Review Article

Targeting EGFR Resistance Mechanisms Using Modular CAR-T Cell Platforms in Non-Small Cell Lung Cancer

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ABSTRACT

Non-small cell lung cancer (NSCLC) remains a major cause of cancer mortality, and epidermal growth factor receptor (EGFR)-mutant disease is a clinically important subset initially responsive to tyrosine kinase inhibitors (TKIs). However, durable benefit is limited by acquired resistance driven by on-target EGFR mutations, bypass pathway activation, histologic transformation, and intratumoral heterogeneity. These mechanisms reduce the effectiveness of sequential EGFR-targeted therapy and create a need for alternative treatment strategies. In parallel, modular CAR-T platforms have emerged as programmable immunotherapeutic systems that separate antigen recognition from T-cell activation, allowing reversible, tunable, and multi-antigen targeting. Adapter-mediated systems, switchable CARs, and logic-gated CAR designs may offer advantages in heterogeneous solid tumors by improving specificity and limiting toxicity. This review summarizes major EGFR resistance mechanisms in NSCLC and evaluates how modular CAR-T technologies could be adapted to overcome resistance and improve antitumor control.

Keywords: NSCLC, EGFR mutations, Targeted therapy, CAR-T cell therapy, Lung cancer immunotherapy.

INTRODUCTION

Lung cancer proves to be problematic all over the world and perhaps the most dangerous form of cancer worldwide, with the greatest number of cancer deaths[1]. In 2020, lung cancer was first and third globally in terms of cancer diagnoses[2]. 80% to 90% of lung cancers are caused by tobacco use, making it the most prevalent cause of the disease[3]. NSCLC has the highest mortality rate among lung cancers, with 1.7 million deaths in 2020 worldwide[4]. Lung cancer research is increasingly leveraging real-world data to revolutionize understanding, diagnosis, and treatment strategies[5]. In lung cancer, 15% are small cell lung cancer, and the remaining 85% are non-small cell lung cancer (NSCLC), specifically the subtype of adenocarcinoma[6]. The NSCLC is also caused by mutations in the epidermal growth factor receptor (EGFR). EGFR mutations activate proteins to promote tumor growth; hence, the mutation-causing genes are considered as biomarkers for lung cancer. To overcome these mutations of EGFR, researchers changed the treatment protocol to develop EGFR-TKI (tyrosine kinase inhibitors), which is the first line of treatment for non-small cell lung cancer (NSCLC)[7]. Therapies such as radiotherapy, surgery, and chemotherapy are effective treatments for cancer patients, but these cause major side effects among patients. This shows oncology needs advanced treatment strategies to combat cancer cells. To revolutionize cancer treatments, researchers have developed the term "targeted therapy," which uses modified drugs to target oncogenic cells, which are the primary cause of spreading cancer cells[8,9].

The first line of targeted therapy for NSCLC was epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKI). It is designed to interfere with the cancer progression pathway for tumor control, which blocks these cascading biological pathways with evidence of anticancer activity[10]. Epidermal growth factor receptors are a glycoprotein that plays a role in the growth of tumor cells. EGFR-targeted therapy is effective in regulating the epidermal growth factor receptor signaling pathway, and polymerase chain reaction detects EGFR mutations, which are biomarkers for NSCLC cancer. In 40%-80% of patients with non-small cell lung cancer, they are affected due to this EGFR mutation[11].

Over the years, immunotherapy has evolved to overcome barriers in cancer treatment, introducing chimeric antigen receptor CAR-T cell therapy, which shows promising results for the treatment of lung cancer[12]. The target for CAR-T cell therapy includes epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER_2), tyrosine kinase-like orphan receptor-1 (ROR1), and programmed death ligand 1 (PD-L1). Chimeric antigen receptors (CAR) are genetically encoded receptors that combine the specific binding domains from a tumor-targeting antibody to redirect T cell activation[13]. The evolution of targeted therapy has shifted from a lack of specificity of drugs towards biomolecules with a mild toxicity profile. A crucial aspect of molecular targeted therapy involves triggering apoptosis in cancer cells. Medications can be engineered to focus on specific biological indicators present in cells within the tumor microenvironment that contribute to cancer growth[14].

