically modified to produce a CAR protein, allowing the T cells to identify and eliminate CD19-expressing normal and malignant cells. The FDA approval of Breyanzi is based on data from the TRANSCEND NHL 001 (017001) trial in which 268 patients with R/R LBCL received Breyanzi, the largest pivotal trial in third line plus R/R LBCL that included patients with a broad range of histology and high-risk disease.
Breyanzi is a CD19-directed CAR T cell therapy with a defined composition and 4-1BB costimulatory domain. Breyanzi is administered as a defined composition to reduce variability of the CD8 and CD4 component dose. The 4-1BB signaling enhances the expansion and persistence of Breyanzi. Breyanzi offers a potentially definitive treatment. A single dose of Breyanzi contains 50 to 110 x 106 CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components).

7.4.1.5. Abecma: Bluebird/Bristol-Myers Squibb

Product Description

Idecabtagene vicleucel (Abecma) is an anti-BCMA (B-cell maturation antigen)-CAR-expressing T-cell therapeutic, developed by Bluebird Bio for the treatment of multiple myeloma. Abecma is a personalized immune cell therapy approved as a one-time infusion with a recommended dose range of 300 to 460 x 106 CAR-positive T cells. As an anti-BCMA CAR T cell therapy, Abecma recognizes and binds to BCMA, a protein that is nearly universally expressed on cancer cells in multiple myeloma, leading to the death of BCMA-expressing cells. The FDA approval of Abecma is based on data from the pivotal Phase II KarMMa trial of 127 patients with relapsed or refractory multiple myeloma who had received at least three prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody.

Table 2: Phase III Studies of the Marketed CAR-T Products submitted to gain Approval.

Drug	Tisagenlecleucel	Lisocabtagene maraleucel	Brexucabtagene autoleucel	Idecabtagene vicleucel	Axicabtagene ciloleucel)
Trial Id /Name	NCT02445248/ JULIET	NCT02631044/TRANSCEND NHL 001	NCT02601313/ZUMA-2	NCT03361748/ KarMMa	NCT02348216/ZUMA -1
Finding	The safety and efficacy of Kymriah were demonstrated in one multicentre clinical trial of 63 paediatric and young adult patients with relapsed or refractory B-cell precursor ALL. The overall remission rate (ORR) within three months of treatment was 83 %.	The overall safety profile was acceptable. 19 patients required admission to ICU and seven patients experienced grade 5 adverse events, 4 out of which were treatment-related and 3 unrelated to liso-cel (fludarabine leukoencephalopathy, septic shock, and progressive multifocal leukoencephalopathy). No grade 5 cytokine release syndrome (CRS) or	The primary efficacy analysis showed that 93% of the 60 patients in the primary efficacy analysis had an objective response; 67% had a complete response. In an intention-to-treat analysis involving all 74 patients, 85% had an objective response; 59% had a complete response.KTE-X19 induced durable remissions in most patients with relapsed or	Ide-cel demonstrated deep, durable responses in heavily pre-treated RRMM pts. Efficacy and safety reflected prior reports and support a favourable ide-cel clinical benefit-risk profile across the target dose range. ORR was	As of the cut-off date of Aug 11, 2018, 101 patients assessable for activity in phase 2 were followed up for a median of 27·1 months. 84 (83%) had an objective response, and 59 (58%) had a complete response. Two treatment-related deaths were previously reported, but no new treatment-related deaths occurred during

		neurological events (NE) were recorded. The study met all primary and secondary efficacy endpoints. Among pts evaluable for efficacy (n=255), Out of 255 pts., ORR in 186pts. was 73%; CR in 135 Pts. rate was 53%	refractory mantle-cell lymphoma. The therapy led to serious and life-threatening toxic effects that were consistent with those reported with other CAR T-cell therapies	94%; CR was 40%	the additional follow-up. These 2-year follow-up data from ZUMA-1 suggest that axicabtagene ciloleucel can induce durable responses and a median overall survival of greater than 2 years and has a manageable long-term safety profile in patients with relapsed or refractory large B-cell lymphoma.

7.4.2.CAR-T: EMERGING THERAPIES

Tab 3.Emerging CAR-T Therapies in the last-stages of Development

Drug Name	Company	Highest Stage of development	Indication
Relmacabtagene autoleucel	JW Therapeutics	Preregistration	• Diffuse large B cell lymphoma • Follicular lymphoma • Mantle-cell lymphoma • Non-Hodgkin's lymphoma
Ciltacabtagene autoleucel	Janssen Biotech/Nanjing Legend Biotech	Preregistration	• Multiple myeloma
HRAIN-001	HRAIN Biotechnology	Phase 3	• Non-Hodgkin’s lymphoma • Acute and chronic lymphocytic leukaemia

7.4.2.1. Relmacabtagene autoleucel

Relmacabtagene autoleucel is a CAR-T cell product targeting CD19, being developed by JW Therapeutics, which is a CD19-directed chimeric antigen receptor (CAR)-T cells, for the treatment of non-Hodgkin's, follicular lymphomas and B-cell malignancies including relapsed and refractory Diffuse large B cell lymphoma (DCBCL).

