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Targeting Cancer at its Core: Cellular and Genetic Approaches Via CAR-T Cell Therapy CAR-T Cell Therapy of Cancer

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Abstract: Cancer has recently overtaken other conditions as the foremost cause of death worldwide. While numerous conventional treatment modalities and cytotoxic immunotherapies are available, the intricate nature of tumor biology—driven by a multitude of genetic and cellular factors underlying tumorigenesis and metastasis—necessitates the development of advanced treatment approaches capable of acting on cellular as well as genetic fronts. Amid these advancements, Chimeric Antigen Receptor (CAR) T-cell therapy has risen as a pioneering frontier in the domain of T-cell engineering. Here, T cells obtained from the patient are engineered ex vivo to carry synthetic receptors designed to recognize tumor-associated antigens. A key feature is that these modified receptors can identify tumor antigens without requiring MHC presentation. Recently, CAR-T cell therapy has achieved significant clinical milestones, inducing remission in up to 80% of patients with hematologic malignancies, particularly those with acute lymphoblastic leukemia (ALL) and certain subtypes of non-Hodgkin lymphoma, such as large B-cell lymphoma. The anti-CD19 CAR design, UCART19, has demonstrated remarkable therapeutic potency in managing relapsed or refractory hematologic malignancies. Furthermore, other surface antigens, including CD20 and CD22, prevalent in various leukemias and lymphomas, are being actively explored as therapeutic targets, with multiple clinical trials underway. Although its application is presently concentrated on blood cancers, the integration of advanced modalities—such as bispecific CARs, tandem CARs, inhibitory CARs, multi-antigen targeting, CRISPR-based gene editing, and nanoparticle-mediated delivery—holds the promise of significantly enhancing its efficacy. These advancements may extend its utility to both hematologic and solid tumors, offering a treatment paradigm that is not only rapid and precise but also safer compared to traditional modalities. The purpose of this review is to offer an in-depth analysis of the benefits and emerging developments in CAR T-cell immunotherapy, while underscoring its rising advantage over conventional treatments like chemotherapy and radiotherapy.

Keywords: *CAR-T Cell Therapy, Cancer Immunotherapy, Hematologic Malignancies, Tumor Antigens, Gene Editing, Targeted Cancer Therapy.*

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I. INTRODUCTION

According to the National Cancer Institute (NCI), the term cancer denotes a spectrum of diseases characterized by abnormal, uncontrolled cell proliferation, with the capacity to invade adjacent tissues and potentially metastasize to distant sites [1]. Numerous people are affected by the well-known, debilitating, and even fatal disease known as cancer. Cancer stands as the second most common cause of death worldwide, transcending all socioeconomic strata.

But once a cell has become malignant due to genetic modification, it divides uniformly until a tumor mass forms. Tumor masses can be solid or liquid, but they differ greatly from other swellings or inflammatory processes. The stepwise progression of cancer involves metastasis, invasive carcinoma, in situ carcinoma, hyperplasia, and dysplasia. The pivotal process of metastasis enables malignant cells to detach from the primary tumor, disseminate to distant sites, and establish secondary growths known as metastatic tumors.

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Table 1 Age-Specific Life Expectancy Estimates for Males and Females

Age	Expectation of Life	
	Female	Male
0	81.1	76.3
45	37.8	34.0
50	33.2	29.6
55	28.8	25.5
60	24.5	21.5
65	20.4	17.8
70	16.5	14.3
75	12.9	11.0
80	9.7	8.2
85	6.9	5.9
90	4.8	4.1
95	3.3	2.9
100	2.3	2.1

➢ *Prevalence*

In 1982, the age-adjusted cancer prevalence was recorded at 1,789 cases per 100,000 males and 2,222 cases per 100,000 females. The elderly had the greatest age-speci2ic prevalence rates; 11% of women and12% of men over 70 had previously received a cancer diagnosis [2]. Breast cancer in women and prostate cancer in men represented the two most prevalent malignant neoplasms. The overall incidence of cancer is projected to rise from 979,786 cases in 2010 to 1,148,757 cases by 2020.