TREATMENT STRATEGIES FOR NSCLC:

Biological therapy, chemotherapy, radiation, and surgery are among the current options for therapy for non-small cell lung cancer. The 5-year survival rate for patients with stage

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1A NSCLC is approximately 49%, whereas for those with stage 1B NSCLC, it is approximately 45%. For stages 2A, 3A, 3B, and 4, the survival rates are 30%, 31%, 14%, and 1%, respectively[15]. The mechanism working of targeted therapy is to interfere with particular molecular targets associated in the development, progression, and proliferation of cancer. Molecular targets include EGFR, ROS1, KRAS, and DDR2. EGFR inhibitors and EGFR-TKIs are used as targeted EGFR therapy[16].

EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR):

EGFR is part of the ErbB family of receptor tyrosine kinases associated with erythroblastic oncogene B. It is also denoted as ErbB1 and HER1[17]. The epidermal growth factor receptor is involved in controlling cell proliferation and survival. The three primary domains of EGFR—the intracellular kinase domain, the across the membrane domain, and the extracellular domain—are responsible for its role in the signal transduction pathway. The roles of EGFR in cancer cells are growth, mutation, proliferation, differentiation, and lack of apoptosis[18].

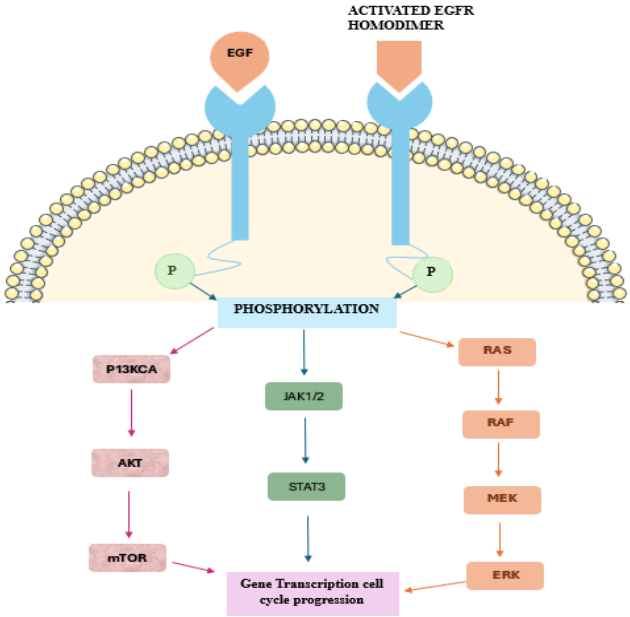


Figure 1: Activation of EGFR Receptor Downstrem Signaling

EGFR MUTATIONS:

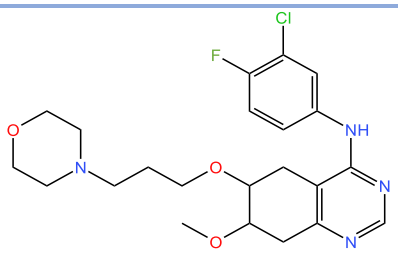
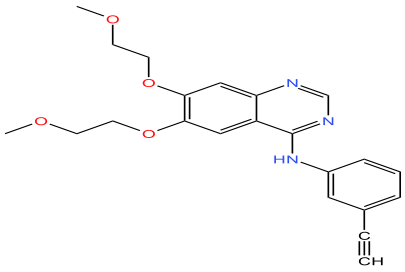
EGFR mutations refer to alterations in the epidermal growth factor receptor (EGFR) gene, which can lead to proliferation and dissemination of cancer cells[19]. Here are four primary categories of mutations: point mutations at codon 719 (G719X), deletions in exon 19, insertion mutations in exon 20, and a point mutation at codon 858 in exon 21[20]. EGFR mutations with categorized sections produce alternate results to kinase inhibitors. For instance, EGFR exon 20 insertions were found to be relatively resistant to gefitinib compared to other mutations. Newly discovered mutations in EGFR-T790M were shown to cause secondary resistance to gefitinib[21].

Most EGFR mutations (85% to 90%) are caused by deletions in exon 19 and point mutations in exon 21 found in NSCLC patients. Clinical studies have demonstrated that mutations show high responsiveness to EGFR inhibitors such as gefitinib and erlotinib[22]. Considering that EGFR mutation status plays a crucial role in determining the most suitable treatment, evaluating EGFR mutations continues to be essential in everyday clinical practice. Various techniques are available for identifying EGFR gene mutations[23]. Evaluating EGFR mutation status in advanced non-small cell lung cancer is hindered by suitable tissue biopsy for molecular testing[24]. A less invasive alternative to tissue biopsy is liquid biopsy based on free nucleic acid, which has gained increased attention. Compared to the traditional biopsy method, ctDNA has the potential to reflect all heterogeneous mutations during patient treatment[25]. Mutation-positive control DNA was combined with normal DNA of equivalent concentration at various ratios; it includes tests for exon 19 deletion and point mutations L858R and T790M[26].