7.4.2.2. Ciltacabtagene autoleucel

Ciltacabtagene autoleucel is an LCAR-B38M CAR-T cell therapy, an autologous T-cells genetically engineered via lentiviral vector technology to express a synthetic receptor directed against B-cell maturation antigen (BCMA) protein target, under development by Nanjing Legend Biotech for refractory or relapsed multiple myeloma. The design comprises a structurally differentiated CAR-T with two BCMA-targeting single domain antibodies.

7.4.2.3. HRAIN-001

HRAIN-001 is a chimeric antigen receptor T-cell (CAR-T) therapy, under development by Hrain Biotechnology for non-Hodgkin’s lymphoma, and acute and chronic lymphocytic leukemia

Tab 4. Ongoing Clinical Trials of the CAR-T drugs in Pre-registration Phase and Phase3 Clinical development and are expected to be launched in next few years-

Drug	Trial ID/ Name/Location		Phase	Primary End Point	Primary Start date	Results
Relmacabtagene autoleucel		NCT04718883, NCT04089215 /China	• Phase3- (NCT04718883) • Phase2- (NCT04089215)	Objective response rate	• Phase3- January 13, 2021 • Phase2 - June 11, 2019	Phase3- not disclosed Phase2- As of the data cutoff on 17 June 2020, Relma-cel met the primary endpoint analysis and demonstrated a high rate of durable responses and low rate of CAR-T-associated toxicities in patients with r/r LBCL in a multicenter trial supporting regulatory submission in China.
Ciltacabtagene autoleucel		NCT03548207/ CARTITUDE-1/ US, Japan	Phase2	Overall Response Rate , Adverse Events	June 29, 2018	As Of Jan. ,2020, Most frequent adverse events were neutropenia (100%), CRS (93%), and thrombocytopenia (93%). Hematologic AEs were neutropenia (100%), thrombocytopenia (69%), and leukopenia (59%). 27 (93%) pts had CRS; 25 Gr 1–2, 1 Gr 3, and 1 Gr 5. ORR was 100%, with 22 (76%) stringent complete responses (sCRs), 6 (21%) very good partial responses (VGPRs), and 1 (3%) PR.. 1 death due to CRS and 1 to acute myeloid leukemia (not treatment-related) occurred during the study
HRAIN-001		NA/ China	Phase3	NA	NA	NA

7.4.3.CAR-T CELL THERAPY- MARKET DRIVERS AND BARRIERS-

CAR-T Cell Therapy: Market Drivers

Advanced Technology

- The emerging technology is the greatest driver to the CAR T-cell therapy market. The incorporation of safety switches and additional co-stimulatory domains are driving the conventional technology to certain heights, where companies are indulging themselves with these technologies, and expecting certain benefits from it in upcoming years.

Increased Collaborations & Acquisitions

- Year by year, new companies are entering in the field of CAR T-cell therapy by the routes of collaborations and joint ventures. These collaborations drive the market to new opportunities, where the technology and business development activities can be explored better with synergy of ideas and technical skills of different organizations.

Increased Safety with new CAR generations

- Recent advancements in this technology have resulted into the development of various CAR generations, which have shown promising results as enhanced safety & efficacy concerns. The criteria established the feasibility of the approach to provide T-cells with additional activating signals. Ultimately, the necessity evolved the second & third generation of CAR T-cells, which overweighed the negatives of first generation CARs.

Increased clinical & Pre-clinical studies with positive results

- The Pre-clinical trials have been increased in recent time, as the increased awareness of different firms in this segment. Companies are collaborating with different research institutes and conducting more studies that have shown more positive results with different target antigens and indications of cancer. These approaches could elaborate the potential of CAR T-cell therapy market.

Wide range of targets & indications

- Different firms are working on the product pipeline with clinical and Pre-clinical studies targeting antigens other than CD19 and exploring many other cancer indications that can be treated with this technology. The area of this market is enlarging itself with respect to research activities.