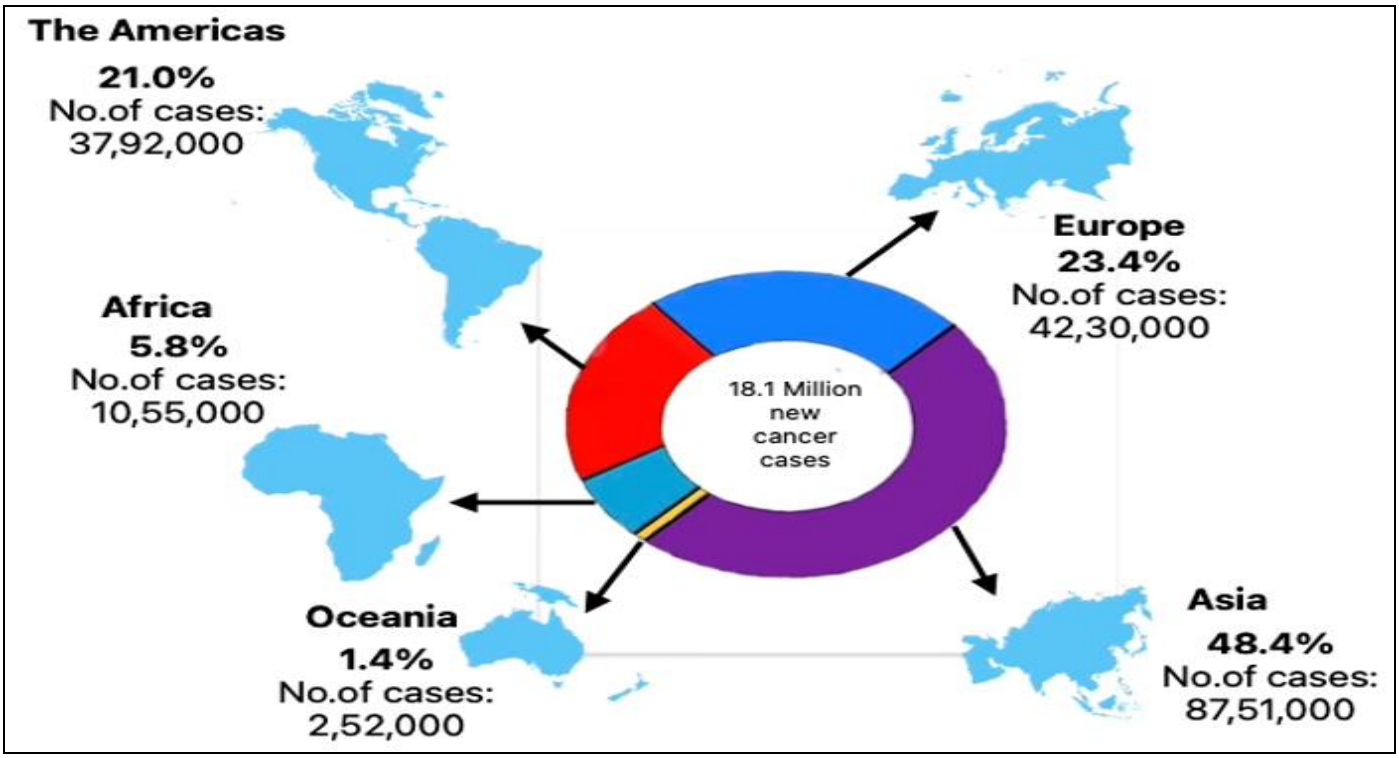

Fig 1 Worldwide Incidence of New Cancer Cases Across Continents

➢ *Symptoms*

A pain clinic assessed the prevalence of 15 physical symptoms and symptom clusters in a cohort of 1,635 cancer patients. On average, patients reported 3.3 symptoms beyond pain. The most frequent manifestations included sleeplessness (59%), anorexia (48%), constipation (33%), sweating (28%), nausea (27%), dyspnea (24%), dysphagia (20%), neuropsychiatric symptoms (20%), and dermatological symptoms (3%). The patient's age, gender, tumor site, level of discomfort, and tumor stage all affect their symptoms [3].

By cancer stage, 51% of patients reported experiencing moderate to severe pain, with prevalence ranging from 43% in stomach cancer to 80% in gynecological tumors. The most common symptoms were nausea (42%) and dyspnea (46%) in cases of gynecological and stomach malignancies, respectively. In stage IV cancer, back pain, chest pain, and neck pain were assessed and consistently associated with increased likelihoods.

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➢ *Diagnostic Tests*

A substantial percentage of diseases go undiagnosed in over a billion people worldwide, which emphasizes the need for more affordable and accurate diagnostic technologies. These instruments could also be applied in areas with limited energy and ecological fragility. Although there is potential in metabolic diagnostics, there are obstacles because of the limited robustness of analytical methods and the applicability of biospecimens [4].

These are a few diagnostic techniques that combine Nanoparticle-Enchanted Laser Desorption/Ionization Mass Spectrometry (NPELDIMS) with Dried Serum Spots (DSS). Multicancer Detection (MCD) assays screen for multiple cancers at once using a single, readily available biospecimen, like blood. MCD testing may help discover malignancies earlier, including those for which there isn't already a reliable screening technique.

➢ *Treatment*

Cancer management may involve chemotherapy, radiotherapy, surgical intervention, and various other therapeutic modalities. Most contemporary cancer treatments use one or more of these methods. If the cancer hasn't spread, removal would be rather simple, and the surgery would be a very successful form of treatment. While many medicinal plants found in nature have anticancer characteristics, only a few numbers of naturally occurring compounds, including taxanes, vinca alkaloids, and podophyllotoxin, are employed as anticancer medications and are sold commercially.

Low-risk patients with early-stage disease are frequently cured through surgery alone, whereas numerous other cases demand a multimodal treatment plan. In particular, hormonal therapy is a key component in treating breast and prostate cancers, as discussed in Hormonal Therapy for Cancer [5].

- *There are Other Few Treatments:*

✓ Biomarker Testing for Cancer treatment.
✓ Hyperthermia.
✓ Immunotherapy.
✓ Photodynamic therapy.
✓ Steam cell transplant [6].