EGFR INHIBITORS:

Drugs designed to inhibit EGFR activity are of two major classes: monoclonal antibodies and small-molecule tyrosine kinase inhibitors (TKIs). In which the monoclonal antibodies bind to an extracellular region of the receptor, and TKIs bind to the ATP binding site of the EGFR kinase domain to inhibit its activity[27]. The FDA approved gefitinib on July 13, 2015, as an initial treatment option for patients with metastatic NSCLC[28]. Erlotinib- and gefitinib-treated NSCLC patients were the subject of an observational study. The safety profiles of the two medications were comparable, with the exception of skin side effects such as rash and acneiform eruption. The PFS of gefitinib and erlotinib did not differ significantly. Thus, in comparison to erlotinib, gefitinib may be a superior choice for patients with non-small cell lung cancer[29]. On November 18, 2004, erlotinib got approval for its EGFR inhibitory action[30]. By targeting HER2 and HER4, in addition to inhibiting EGFR, second-generation TKIs offer a wider range of action against cancers that may express several ErbB family members.

Table 1: Effective EGFR inhibitors approved by the FDA

Drugs	Structure
Gefitinib (First Generation Drug)	
Erlotinib (First-Generation Drug)	

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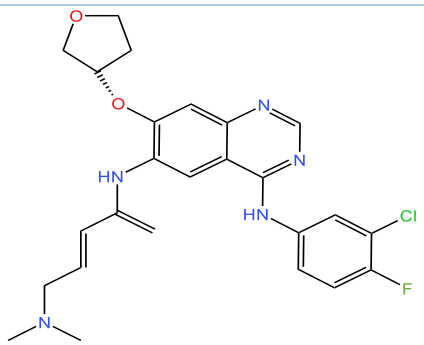
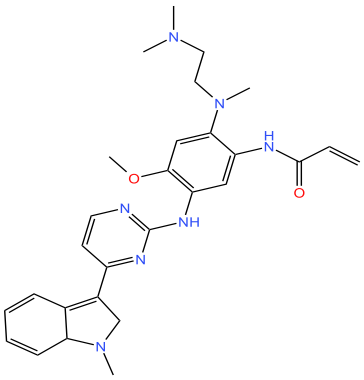
Afatinib (Second-Generation Drug)	
Osimertinib (Third-Generation Drug)	

For patients with EGFR mutations who have had progression after first-generation TKIs, afatinib is a major improvement in the available therapy options[31]. The FDA first authorized afatinib on July 12, 2013, to treat patients with metastatic non-small cell lung cancer (NSCLC). In 2016, the FDA approved afatinib for the treatment of metastatic squamous NSCLC that had progressed following platinum-based chemotherapy[32].

Osimertinib was authorized by the U.S. Food and Drug Administration (FDA) on March 30, 2017, to treat patients with metastatic epidermal growth factor receptor (EGFR) T790M[33]. For adult patients with locally advanced, unresectable (stage III) non-small cell lung cancer (NSCLC) whose disease has not advanced during or after concurrent or sequential platinum-based chemoradiation therapy and whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as identified by an FDA-approved test, the Food and Drug Administration approved osimertinib on September 25, 2024. The international phase 3 LAURA trial reported no disease progression after 24 months of platinum-based chemoradiotherapy[34].

TOXICITY OF EGFR INHIBITORS:

EGFR inhibitors, while effective in treating cancers with EGFR mutations, also have side effects that kill healthy cells. These side effects primarily occur as skin reactions but can also include issues like diarrhea, hepatotoxicity, and interstitial lung disease. EGFR inhibitors are less effective for advanced disease and can lead to resistance and toxicity.

Gefitinib has a 60% bioavailability in humans and is absorbed gradually after oral treatment. Cytochrome P450s substantially metabolize gefitinib in the liver into five metabolites, mostly by CYP3A4 and to a lesser degree by CYP3A5 and CYP2D6. After intravenous treatment, gefitinib is primarily removed hepatically, with a total plasma clearance of 595 mL/min[35]. When gefitinib therapy is used, the majority of side effects — which include diarrhea, dry skin, rash, nausea, and vomiting — are mild to moderate in intensity and are typically treatable with the right care. Serious adverse effects, including allergic responses, breathing difficulties, tongue and lip edema, and increased liver enzymes, have been recorded after using gefitinib[36].

