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# Chimeric Antigen Receptor T-cell Therapy (CAR-T): Insights into Clinical Efficacy, Emerging Perspectives, and Future Innovations in Hematology Malignancies Treatment.

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## Abstract

*Chimeric antigen receptor (CAR) T-cell therapy has improved the outcome for patients with hematological malignancies. FDA-approved CAR-T-cell medications, such as tisagenlecleucel and axicabtagene ciloleucel, have significantly increased overall survival (OS) and progression-free survival (PFS) in patients with relapsed or refractory B-cell malignancies, particularly in pediatric acute lymphoblastic leukemia and diffuse large B-cell lymphoma. However, challenges remain, in particular in translating these successes to solid tumors, owing to issues such as tumor antigen heterogeneity, the immunosuppressive tumor microenvironment and antigen escape. Efforts to improve CAR-T-cell efficacy include exploring dual-target CAR constructs and combining CAR-T cells with radiotherapy, chemotherapy, or immunomodulatory agents. Additionally, the high costs of complex manufacturing processes and side effects, including cytokine release syndrome and neurotoxicity, remain significant issues. Research efforts are now focused on optimizing CAR-T-cell design, improving patient accessibility, and identifying biomarkers to predict patient outcomes. The use of real-world evidence and advanced computational modeling further highlights the important future role of CAR-T-cell therapy in cancer treatment. Overall, CAR-T-cell therapy has improved the outcomes of patients with hematologic malignancies and has potential for use in solid tumor therapy.*

**Keywords:** Chimeric antigen receptors (CARs), Hematology malignancies, Adoptive cell transfer, Immune checkpoint inhibitors, Bispecific, Biomarkers.

## Introduction

Chimeric antigen receptor T-cell (CAR-T) therapy, a treatment that involves the genetic engineering of a patient's own T cells to express CARs that are designed to specifically recognize and bind to tumor-associated antigens (TAAs), has become a revolutionary approach for treating certain hematological malignancies, such as acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL).

CAR-T-cell therapy shows promise, with some clinical trials demonstrating remission rates reaching nearly 80% (1). These successes have led to the FDA's approval of numerous CAR-T-cell products (**Table 1**).

| CAR T-cell Therapy | Indication | Target/Action |
|---|---|---|
| **Kymriah (Tisagenlecleucel)** | - R/R ALL (pediatric & young adult)<br>- R/R LBCL (adults) | Targets **CD19** on B cells, leading to their destruction. |
| **Yescarta (Axicabtagene Ciloleucel)** | - R/R LBCL<br>- R/R PMBCL<br>- R/R FL (3rd-line therapy) | Targets **CD19** on B cells, causing their depletion via T-cell-mediated killing. |
| **Tecartus (Brexucabtagene Autoleucel)** | - R/R MCL<br>- R/R ALL (adults) | Targets **CD19**, leading to the destruction of cancerous B |
| **Breyanzi (Lisocabtagene Maraleucel)** | - R/R LBCL<br>- 3rd-line therapy for R/R FL | Targets **CD19** to eliminate malignant B cells. |
| **Carvykti (Ciltacabtagene Autoleucel)** | - R/R MM (after 4 prior lines of therapy) | Targets **BCMA**, which is expressed on malignant plasma cells. |
| **Abecma (Idecabtagene Vicleucel)** | - R/R MM (after 4 prior lines of therapy) | Targets **BCMA** to eliminate myeloma cells by engaging the patient's T cells. |
| **Brexu-Cel (Brexucabtagene Autoleucel)** | - R/R MCL<br>- R/R ALL (adults) | Targets **CD19** for mantle cell lymphoma and acute lym- |
| **Orva-Cel (Oroval-CAR T; investigational)** | - R/R MM (in clinical trials) | Targets **BCMA**, designed for high efficacy with reduced neurotoxicity and cytokine release syndrome (CRS). |
| **JCAR017 (Lisocabtagene Maraleucel; investigational)** | - R/R LBCL<br>- R/R FL | Targets **CD19**, in clinical trials for LBCL and FL with |
| **CT053 (Investigational)** | - R/R MM | Targets **BCMA**, currently in clinical trials for treating MM with high efficacy and durable responses. |
| **P-BCMA-101 (Investigational)** | - R/R MM | Targets **BCMA**, using a novel CAR scaffold to reduce CRS and neurotoxicity, in development for MM. |
| **CART-ddBCMA (Investigational)** | - R/R MM | Targets **BCMA**, utilizes dual CAR domains to enhance specificity and reduce resistance (in clinical trials). |
| **AUTO3 (Investigational)** | - R/R LBCL | Targets both **CD19** and **CD22**, developed for enhanced efficacy and overcoming CD19 antigen escape. |
| **AUTO1 (Investigational)** | - R/R ALL (adults) | Targets **CD19**, designed to reduce CRS and improve persistence in treating adult ALL (in trials). |
| **bb21217 (Investigational)** | - R/R MM | Targets **BCMA**, developed from a previous product with enhanced T-cell memory for longer-lasting responses. |
| **MB-CART2019.1 (Investigational)** | - R/R LBCL | Targets **CD19** and **CD20**, in trials for more comprehensive targeting of B-cell malignancies. |
| **PRGN-3006 (Investigational)** | - R/R AML | Targets **CD33**, an innovative CAR-T for relapsed or refractory acute myeloid leukemia (AML), in clinical trials. |