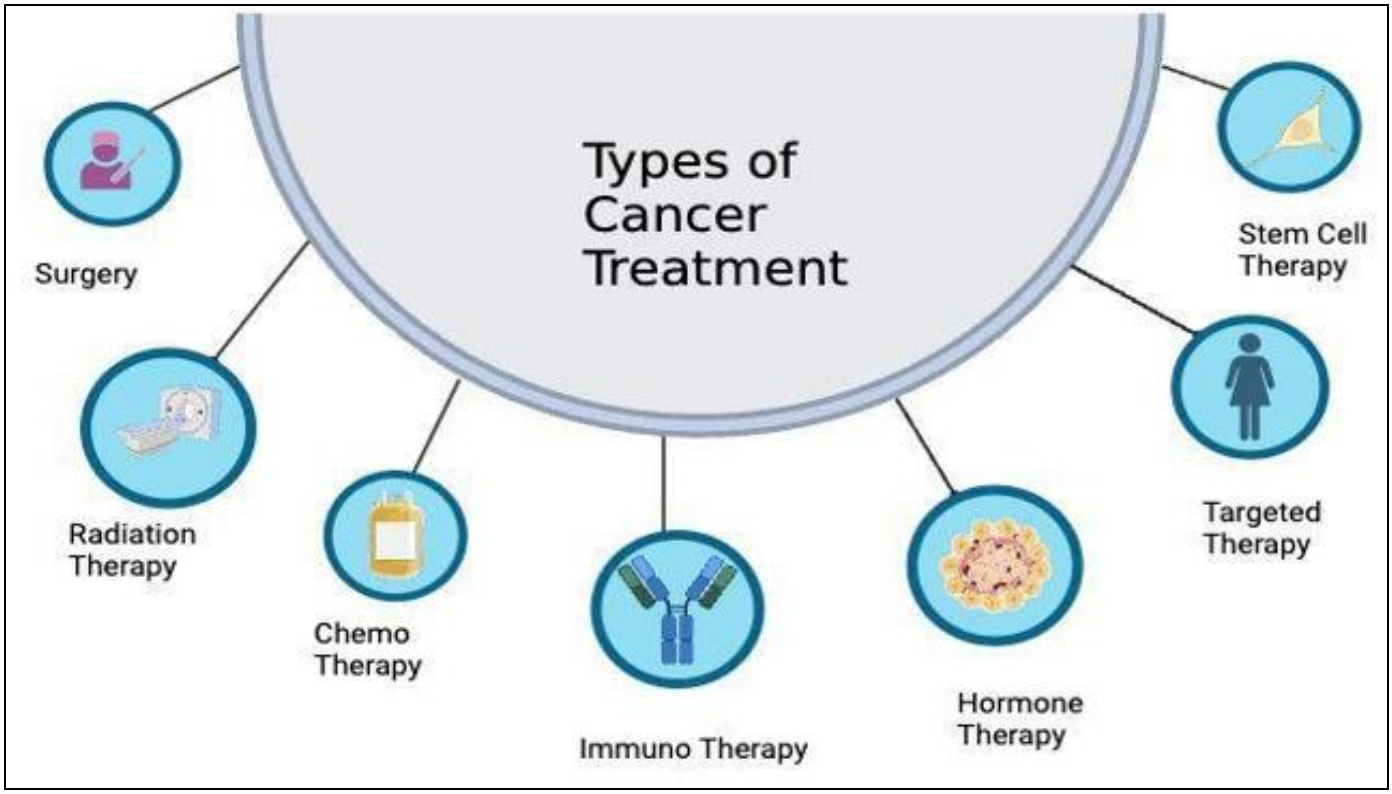

Fig 2 Overview of Major Cancer Treatment Modalities

- *Adverse Effects*

✓ Indifferent
✓ Change in flavour
✓ Feeling numb
✓ Bulimia.
✓ Having trouble passing the stool
✓ Throwing up
✓ Depression
✓ Parts of the body swelling
✓ Reduced weight
✓ Lesions and Rash [7]

- *Self-Care*

A few self-care techniques that may be able to stop certain negative consequences are as by reducing the negative effects of chemotherapy and promoting self-care behaviors, education about cancer treatment and side effects might enhance quality of life [8].

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- ✓ If you're fatigued, take frequent naps.
- ✓ Engage in physical activity.
- ✓ Emotional exchange regarding depression.
- ✓ Apply massage to numb areas.
- ✓ Eating a well-balanced diet.

➢ *Chimeric Antigen Receptor T-Cell Therapy*

Chimeric antigen receptors (CARs) are specially designed receptors that enabled T lymphocytes to recognize and destroy cancer cells by targeting specific tumor antigens. This novel approach reengineers a patient's immune cells to combat malignancies and has emerged as a promising modality in immunotherapy, gene therapy, and cancer treatment [9].

As a pioneering experimental strategy, CAR-T therapy involves reprogramming a patient's T cells to augment their ability to detect and eradicate cancer cells. The process begins with leukapheresis, a standard and safe procedure used to collect peripheral blood. Following blood collection, the sample is fractionated, T cells are isolated and engineered to express CARs, and then reinfused into the patient's circulation [10]. Apheresis is routinely used in blood banks and clinical settings to treat various blood-related and kidney disorders, underscoring its safety.

The fundamental principle of this therapy lies in leveraging the immune system's innate ability to combat disease. T cells play a pivotal role in identifying and destroying cancerous cells [11]. By customizing CARs for specific types of cancer, this approach offers a powerful alternative to traditional treatments like chemotherapy and radiation.

Chimeric antigen receptors (CARs) are generally structured with an extracellular ligand-binding domain—most commonly a single-chain variable fragment (scFv)—connected to a spacer, a transmembrane segment, and one or more intracellular signaling domains. Among the most notable successes of CAR-T cell therapy is the targeting of CD19, a surface antigen abundantly expressed on B-cell leukemias and lymphomas. Anti-CD19 CAR-T cells have produced remarkable outcomes, particularly in patients with relapsed or refractory disease. This therapeutic approach has yielded substantial clinical benefit in the management of aggressive hematologic malignancies, including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and non-Hodgkin lymphoma (NHL). By targeting CD19, CAR-T therapy has proven especially valuable for individuals unresponsive to conventional treatments, providing durable remissions and renewed therapeutic promise. [12].