A FAERS (FDA Adverse Event Reporting System) study that primarily examined the cardiotoxicity of osimertinib between January 1, 2016, and September 30, 2018, found that the drug's incidence of cardiotoxicity was higher than that of other FDA-approved medications and, more particularly, other EGFR-TKIs[37]. After diagnosis, all patients stopped using osimertinib. To address the decrease in LVEF, all 17 of our patients received treatment with a combination of beta-blockers, diuretics, and ACE inhibitors. All of these patients were sent to a cardiologist. Following the discontinuation of osimertinib and the administration of HF medication, 14 patients (64.71%) demonstrated some degree of symptom improvement and EF recovery; nevertheless, the majority did not reach their baseline EF levels. One patient died due to cardiac toxicity from osimertinib. Rechallenge with osimertinib was attempted because of a severe toxicological profile, which results in potential recurrence of cardiac toxicity[38].

Both gefitinib and afatinib caused liver toxicity in zebrafish embryos; pathological analysis revealed that both drugs could cause embryo liver inflammation, but afatinib at high concentrations had a greater impact than gefitinib; liver cell apoptosis analysis revealed that both drugs partially induced apoptosis of liver cells; and no correlation between pharmacokinetic parameters and electrocardiogram (ECG) variables or treatment-related morphological ECG abnormalities were found[39,40].

EGFR RESISTANCE:

Acquired resistance to EGFR-targeted therapy is a dynamic evolutionary process rather than a single event. On-target mechanisms include secondary EGFR mutations such as T790M and C797S, which directly interfere with drug binding, whereas off-target escape routes include MET amplification, HER2 activation, and downstream signaling reactivation. In addition, lineage plasticity can drive transformation to small-cell or squamous histology, and intratumoral heterogeneity can produce mixed resistant subclones across different metastatic sites[41,42]. Together, these processes explain why many patients experience only temporary benefit from EGFR TKIs and why combination or next-generation approaches are increasingly needed[43].

CAR-T CELL THERAPY:

CAR-T cell stands for chimeric antigen receptor T-cell. The process of CAR T-cell treatment involves obtaining a patient's own T-cells and then modifying and growing them genetically. An extracellular domain that binds to antigens, a spacer region, a transmembrane domain, and several intracellular signaling components make up chimeric

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antigen receptors. Through processes like perforin pathways and others, these CAR T-cells may identify unprocessed antigens without the assistance of the Major Histocompatibility Complex (MHC)[44].