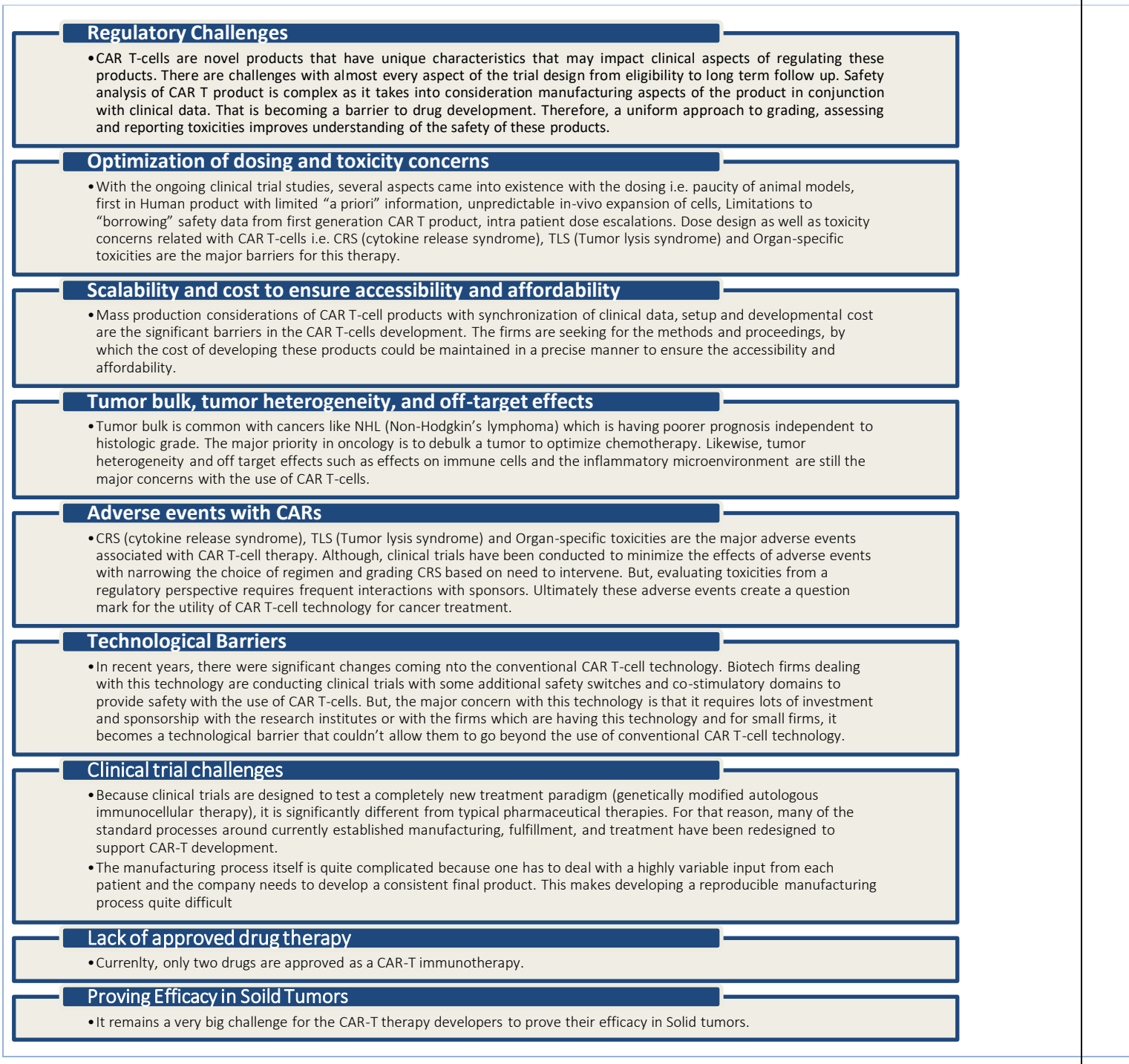
Competition among biotech and pharma giants

- In recent years, so many biotechnology and pharma firms are emerging in this segment. Many of them are coming up with their advanced technologies with existing products and some of them are aggressive with their business development tactics of collaborations and acquisitions. Therefore, this competitive landscape is providing the firms a platform, where any small firm can grow itself with the technicalities of CAR T-cell therapy and gradually the competition is making this platform much better than the recent times.

The expansion of targetable biomarkers for CAR-T cell therapy

- Recently, with the advent of Chimeric Antigen Receptor (CAR) T cell therapy, a new category of targetable biomarkers has emerged. These biomarkers are associated with the surface of malignant cells and serve as targets for directing cytotoxic T cells. The first biomarker target used for CAR T cell therapy was CD19, a B cell marker expressed highly on malignant B cells. With the success of CD19, the last decade has shown an explosion of new targetable biomarkers on a range of human malignancies.