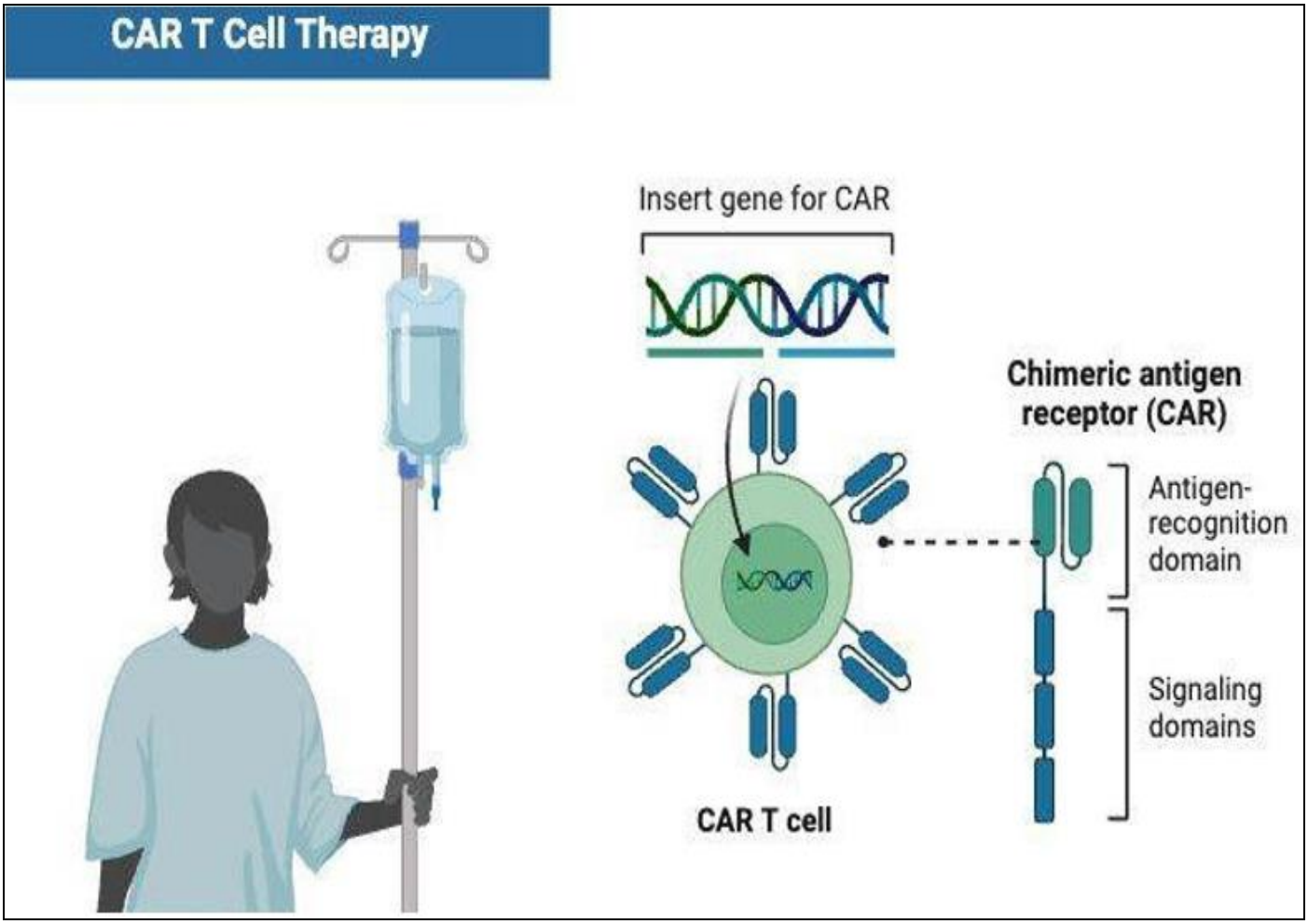

Fig 3 Illustrative Representation of CAR-T cell Therapy Mechanism

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➢ *Structure and Development of Chimeric Antigen Receptors (CARs)*

Chimeric Antigen Receptors (CARs) are engineered proteins that reprogram T cells to identify and eliminate specific cancer cells. From a structural standpoint, CARs consist of four principal domains:

- Antigen Recognition Domain – usually a single-chain variable fragment (SCFV) of antibody origin, which mediates binding to the target antigen.
- Hinge Region – provides flexibility and spatial separation between domains.
- Transmembrane Domain – secures and stabilizes the receptor within the T-cell membrane.
- Intracellular Signaling Domain (Endo domain) – responsible for triggering T-cell activation upon antigen binding [13].

➢ *Historical Perspective and Early Innovations*

CAR technology was first conceptualized in 1987 by Dr. Yoshikazu Kurosawa and his team in Japan first introduced the concept of combining antibody-derived regions with T-cell receptor components [14]. Their pioneering work demonstrated that introducing chimeric receptors into mouse T-cell lymphoma (EL4) cells triggered calcium influx when the cells encountered specific antigens, indicating successful T-cell activation.

This concept advanced significantly in 1989, when Dr. Zelig Eshhar and his colleagues at the Weizmann Institute in Israel further enhanced and refined the approach. The team created chimeric T-cell receptors (cTCRs) capable of antigen recognition in an MHC-independent manner [15]. Their construct incorporated the variable regions of an antibody specific to the chemical trinitrophenol (TNP), fused with the constant regions of T-cell receptor α and β chains. When introduced into mouse cytotoxic T-cell hybridomas, these modified cells expressed the chimeric receptors on their surface. When exposed to TNP antigens, the engineered cells were activated and secreted interleukin-2 (IL-2), a hallmark of T-cell activation. Remarkably, this response was achieved independently of MHC-mediated antigen presentation, representing a pivotal breakthrough in adoptive T-cell therapy.

II. METHODOLOGY OF CAR T CELL THERAPY

CAR T-cell therapy is often described as giving patients a “living drug,” since it involves using their own immune cells to fight cancer. As highlighted by Dr. Renier J. Brentjens of Memorial Sloan Kettering Cancer Center, these cells are engineered to actively locate and eliminate cancer cells within the body [16]. The process begins with the collection of a patient's T-cells - immune cells essential for orchestrating the body's defense mechanisms. Using a technique known as apheresis, blood is withdrawn from a vein, processed through a machine that separates the T cells, and the remaining blood components are subsequently returned to the patient [17].

After collection, the T cells are transferred to a specialized laboratory, where they are genetically modified to express a chimeric antigen receptor (CAR) on their surface. This receptor functions as a molecular guide, enabling the T cells to identify and bind to specific antigens present on cancer cells [18]. Following genetic modification, the engineered CAR T cells are expanded in the laboratory for approximately two to three weeks. Once a sufficient number is generated, they are reinfused into the patient. Before infusion, patients typically receive a brief course of chemotherapy - not to directly treat the cancer, but to condition the body to better accommodate and sustain CAR T-cell activity [19].

This entire process—collection, engineering, and reinfusion—usually takes a few weeks and may occur either in a hospital setting or at an outpatient infusion center, based on the patient's clinical status and therapeutic regimen.

➢ *Monitoring and Recovery*

After infusion, patients are carefully observed for any adverse effects. Some common symptoms include fever, fatigue, headaches, breathing difficulties, dizziness, and chills. These effects are frequently attributed to a transient condition known as cytokine release syndrome (CRS), which arises when activated CAR T cells secrete large amounts of immune-signaling molecules called cytokines [20]. Healthcare providers also check for signs of neurological changes by asking patients to complete simple tasks, helping to assess brain and body function. Most patients remain under close observation for about a month. If all goes well, they can return home and continue their care under the supervision of their local medical team.

➢ *CAR T Cell Treatment*

The initial development of CAR T-cell therapies centered on acute lymphoblastic leukemia (ALL), the most prevalent pediatric malignancy. A recent NCI-led study presented long-term follow-up data from children with relapsed ALL treated in a CAR T-cell clinical trial. The study showed that over half of the patients proceeded to potentially curative stem-cell transplants, with almost 60% of them surviving beyond five years without relapse or disease-related complications [21].

CD19-directed CAR T-cell therapies have also provided new hope for both adults and children with advanced, aggressive lymphomas. Prior to their introduction, many of these patients were considered "virtually untreatable," noted Dr. James Kochenderfer of the NCIs Center forCancer Research. Dr. Kochenderfer has led several clinical trials, including those evaluating CAR T-cell therapy for patients with diffuse large B-cell lymphoma [22].