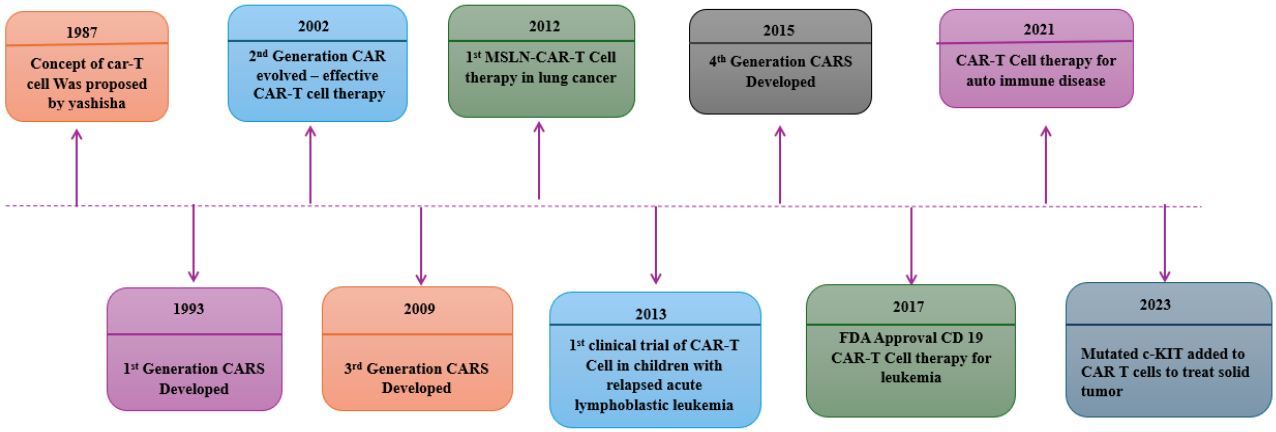

Figure 2: Evolution of CAR-T cells

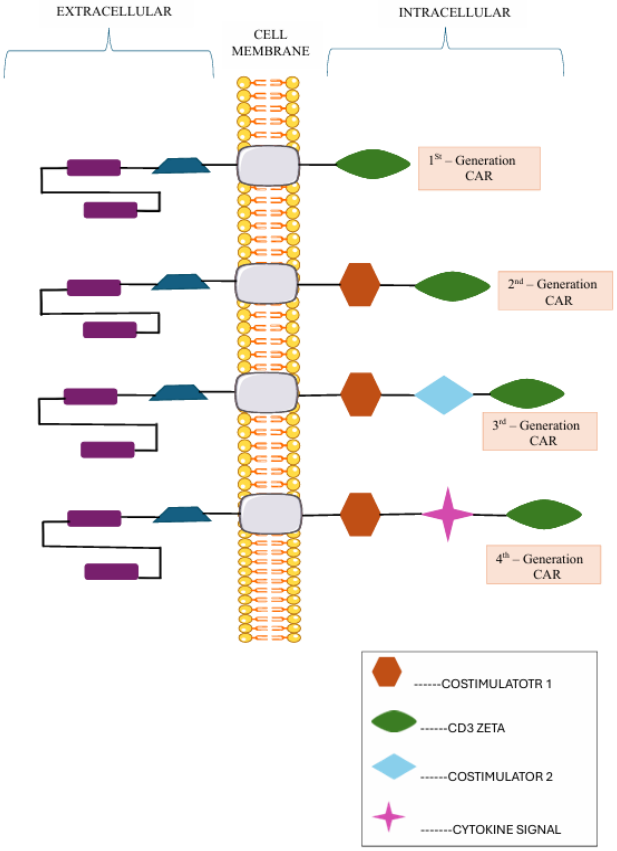

Figure 3: Types of CAR-T Cell generations are given below

CAR-T cell therapy has progressed significantly through four generations, demonstrating positive clinical outcomes in the treatment of hematologic malignancies.

- First-generation CARs: These cells have a single-chain variable fragment (scFv) attached to a CD3 zeta signaling domain that is intended to target particular tumor antigens.
- Second Generation CARs: These CARs have better anti-tumor responses than the first generation because they include one or more co-stimulatory signals, including CD28 or 4-1BB, which increase T cell activation, proliferation, and lifespan[45].
- Third-Generation CARs: This generation incorporates various co-stimulatory domains, including CD28 and 4-1BB, aimed at further boosting T cell activation, longevity, and cytotoxic effectiveness.
- Fourth-generation CARs: T cell redirections with global cytokine release, also known as fourth-generation CARs. These CARs can target and kill tumor cells, but they can also change the tumor microenvironment by releasing cytokines that promote inflammation. This could lead to a broad immune response against the tumor[46].

MODULAR CAR-T CELL THERAPY:

Modular CAR-T platforms were developed to solve two major limitations of conventional CAR-T therapy: fixed antigen specificity and limited safety control[47]. In adapter-based systems, the CAR recognizes a universal tag or inert receptor, while the soluble adapter molecule determines the tumor antigen target, making activation dependent on co-administration of the adapter. This design allows rapid retargeting to different antigens, reversible control of T-cell activity, and potential adaptation to antigen loss or heterogeneous expression[48,49]. Logic-gated systems further improve precision by requiring multiple antigen cues before activation, which may be particularly useful for solid tumors where off-tumor toxicity is a major concern.

Unlike conventional CAR-T cells with fixed antigen specificity, modular CAR platforms use adapter molecules or engineered receptor-ligand pairs to enable tunable, reversible, and multi-antigen targeting, which is especially attractive in solid tumors with heterogeneous antigen expression[50].

Modular CARs separate antigen recognition from T-cell signaling, allowing external control of activation.

Adapter-mediated systems can retarget one CAR to multiple antigens without reengineering the cell product.

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Switchable systems may reduce toxicity by enabling dose-dependent control and stopping activity when the adapter is withdrawn.

Logic-gated designs improve selectivity by requiring one or more antigen inputs before activation[51].

CAR-T CELL PREPARATION:

The origin of the cellular material employed in the production of any cellular therapy has a significant impact on the process. CAR T-cells and other genetically modified cell treatments that need to be HLA compatible with the recipient are often made from the patient's autologous cells.

T-CELL COLLECTION (Apheresis) - Even while individual patients' blood contains enough lymphocytes for the production of autologous CAR T-cells in as little as a few hundred milliliters, the number of lymphocytes in circulation varies greatly and is frequently low because of the patient's illness and previous chemotherapy[52]. Therefore, blood cell separators that are specifically made for collecting blood cells and are operated with instrument settings that maximize the collection of mononuclear leukocytes are usually used to collect autologous lymphocytes. A vein or venous access port is used to extract whole blood, mononuclear leukocytes are separated from other blood cells according to cell density, and then red blood cells (RBCs), platelets, and plasma are returned to the patient via a different vein or venous access port.