**Table 1**: FDA-approved and investigational CAR-T-cell therapies (R/R = Relapsed or refractory, ALL = Acute lymphoblastic leukemia, LBCL = Large B-cell lymphoma, PMBCL = Primary Mediastinal B-cell lymphoma, FL = Follicular lymphoma, MCL = Mantle cell lymphoma, MM = Multiple myeloma, AML = Acute myeloid leukemia).

Although CAR-T-cell therapy has been successful in treating hematological cancers, there are several challenges that impact its potential for broader application, particularly in solid tumors.

A primary obstacle is the identification of suitable tumor antigens that are not only specific to cancer cells, e.g., not expressed in normal tissue but also present in sufficient quantities to elicit a robust immune response (2).

Furthermore, the immunosuppressive microenvironment of the tumor can act as a significant barrier to T-cell infiltration, often leading to suboptimal therapeutic efficacy (2). Additionally, and importantly, the observation of severe side effects, such as cytokine release syndrome (CRS) and neurotoxicity, raises concerns about the safety of CAR-T-cell therapy (3).

Research continues with CAR-T-cell therapy to improve its efficacy and increase its usability, with a particular focus on optimizing CAR-T-cell designs and exploring novel antigen targets. Another area of intense investigation is the combination of CAR-T-cell therapy with other approved treatments, including chemotherapy and radiation, with the desired outcome of enhancing overall survival while mitigating adverse effects (3).

Compared to other immunotherapeutic strategies, CAR-T-cell therapy offers advantages, particularly because of its ability to maintain an antitumour response. However, the use of CAR-T-cell therapy must be carefully considered over traditional therapies, such as monoclonal antibodies and immune checkpoint inhibitors. These considerations include both scientific, e.g., different risk profiles and mechanisms of action, and real-world issues, e.g., manufacturing processes, costings, and time constraints to treatment (1).

Overall, CAR-T-cell therapy offers hope for patients with hematological malignancies, as it has the potential to be useful for extending into solid tumors. However, its utility is fraught with challenges that require further research and a deeper understanding of its mechanism of action.

This review explored the current understanding of CAR-T-cell therapy mechanisms and their role in treating hematopoietic malignancies and solid tumors. Finally, future research directions and potential expansions of CAR-T-cell applications are discussed.

## Overview of CAR-T-cell therapy and mechanism of action

The generation of CAR-T cells involves the genetic engineering of a patient's own T cells to express CARs, which are synthetic receptors designed to recognize specific TAAs that are expressed on the outer membrane of cancer cells.

CAR structures consist of an extracellular antigen recognition domain, often derived from a single-chain variable fragment (scFv) of an antibody, a transmembrane domain, and intracellular signaling domains that activate T-cell functions upon antigen binding. This configuration allows CAR-T cells to

be MHC independent, increasing their ability to target tumor cells and, importantly, to remain effective against tumors that downregulate MHC expression to evade immune detection (4).