ISSN No: 2456-2165 https://doi.org/10.38124/ijisrt/25jun1371

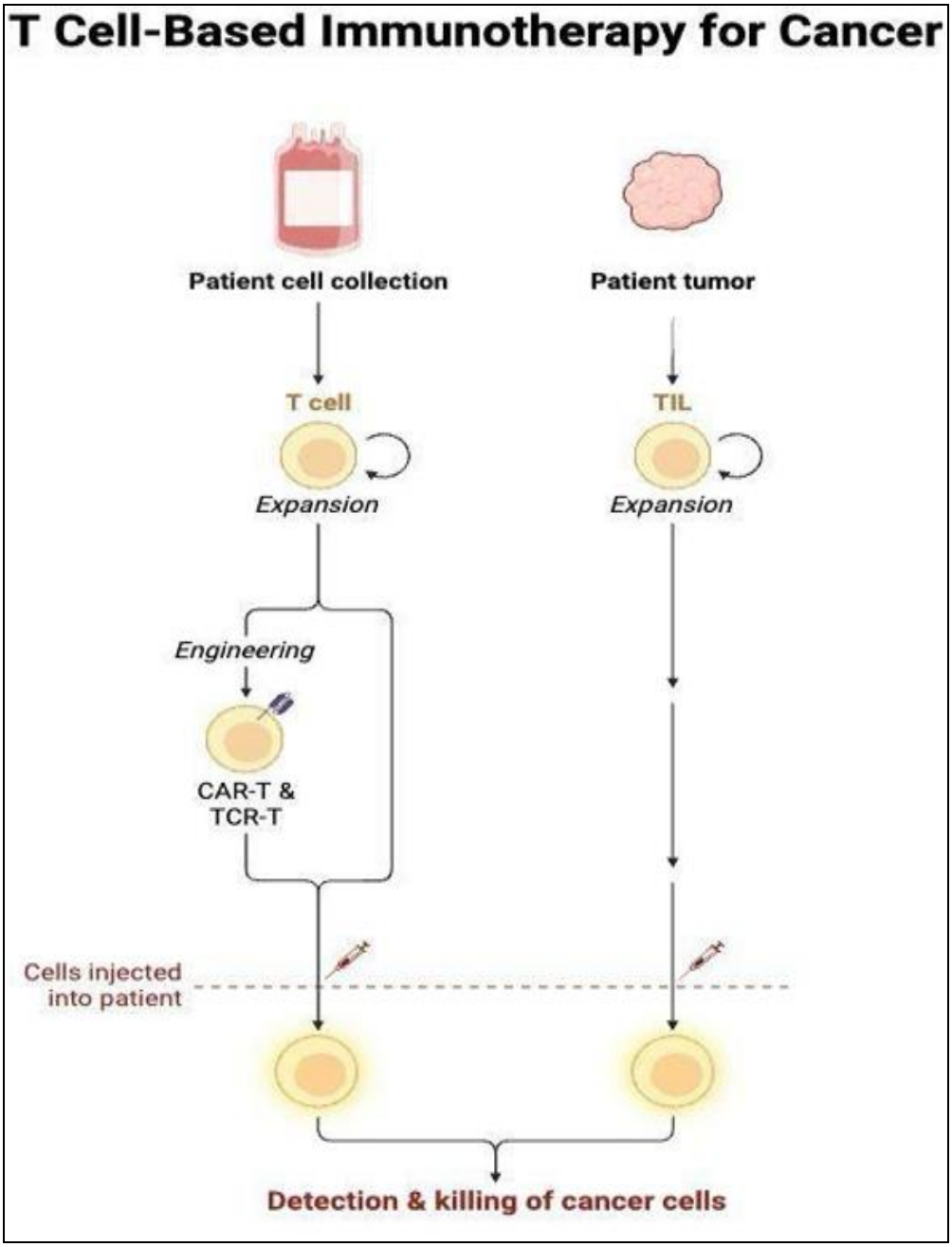

Fig 4 Schematic Representation of T Cell-Based Immunotherapy Approaches in Cancer

➢ *Relevant Drugs*

- *Pembrolizumab:*

Immune regulation is critically influenced by the programmed death receptor-1 (PD-1) pathway. PD-1, an inhibitory checkpoint receptor, maintains immune tolerance by controlling autoimmunity and is found on activated T-cells, B cells, NK cells, monocytes, dendritic cells, myeloid cells, and specific thymocyte subsets. By modulating effector T-cell function triggered by inflammatory cues, PD-1 functions as a feedback mechanism that restrains excessive immune activation. Interferon and other pro-inflammatory cues stimulate PD-L1, a PD-1 ligand that inhibits the immune system [23].

Pembrolizumab (MK-3475) is a monoclonal antibody that specifically targets the PD-1 transmembrane receptor on T cells, blocking its function. By preventing PD-1 on T cells from binding to its ligand PD-L1 on tumor cells, pembrolizumab enhances immune activation, enabling the immune system to eliminate malignant cells more effectively. In the phase 1b, nonrandomized, multi-cohort KEYNOTE-01231 trial, a subgroup of patients with metastatic triple-negative breast cancer (TNBC) was included.

Tumor specimens were analyzed for PD-L1 expression using the anti-human PD-1 antibody 22C3 (Merck & Co., Kenilworth, NJ, USA). PD-L1 positivity—defined as expression in at least 1% of tumor or stromal cells—was identified in nearly 60% of the patients evaluated [24].

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In the multi-center, single-arm, phase I/II KEYNOTE-150 study, the combination of pembrolizumab and eribulin was investigated to assess its safety and therapeutic efficacy in patients with metastatic TNBC. Eribulin may have anti-microtubule properties and be used as a chemotherapy medication for metastatic breast cancer that has already been treated. For metastatic disease, the participants in this research may have previously had 0–2 lines of chemotherapy. Of the 107 enrolled patients, 106 were evaluated irrespective of their PD-L1 status.

Among them, three achieved a complete response (CR) and twenty-five achieved a partial response (PR), resulting in an overall response rate (ORR) of 26.4% and a clinical benefit rate (CBR) of 32.8%. Importantly, no significant variation in ORR was observed across PD-L1 subgroups, with response rates of 30% in PD-L1–positive patients compared to 22% in PD-L1–negative patients [25].