Cell collection followed by

- ✓ T-cell enrichment,
- ✓ T-cell transduction,
- ✓ T-cell expansion,
- ✓ cell concentration,
- ✓ CAR-T cell packaging,
- ✓ CAR-T cell storage,
- ✓ CAR-T cell infusion

Several manufacturing techniques are used to produce autologous CAR T cells, but they all follow the same general procedures[53]. First, leukapheresis is used to separate and wash the patient's white blood cells (WBCs). T-cell enrichment involves utilizing activated cytokines to enrich T-cells from gathered PBMNCs (peripheral blood and mononuclear cells) and then growing them in culture systems[54]. The genetic engineering process of introducing the chimeric antigen receptor gene into T-cells using non-viral or viral vectors. Retroviral and lentiviral gene transfer are examples of viral techniques. Using plasmid-based transposon/transposase systems or electroporating naked DNA are examples of non-viral techniques[55]. T-cell subset selection prepares particular T-cell subsets, including CD4+ and CD8+ cells, independently to maximize treatment and occasionally prevent unbalanced populations. Culture systems of T-cells are grown under regulated circumstances in closed systems, such as flasks, sacks, or bioreactors, guaranteeing uniformity and sterility[56]. Post-expansion Processing Before the final formulation, any culture media, beads, or cytokines must be cleaned, concentrated, and eliminated. Cryopreservation of CAR T-cells involves freezing using cryoprotectants for later injection and storage. The T cells are then formed, filled, expanded to the necessary cell counts for therapy, transduced with the CAR transgene, and activated[57]. The product is injected into the patient following quality control testing and a course of lymphodepleting chemotherapy. There are several ways to carry out process steps throughout the manufacturing of the CAR T cell product[58].

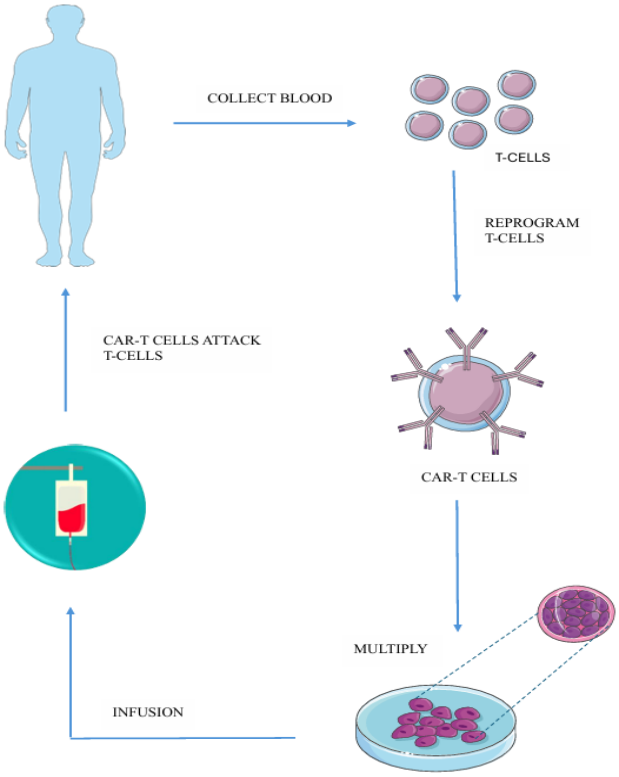

Figure 4: Steps involved in CAR-T Cell Preparation

LABORATORY TESTING OF CART-CELLS:

Every time CAR T-cells are manufactured, new cells are created, which are recognized as a new batch of cells. Every batch of CAR T-cells is examined both during and after production. The procedure of assessing CAR T-cells while they are being processed is called "in-process testing," and it uses phenotypic and cell counts to assess how well the manufacturing process is going[59]. Lot release testing is the term for testing conducted after manufacturing. The efficacy of T-cell transduction is assessed through the use of flow cytometry. Each type of CAR T-cell product has a different range of acceptable transduction efficiencies, although generally speaking, they fall between 20% and 80%.