Upon encountering TAAs, CAR binds to the antigen and triggers a cascade of intracellular signaling pathways that leads to T-cell activation and the release of cytotoxic molecules, such as perforin and granzymes, which activate the apoptotic pathway in the target cell. The incorporation of costimulatory domains within the CAR structure enhances CAR activity by providing additional signals that improve T-cell function and survival. Moreover, incorporating signaling domains into CAR constructs has been shown to enhance T-cell expansion and efficacy against hematological malignancies. Interestingly, studies have shown that the absence of these costimulatory signals can lead to T-cell exhaustion and reduced efficacy, emphasizing the importance of a well-designed CAR construct that can effectively engage both T cells and the TME (5).

Recognition of TAAs by CAR-T cells leads to the release of cytokines, particularly interferon-gamma (IFN-γ), which are critical for CAR-T-cell-mediated myeloid activation and the induction of endogenous immunity. This cytokine activation is vital for enhancing the antitumour effects of CAR-T cells in solid tumors such as glioblastoma (6). This is clinically supported, as CAR-T-cell responses are associated with increased inflammatory cytokines and activated endogenous immune cells (6, 7).

Cytokine production is dependent not only on the CAR-T cells themselves but also on their interactions with the TME. This interplay between CAR-T cells and the TME is crucial because while it can increase the efficacy of treatment, it can also increase the potential for adverse effects, such as CRS. CRS, in which excessive cytokines, particularly IL-6 and TNF-α, are released, can lead to severe systemic toxicity (8).

In addition to the impact of CAR-T cells on tumor cells, they can also activate bystander T cells and other immune cells within the TME, leading to an increased antitumor impact. This is particularly relevant in relation to solid tumors, where the TME can be immunosuppressive. The ability of CAR-T cells to reshape the TME by promoting the activation of endogenous immune cells is a promising area of research that could enhance the efficacy of CAR-T-cell therapies in previously resistant tumors (9).

## Clinical application of CAR-T-cell therapy in hematological malignancies and solid tumors

The treatment of hematological malignancies, including various forms of leukemia and lymphoma, has been transformed thanks to CAR-T-cell therapy. The FDA has approved several CAR-T-cell products for specific indications, primarily focusing on relapsed or refractory hematological malignancies.

The most notable CAR-T-cell products currently approved by the FDA include tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta), both of which target CD19 in B-cell malignancies.

Tisagenlecleucel is indicated for pediatric and young adult patients with ALL and for adult patients with relapsed or refractory DLBCL. Axicabtagene ciloleucel is approved for adult patients with DLBCL who have not responded to two or more lines of systemic therapy (10). Clinical trials

of these treatments have consistently demonstrated substantial improvements in overall survival (OS) and progression-free survival (PFS) in patients with refractory B-cell malignancies (**Table 2**).

| CAR T-Cell Therapy | Indication (R/R Cancer Type) | Overall Response Rate (ORR) | Complete Response Rate (CRR) | Progression-Free Survival (PFS) | Overall Survival (OS) |
|---|---|---|---|---|---|
| **Kymriah (Tisagenlecleucel)** | R/R ALL (pediatric) | 81% | 60% | N/D | N/D |
| | R/R LBCL | 52% | 40% | 6.8 months | Median: 12.1 months |
| **Yescarta (Axicabtagene Ciloleucel)** | R/R LBCL | 82% | 54% | N/D | 52% at 18 months |
| **Tecartus (Brexucabtagene Autoleucel)** | R/R MCL | 93% | 67% | 18.5 months | Median OS: 39 months |
| **Breyanzi (Lisocabtagene Maraleucel)** | R/R LBCL | 73% | 53% | 6.8 months | 60% at 12 months |
| **Carvykti (Ciltacabtagene Autoleucel)** | R/R MM (heavily pretreated patients) | 97% | 67% | 24 months | N/D |
| **Abecma (Idecabtagene Vicleucel)** | R/R MM (after at least 3 prior lines of therapy) | 73% | 33% | 8.8 months | Median OS: 19.4 months |

**Table 2:** FDA-approved CAR-T-cell therapies and their clinical trial outcomes for relapsed or refractory cancers, including response rates and survival improvements (R/R = relapsed or refractory, ALL = acute lymphoblastic leukemia, LBCL = large B-cell lymphoma, MCL = mantle cell lymphoma, MM = multiple myeloma) (11-18).