- *Avelumab:*

Among the patients with metastatic cancer, there were 42 patients with SD, 4 PRs, and 1 CR, with an ORR of 3.0%. Three of the five patients who showed improvement had TNBC. Among the group of individuals diagnosed with metastatic breast cancer, 58 individuals (34.5%) were identified as having triple-negative breast cancer (TNBC). In the TNBC cohort, no patients achieved a complete response, while 3 showed a partial response and 15 maintained stable disease, resulting in an overall response rate (ORR) of 5.2%. Of the 58 individuals with TNBC, 48 demonstrated PD-L1 expression greater than 1%.

The overall response rate (ORR) was 6.1% [PD-L1 ≥ 1% (n=33)], 7.7% [PD-L1 ≥5% (n=13)], and 0% [PD-L1 ≥25% (n=2)] in TNBC cases stratified by PD-L1 status. Additionally, the ORR reached 22.2% in immune cells linked to tumors with PD-L1 expression between 1-10% [26].

- *Atezolizumab:*

Similar to avelumab, atezolizumab (MPDL3280A) is a monoclonal antibody directed against the transmembrane protein programmed death-ligand 1 (PD-L1) expressed on tumor cells. Unlike avelumab, however, atezolizumab is a humanized IgG1 monoclonal antibody that selectively binds to PD-L1.

In the phase III randomized IMpassion-130 trial, patients with metastatic TNBC who had not received prior therapy and demonstrated good performance status (0–1) were assigned to either placebo or a regimen consisting of nab-paclitaxel (100 mg/m² on days 1, 8, and 15) combined with atezolizumab (800 mg on days 1 and 15), administered weekly over a 28-day cycle [36, 70].

Forty Prior medical interventions, such as radiation therapy and chemotherapy, which included taxanes, were permitted as long as they were completed no less than a year prior to randomization. Eligible patients had treated asymptomatic CNS metastases. Patients were stratified based on the presence of liver metastases, previous exposure to adjuvant and/or neoadjuvant taxanes, and PD-L1 expression within tumor-infiltrating immune cells.

Even in cases where immunotherapy was not administered as first-line treatment, the use of anti-PD-1 and/or anti-PD-L1 agents appears to play a significant role in improving survival outcomes. However, further studies are necessary to validate their efficacy in patients lacking a positive immune infiltrate. Moreover, new clinical trials exploring the integration of immunotherapy with other therapeutic agents as first-line treatment are warranted. Moreover, the development of innovative predictive biomarkers remains an urgent necessity. Immunohistochemistry (IHC) remains the sole FDA-approved technique currently available for assessing PD-L1 expression [27].

CAR-T therapy provides a significant advantage over earlier immunotherapies owing to its relatively rapid treatment process and minimal risk of disease relapse. It has emerged as a viable option for patients in whom transplantation is unlikely to achieve cure or for those who relapse following a transplant. However, the degree to which this therapy is successful in the future will determine whether it is widely available to everybody.

➢ *CAR-T Cell Uses in a Range of Hematological Malignancies*

CAR-T cell in acute lymphoblastic leukemia and chronic lymphocytic leukemia:

- *CAR-T Cells Therapy in Acute Lymphocytic Leukemia:*

Among the different subtypes of ALL, relapsed or refractory B-ALL - which is associated with high mortality - has proven to be the most appropriate candidate for CAR T-cell therapy thus far. The most effective CAR construct for treating ALL targets CD19, a key marker of the B-cell lineage that is highly expressed in B-ALL. Additional potential targets under investigation include immunoglobulin light chains and CD206. With simply a CD3 chain included, the initial generation of CAR was unable to produce strong antitumor effects or long-lasting effects.

This challenge prompted scientists to innovate, giving rise to the second generation of CARs. While CAR-T cells incorporating either CD28 or 4-1BB co-stimulatory domains demonstrated enhanced efficacy, combining these elements offered the potential for even greater therapeutic benefit, ultimately leading to the development of third-generation CAR-T cells [28].

Published clinical trial data on CD19-targeted CAR-T cells in both adults and children with B-ALL have demonstrated promising outcomes. Rates of partial remission (PR) and complete remission (CR) were notably encouraging. In one study, patients received CD19 CAR-T cells following cyclophosphamide-based conditioning, and 15 of the 16 participants achieved an adequate T-cell yield, resulting in an impressive CR rate of 88%. Moreover, the depth of remission was remarkable, as highly sensitive

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molecular assays—including real-time PCR and deep sequencing—detected minimal residual disease. Additional trials in patients aged 1 to 30 years reported a molecular CR rate of 60% and an overall CR rate of 70% among 20 individuals with B-ALL.

Research has also suggested that the composition of CD4+ and CD8+ CAR-T cells within a single intravenous infusion may serve as a key factor in evaluating efficacy, toxicity, cellular expansion, and persistence of combination products. Understanding the correlation between CAR-T cell dose, in vivo proliferation, and toxicity risk could help refine adjunct therapies such as lymphodepletion and anti-tumor agents.

This knowledge would further enable dose adjustments aimed at minimizing the risk of cytokine release syndrome (CRS) and neurotoxicity. Although CD19 remains the leading target for CAR-T cell therapy in ALL, studies have highlighted the issue of "antigen escape," posing a significant hurdle in advancing immunotherapy. Hence, continuous optimization, particularly in identifying reliable targets, is critical [29].

- *CAR-T Cells Therapy in Chronic Lymphocytic Leukemia:*

Chemotherapy-refractory lymphoma (CRL) presents with a highly variable clinical course and prognosis. Currently, allogeneic stem-cell transplantation remains the only curative treatment option for CLL. In recent years, patients with high-risk or relapsed CLL have been treated with CD19-targeted CAR-T cells, with studies reporting comparable complete response (CR) and partial response (PR) rates in certain cases. Beyond CD19, other potential targets such as the tyrosine-protein kinase transmembrane receptor 36 have been explored.

Over the past few years, several investigations have evaluated the impact of CAR-T cell therapy in CLL patients. However, the early immune dysfunction inherent to CLL pathogenesis makes ex vivo T-cell expansion from patients and their donors difficult, thereby limiting the overall therapeutic efficacy of CAR-T cell therapy [30].