A facility that produces multiple CAR T-cell types has to test the cells to make sure the right vector was utilized[60]. After the completion of the manufacturing process, the CAR-T cells are cryopreserved. Since most cryoprotectants are

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harmful to cells, they are often thawed quickly and then administered as soon as possible[61]. The product must be infused using the manufacturer's recommended infusion set and within the time frame given by the manufacturer[62]. After determining the cell viability, the center infusing the CAR T-cells may thaw and wash the cells before adjusting the dose of viable CAR T-cells to a predetermined dose per kilogram of patient weight for early-phase clinical trials. However, all of the cells acquired are usually frozen and injected for late-phase research employing centrally produced CAR T-cells. The time the cells are thawed is recorded by the cell processing lab. After thawing, the cells are typically administered within an hour or two[63].

PATIENT SAFETY- CAR T-cell therapy-eligible patients have either recently received anticancer treatment or have undergone extensive multi-treatment. Patients also have a significant risk of infection, are highly sensitive to changes in their biochemistry, and have trouble getting peripheral venous access[64]. In conclusion, we have to treat them as frail patients [39], which could raise the risk of negative outcomes during the apheresis operation.

Healthcare professionals who provide apheresis operations to patients may foresee possible negative outcomes and are equipped to handle unforeseen circumstances. For this, the application of eligibility clinical and laboratory criteria is beneficial[65].

APPROVED CAR-T CELL THERAPIES FOR CANCER:

The Food and Drug Administration (FDA) has approved six CAR T-cell therapies:

- Abecma (idecabtagene vicleucel)
- Breyanzi (lisocabtagene maraleucel)
- Kymriah (tisagenlecleucel)
- Tecartus (brexucabtagene autoleucel)
- Yescarta (axicabtagene ciloleucel)
- Carvykti (ciltacabtagene autoleucel)[66].

The above-mentioned therapies are for treating blood cancers, including leukemia, lymphoma, and myeloma. There were several trials with CAR-T cell therapies targeting specific antigens for treating lung cancer. CAR T-cell therapies are not approved yet for solid tumors like lung cancers[67]. The development of multispecific CAR-T cells that target several antigens, including CD19, CD20, and CD22, has also advanced to boost efficacy in B-cell malignancies and counter tumor escape mechanisms[68]. Despite ongoing issues with tumor microenvironment and targeting specificity, these developments are intended to increase safety, lower relapse rates, and make it easier to apply CAR-T treatments to solid tumors[69].

ONGOING CLINICAL TRIAL:

CAR-T CELL INFUSION FOR TYROSINE KINASE INHIBITORS (TKIs)

1. CXCR5-modified EGFR chimeric antigen receptor autologous T cells:

Anti-EGFR Chimeric Antigen Receptor (CAR) T cells that have been altered by C-X-C Chemokine receptor type 5 (CXCR5) are administered intravenously to patients with advanced adult non-small cell lung cancer (NSCLC).

Under the dose (number of cells by body weight), and the infusion time should be meticulously documented in the study. By monitoring the side effects following cell therapy, the safety of treating patients with chimeric antigen receptor T (CAR-T) cells was assessed. Initially, the outcomes of the patient's prior standard treatment plan were compared to the efficacy of CAR-T treatment. Blood was drawn both before and within a year following infusion to assess the pharmacokinetics and determine the quantity and activity of CAR-T cells[70].

2. TGFβR-KO CAR-EGFR T Cells in EGFR-Positive Solid Tumors:

Hematologic cancers have been found to respond well to chimeric antigen receptor-modified T (CAR-T) cell treatment. In the investigation of solid tumors, CART cell treatment did not, however, produce any encouraging efficacy evidence. The complex immunosuppressive tumor microenvironment (TME) in solid tumors is one of the main obstacles. According to reports, one of the main regulating variables in the TME is transforming growth factor-β (TGF-β). To investigate the anti-tumor activity and safety profiles of CAR-EGFR-TGFβR-KO T cells in advanced EGFR-positive solid tumors that have already undergone treatment, we create CAR-EGFR-TGFβR-KO T cells by using CRISPR/Cas9 to knock out TGF-β receptor Ⅱ[71].

Clinical trial number: not applicable.

DISTINGUISH BETWEEN CAR-T CELL THERAPY AND OTHER ADOPTIVE CELL THERAPY:

CAR-T cell therapy has demonstrated significant efficacy in treating haematological cancers, with enhanced clinical outcomes observed from the initial development of first-generation CAR-T cells to the currently approved second-generation therapies. Furthermore, numerous combination strategies are under investigation for the effective treatment of solid tumors, which remains a challenge. Adoptive cell therapy (ACT) encompasses various immunotherapeutic modalities that redirect cytotoxic T cells from the patient to achieve an effective antitumor response. These therapies can be categorized into those that do not involve genetic manipulation of tumor-infiltrating lymphocytes (TILs) and those that involve genetic modification and reprogramming of patients' T cells to enhance and target their cytotoxic activity against tumors[72].