CAR-T Cell Therapy: Market Barriers



7.5. Limitations of CAR-T cell Therapy

One of the most challenging limitations of CAR-T cell therapy is the development of tumor resistance to single antigen-targeting CAR constructs[4]. Although initially single antigen targeting CAR-T cells may provide high response rates, malignant cells of a significant proportion of patients treated with these CAR-T cells show partial or complete loss of target antigen expression. This phenomenon is known as antigen leakage.

The main challenge in selecting solid tumor antigens is that solid tumor antigens are also often expressed in normal tissues to varying degrees. Therefore, the selection of antigens is crucial in the design of CAR not only to

ensure therapeutic efficacy, but also to limit toxicity "on the target outside the tumor". A potential way to overcome the targeting of antigens in solid tumors that are also present in normal tissues is targeting tumor-limited posttranslational modifications, such as O-glycans from overexpressed truncated solid tumors as Tn (GalNAca1-O-Ser/Thr) and sialyl-Tn (STn) (NeuAca2-6-GalNAca1-O-Ser/Thr).

In comparison to hematological malignancies, CAR-T cell therapy of solid tumors is limited by the ability of CAR-T cells to transit and infiltrate solid tumors, since the immunosuppressive tumor microenvironment and physical barriers of the tumor, such as the tumor stroma, limit the penetration and mobility of the car[6,7]. T cells. One strategy to improve these limitations is using administration routes other than systemic administration, as local administration (1) eliminates the need for CAR-T cells to travel to disease sites and (2) limits non-tumor target toxicity since the target activity of CAR-T cells is directed to tumor cells, minimizing interaction with normal tissues.

Many immunosuppressive cell types, such as myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells, can infiltrate solid tumors in the tumor microenvironment (Tregs). Tumor-promoting cytokines, chemokines, and growth factors are produced by these infiltrates and tumor cells. Furthermore, immune checkpoint pathways like PD-1 and CTLA-4 can reduce antitumor immunity. Poor T cell multiplication and short-term T cell persistence are two of the most common causes of no response or a limited response to CAR-T cell treatment. Co-inhibitory pathways are thought to be responsible for the development of T cell fatigue. Combination immunotherapy with CAR-T cells and checkpoint blockade is thought to be the next immunotherapy frontier because it combines the two elements required for strong immune responses:1 CAR-T cells, which provide the infiltrate, and2 PD-1/PD-L1 blockade, which ensures T cell persistence and function.

A CAR-T cell antigen-binding domain must engage its target epitope and reach a minimum threshold level to activate CAR-T cell activation and cytokine release in order to achieve successful therapeutic responses. However, there is a threshold level of activation that, when exceeded, results in hazardous quantities of cytokines and immune system activation. In other words, the CAR-T cell must remain within its therapeutic window to be clinically effective as overshooting the therapeutic window will lead to toxicity. Several parameters, including but not limited to the proportion of tumor antigen expressed on malignant cells, tumor burden, antigen binding domain affinity to its target epitope, and the CAR's costimulatory components, determine the degree of CAR-T cell activation and activation kinetics[8]. Therefore, to maximize therapeutic efficacy while limiting toxicity, careful study of numerous components of the CAR's modular structure is required.

7.6. Conclusion

Chimeric antigen receptor T-cell (CAR T) therapy is a revolutionary immunotherapy that uses cells from the patient's immune system to fight certain kinds of cancer. These therapies have been established in the treatment of relapsed or refractory tumors, particularly for hematological malignancies.

Currently there are 5 potential CAR-T therapies have been approved and 3 are in Phase III stage of development. The clinical successes with CD19 CAR T cells in leukemia and lymphomas have boosted the field and led to significant pharmaceutical and venture capital funding of the biotech sector, as well as promoting innovative academic-industrial partnerships to explore new discoveries in basic research that may translate into clinical and commercial development.

Current Trends suggest that there are ~700 CAR-Therapies in the pipeline and approximately ~593 CAR T-cell therapy clinical trials registered on ClinicalTrials.gov database1.

The global car-t therapy pipeline analysis market is expected to grow from $1.08 billion in 2020 to $1.4 billion in 2021 at a compound annual growth rate (CAGR) of 29.6%.2

In conclusion, CAR-T technology has great potential for broad clinical use in the malignant cancer. The Recent progress of the novel therapy is paving the way to better and more durable outcomes and allowing patients to live longer and more meaningful lives and changing the treatment landscapes for advanced hematological cancers.

However, given the competitive nature of drug development, the high costs of conducting clinical trials and the significant risks of toxicity to patients, careful selection, and prioritization of next-generation CAR designs to translate to the clinic will be increasingly important in successfully moving this field forward.3

7.7. Reference:

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