Ibrutinib, an irreversible inhibitor of Bruton's tyrosine kinase, has the potential to enhance T-cell antitumor activity while minimizing negative effects on these cells. In a cohort study, Fraietta et al. investigated the phenotype and function of T cells in CLL patients undergoing ibrutinib therapy to evaluate its influence on T-cell responses. Their results showed that five treatment cycles of ibrutinib promoted the expansion of CD19-targeted CAR-T cells (CTL019, a second-generation CD19 CAR-T product), reduced the expression of the immunosuppressive receptor PD-1 on T cells, and increased CD200 expression in B-cell CLL. Notably, the CD200/CD200 receptor axis plays a key role in regulating antitumor immunity.

In CLL, the overexpression of CD200 contributes to the functional impairment of CD8+ T-cell activity. Importantly, when CAR-T cells are administered in combination with ibrutinib, their functionality is not only preserved in vitro but also enhanced in human xenograft models of refractory ALL and CLL, leading to improved survival, better CAR-T cell engraftment, and more effective tumor clearance. Nevertheless, a case report indicated that in certain patients with CLL, ibrutinib alone produced more favorable outcomes than CAR-T cell therapy [31].

Moreover, patients who experience relapse of B-cell malignancies after undergoing allogeneic hematopoietic stem cell transplantation (Allo-HSCT) may benefit from CAR-T cell therapy. Conventionally, such relapses have been managed with donor lymphocyte infusions, utilizing naturally derived allogeneic lymphocytes from transplant donors following Allo-HSCT.

But the most common adverse consequence is graft-versus-host disease (GVHD), of which roughly one-third of patients who get infusions of donor lymphocytes develop the acute form. The 11% death rate with donor lymphocyte infusion is primarily caused by GVHD [32].

Consequently, studies have explored the use of CAR-T cell infusions in patients with CLL and B-ALL relapses after allo-HSCT. While larger clinical trials are still necessary, existing findings suggest that donor-derived CAR-T cell therapy is both safe and effective for treating recurrent B-cell malignancies in this setting.

Table 2 Clinical Outcomes of CD19-Directed Second-Generation CAR-T Cell Trials Across Leading Institutes

Institute	**Target and generation of CAR**	**Sample**		**Number of participants in effect**	**Results**	**Year of Publication and Reference.**
		Number (M/F)	***Age***			
Memorial Sloan-Kettering Cancer Center	CD19 2nd CD28	16 (12/4)	Adult	15	CR rate: 88%	2014
Fred Hutchinson Cancer Research Center	CD19 2nd 4-1BB	29	Not available	26	CR rate: 93%	2015
National Cancer Institute	CD19 2nd CD28	21 (14/7)	14.71 ± 6.64	21	CR rate :66.7%	2014

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University of Pennsylvania	CD19 2nd 4-1BB	30 (18/12)	Children & Adult	30	CR rate: 90%	2014
University of Pennsylvania	CD19 2nd 4-1BB	27	Adult	27	3 CR in cohort 1 and 2; 3 CR in cohort 3; 75%CR and 8.3%PR in cohort 4	2016

- *CAR-T Cell Therapy in Lymphoma:*

Although significant progress has been made with cytotoxic chemotherapy and monoclonal antibody therapies, patients with lymphoma that advances after primary and secondary treatments continue to face a poor prognosis. For those who fail to respond to multiple chemotherapy regimens, a promising therapeutic option has emerged. CAR-T cell therapy represents one of the most advanced immunotherapeutic strategies for relapsed or chemotherapy-resistant B-cell non-Hodgkin lymphoma (NHL) [33].

Among the different CAR subtypes engineered on T cells—whether autologous or allogeneic—the anti-CD19 CAR-T cell is the earliest and most widely studied. However, unlike second- and third-generation constructs, the first-generation CAR-T cells demonstrated limited efficacy, showing poor proliferation, persistence, and tumor-targeting ability in lymphoma patients [34].

Preclinical evidence from two independent studies, conducted both in vitro and in vivo, has shown that second- and third-generation CAR-T cells incorporating CD28 or 4-1BB signaling domains exhibit superior proliferative capacity and antitumor activity. While CD28 serves effectively as an early signal to drive T-cell growth and persistence, some studies suggest that CARs utilizing 4-1BB as a later costimulatory signal result in more pronounced expansion.

CD30, a member of the TNFR superfamily, represents another potential therapeutic target. In Hodgkin lymphoma (HL), it serves as the antigen for the Ki-1 antibody, binding specifically to Reed–Sternberg cells. While CD30-positive lymphocytes are less common in germinal centers, they are predominantly found adjacent to the follicular regions of lymphoid tissue. In the context of lymphomas, CD30 expression is observed in classical HL, diffuse large B-cell lymphoma (DLBCL), anaplastic large cell lymphoma, primary mediastinal B-cell lymphoma, and peripheral T-cell lymphomas. In a recent study by Wang et al., 18 patients with relapsed/refractory HL who received conditioning chemotherapy followed by CD30 CAR-T cell infusion demonstrated clinical improvement compared with their pre-infusion status [35].

Table 3 Clinical Outcomes of Early CAR-T Cell Therapy Trials Targeting CD19 and CD20

Institute	**Target and generation of CAR**	**Sample**		**Number of participants in effect**	**Results**	**Year of Publication and Reference**
		Number (M/F)	***Age***			
University of Pennsylvania	CD19 2nd 4-1BB	23 (14/9)	Adult	20	CR rate: 13%; PR rate: 4%;	2014
National Cancer Institute	CD19 2nd CD28	8	55.88±5.77	8	5 PRs; 1 CR; 1 SD	2012
National Cancer Institute	CD19 2nd CD28	15 (8/7)	51.67±11.22	15	CR rate: 53%; PR rate: 26%; SD rate: 7%	2014
National Cancer Institute	CD19 2nd CD28	9 (8/1)	Adult	9	1 CR; 5 PRs	2014
Fred Hutchinson Cancer Research Center & National Cancer Institute	CD20 1st CD3z	9 (8/1)	Adult	7	2 CRs; 1 PR; 4SDs	2008
Fred Hutchinson Cancer Research Center	CD19 (the generation is unknown)	28	Adult	24[i]	In 12 patients received lymphodepletion with Cy-based regimens without fludarabine, the CR rate is 8.3% and PR rate is 41.7%; In 16 patients received lymphodepletion	2015

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					with addition of fludarabine, the CR rate is 42% and PR rate is 25%	
		6	Adult	6	3 CR ;1 PR	2015
Chinese PLA General Hospital	CD20 2nd 4-1BB	7 (6/1)	65	6[j]	1 CR; 3PRs; 2 PDs	2014

- *CAR-T Cell in Multiple Myeloma:*

Another promising target identified is BCMA, a molecule expressed exclusively on mature B cells and plasma cells within normal lymphoid tissues. BCMA plays a key role in supporting the survival of long-lived plasma cells in patients with multiple myeloma. In a dose-escalation clinical trial, CAR-T cells engineered against BCMA (anti-BCMA/CD269) were administered to patients with MM, and this study further confirmed the therapeutic potential previously reported.