The distinguishing between CAR-T cell and other adoptive cell therapy are listed below in table 2.

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Table 2: Distinguish between CAR-T cell and other adoptive cell therapy

CHARACTERISTICS	TIL	TCR	CAR
First evidence of clinical benefit	1994	2006	2013
Production method	Isolation of T cells from tumors and expansion ex vivo	Isolation of peripheral T cells via apheresis and ex vivo transduction with a TCR against tumor antigen	Isolation of peripheral T cells via apheresis and ex vivo transduction with a CAR against tumor antigen
Target	MHC-peptide complex	MHC-peptide complex	Non-MHC cell surface proteins
Lymphodepleting preparative regimen	Yes	Yes	Yes
Supportive IL-2	Yes	Varying	No
Specificity	Polyclonal	Monoclonal	Monoclonal
Main toxicity	Lymphodepleting regimen IL-2 mediated (chills, fever, edema) Seldom autoimmune	Lymphodepleting regimen "On-target, off-tumor" CRS	Lymphodepleting regimen "On-target, off-tumor" CRS Neurological
Restrictions	Complex Heterogeneous infusion product	MHC-restricted Currently not yet tumor-specific Toxicity	Currently only effective for treatment of hematological malignancies Toxicity [73]

Challenges of EGFR as A CAR-T Cell target in Solid Tumors:

In syngeneic mouse models, treatment with CAR T cells alone can be sufficient to stimulate an endogenous anti-tumour immune response. Epidermal growth factor variant III (EGFRvIII), is a mutant form of EGFR, resulting from a coding sequence deletion, which generates a novel extracellular epitope. In a glioma model, mice treated with EGFRVIII-CAR T cells were resistant to re-challenge with antigen-negative tumours. Although specific mechanisms of such resistance were not explored, the authors suggest that treatment with CAR T cells might promote host immunity against tumour antigens other than EGFR [64]. Unlike many other solid tumor markers, expression of EGFRvIII appears to be entirely limited to malignant tissue and is found in approximately 30% of cases of GBM[74,75].

CONCLUSION

Much progress has been made in treating non-small cell lung cancer, the leading cause of cancer death. EGFR inhibitors are used effectively for cancers with minor side effects, in some cases with life-threatening adverse effects, although they are still in use as effective cancer treatments. To enhance the treatment efficiency and patient safety, CAR-T cells were developed for blood cancers. It remains challenging to treat solid tumors by CAR-T cell therapy due to poor infiltration of T-cells in the solid tumor microenvironment, yet we don't have any FDA-approved CAR-T cell therapies with specific chimeric antigens for non-small cell lung cancer targeting EGFR. Hence, clinical trials are ongoing with various antigens responsible for causing NSCLC, including EGFR CAR-T cells, with the target of signaling molecules such as chemokine receptors and transforming growth factor-β. Other signaling molecules such as interleukin-6, galectin-1, and vascular endothelial growth factor receptor can also be incorporated with EGFR CAR-T cells for better advancements.

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ABBREVIATION:

NSCLC- Non- small cell lung cancer

EGFR - Epidermal growth factor receptor

HER_2 - Human epidermal growth factor receptor 2

ROR_1 - Tyrosine kinase-like orphan receptor-1

PD-L1 - Programmed death ligand 1

CAR - Chimeric antigen receptors

ErbB - erythroblastic oncogene B

ECG - electrocardiogram

MHC - Major Histocompatibility Complex

ScFv - single-chain variable fragment

HLA – Human Leukocyte Antigen

PBMNCs - peripheral blood and mononuclear cells

CXCR5 – C-X-C Chemokine receptor type 5

TME - tumor microenvironment

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TGF-β - transforming growth factor-β

FAERS – FDA Adverse Event Reporting System

LVEF – Left Ventricular Ejection Fraction

EF levels - Ejection fraction

ECG – Electrocardiogram

LAURA – A Global study to assess the effects of Osimertinib following chemocardiation in patients with stage 3 unresectable non-small cell lung cancer.

PFS – Progression free survival

CRS – Cytokine Release Syndrome

IL – Interleukin

MHC – Major Histocompatibility Complex

TIL – Tumor-Infiltrating Lymphocyte(s)

TCR – T-Cell Receptor

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