Revealed that all patients received pretreatments consisting of fludarabine and cyclophosphamide to increase the activity of adoptively transferred T cells. There was minimal anti-myeloma activity or toxicity observed in these 6 patients receiving treatment at the lowest 2 dose levels. Moreover, level 1 patients at the third dosage [36].

➢ *CAR-T Cell Uses in a Range of Hematological Malignancies*

- *Benefits of CAR-T Cell Treatment for Hematological Cancers:*

CAR-T cells differ from other adaptive immune cells by their unique ability to selectively eliminate cancer cells expressing tumor-associated antigens (TAAs), thereby minimizing unnecessary damage to healthy tissues. Unlike conventional T cells, they can recognize surface antigens independently of HLA expression—an advantage since many tumors downregulate HLA or other antigen-presenting molecules to escape immune detection. Additionally, the modular nature of CAR intracellular signaling domains allows these cells to counteract cancer-driven suppression of co-stimulatory pathways, either directly or indirectly. Notably, CAR-T cells are capable of targeting a broad range of antigens, including proteins, lipids, and carbohydrates [37].

- *CAR-T Cell Therapy's Drawbacks in Hematological Malignancies:*

Activating the antitumor immunity of engineered T cells leads to a spectrum of cytokine-mediated toxicities in hematological malignancies, including hemophagocytic lymphohistiocytosis, macrophage activation syndrome, and, most notably, cytokine release syndrome (CRS). CRS, triggered by elevated cytokine levels, presents with clinical features such as fever, hypotension, hypoxia, and neurological dysfunction. Because severe CRS occurs more frequently in patients with a high baseline disease burden or those receiving larger CAR-T cell doses, risk-adapted dosing strategies have been introduced. In life-threatening CRS cases, systemic corticosteroids are employed to suppress or eliminate hyperactivated CAR-T cells. However, this approach carries the significant drawback of potentially diminishing therapeutic efficacy.

Neurotoxicity is another significant potential adverse effect of CAR-T cell therapy, observed in some patients treated with CD19-targeted CAR-T cells. Symptoms may include visual hallucinations, delirium, dysphasia, seizures, or epilepsy. Clinically, neurotoxicity is associated with endothelial dysfunction, leading to vascular instability, capillary leakage, blood–brain barrier disruption, and disseminated intravascular coagulation. Imaging findings on brain MRI, such as multifocal microhemorrhages, leptomeningeal enhancement, and vasogenic edema, can serve as diagnostic indicators. Alongside CRS, proinflammatory cytokines including IL-6, IFN-γ, and TNF play a central role in acute neurotoxicity, for which tocilizumab is used to block IL-6–mediated inflammatory pathways. Despite the relative specificity of CAR-T cells, therapy may still cause collateral tissue injury, since some normal tissues—particularly lymphoid organs—express the same molecular targets. This phenomenon, termed on-target/off-tumor toxicity, includes B-cell aplasia seen with anti-CD19/CD20 CAR-T therapies. Additionally, antigen escape, most commonly manifested as CD19-negative relapse in B-cell malignancies, poses another barrier to sustained therapeutic success.

III. RESEARCH TOPICS FOR THE FUTURE

Respondents were asked to list any key research topics regarding fertility following CAR T-cell therapy in the last, open-ended question [39]. Thirteen of the 31 institutions that responded to our request (47% of all centers) questioned the clinical relevance or feasibility of doing fertility research in a group that is so substantially pretreated [40]. From the remaining eighteen responses, three overarching themes regarding CAR T-cell therapy and fertility research were identified. These included: (1) the need to establish standardized fertility guidance in the peri-CAR T-cell setting, (2) the collection of long-term data on post-therapy fertility outcomes, and (3) understanding the potential impact of circulating CAR T-cells on fetal development. All free-text responses were categorized within these three thematic areas, highlighting several critical considerations [41–43].

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Table 4 Fertility Considerations and Reproductive Outcomes in CAR-T Cell Therapy

Theme	Detailed Comments	Future Suggestions
Standardized peri-CAR T-cell fertility guidance	1. This is a crucial concern for younger patients. 2. Determining the function of pre-CAR T-cell fertility testing. 3. Pregnancy and child-fathering timing following CAR T-cell therapy. Does fertility get affected by CRS?	Existing committees and working groups are debating developing expert consensus recommendations for CAR T-cell recipients' fertility preservation.
Long-term outcomes	1. Long-term fertility status statistics. 2. Following a single lymphodepletion treatment, fertility monitoring. 4. How many women become pregnant after receiving CAR T-cells? How successful is the pregnancy?	Create a multicentre collaboration to gather future fertility data from patients receiving CAR T-cell therapy and their future children, then compare the results with those of patients receiving conventional treatments (such as radiation, chemotherapy, and stem cell transplantation).
Impact of CAR T-cells on developing fetus	1. Does the newborn have B-cell aplasia as a result of CAR T-cells that are transferred through the placenta? 3. Outcomes of pregnancies/live births after CAR T-cells.	

IV. CONCLUSION

In summary, the clinical development of CAR-T cell therapy in solid tumors remains at an early stage. Phase I trials across diverse solid malignancies have demonstrated not only a favorable safety profile but also promising signals of efficacy in terms of overall response rates. However, the durability of these responses is still uncertain, and survival outcomes remain immature. Future exploration of combination strategies, particularly with other immunotherapeutic agents, may enhance and prolong the therapeutic benefit of CAR-T therapy. Enrollment in ongoing CAR-T clinical trials should be strongly advocated for all eligible patient.

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