Furthermore, the integration of CAR-T-cell therapy into treatment regimens has been associated with improved leukemia-free survival (LFS) and OS rates, particularly when CAR-T-cell therapy is used as a bridging therapy prior to hematopoietic stem cell transplantation (HSCT) (19).

While CAR-T-cell therapy has revolutionized the treatment landscape for hematological malignancies, this success has not translated to solid tumors due to significant challenges. There have been limited achievements. Recently, the first in trial of a CAR-T therapy directed at prostate stem cell antigen (PSCA) resulted in PSA falls in around 30% of men with metastatic castrate resistant prostate cancer (20). Additionally, GD2-specific CAR-T cells have shown encouraging results in pediatric patients with H3k27m-mutated diffuse midline gliomas, indicating the feasibility of this approach in challenging neuroanatomical locations (21). Larger studies have revealed significant antitumour effects of GD2-specific CARs in patients with neuroblastoma (22) and claudin 18.2-targeted CAR-T cells in patients with gastrointestinal tumors (23), with efficacy observations equivalent to those of CD19-targeted CAR-T cells in lymphoma.

Research into solid tumors continues, particularly in the preclinical setting. For example, anti-CD70 and anti-B7-H3 CAR-T cells have demonstrated

efficacy in preclinical models of Clear Cell Renal Cell Carcinoma and osteosarcoma respectively (24, 25).

One reason for the difficulty in targeting solid tumors with CAR-T cells lies in the identification of suitable TAAs that are solely present or expressed at high levels on tumor cells compared to those in normal tissues. This approach is important for preventing on-target, off-tumor toxicity, which can lead to severe adverse effects (26). For example, while mesothelin is a promising target in pancreatic cancer, it is expressed in normal tissues, raising concerns about potential off-tumor toxicity (26, 27).

Furthermore, the issue of antigen heterogeneity poses a significant challenge. In hematological malignancies, target antigens are often uniformly expressed on malignant cells. However, solid tumors frequently exhibit heterogeneous expression of antigens between tumor cells. This variability can lead to tumor escape mechanisms, where subpopulations of tumor cells that do not express the target antigen survive and proliferate, ultimately leading to treatment resistance. To counteract this, strategies such as dual-target CAR-T cells have been proposed that aim to target multiple antigens simultaneously, thereby reducing the likelihood of tumor escape (28).

The TME presents another challenge in solid tumors. The TME is often characterized by immunosuppressive factors, such as regulatory T cells, myeloid-derived suppressor cells, and various inhibitory cytokines, that can dampen the activity of CAR-T cells . For example, the presence of programmed death-ligand 1 (PD-L1) in the TME can lead to T-cell exhaustion and reduced efficacy of CAR-T-cell therapy. To counteract these effects, researchers are investigating the addition of a PD-L1 chimeric costimulatory receptor, which has shown promise in improving the efficacy of CAR-T cells against PD-L1-positive solid tumors (29).

In addition to these strategies, the combination of oncolytic viruses and other immunotherapeutic agents with CAR-T-cell therapy has emerged as a promising approach to enhance the treatment efficacy in solid tumors. Oncolytic viruses can selectively infect and lyse tumor cells, potentially delivering CAR targets directly to the tumor site and enhancing the overall immune response (30). This combinatorial approach may help to overcome the barriers presented by the TME and improve the persistence and activity of CAR-T cells within solid tumors.

Overall, while CAR-T-cell therapy has shown success in treating hematological malignancies, its potential use in treating solid tumors remains unclear.

## Combination therapies

To address the treatment limits in solid tumors and to improve hematological malignancy outcomes, researchers have started to investigate combination therapies that involve CAR-T-cell therapy with other treatment types.

One obvious strategy involves combining CAR-T-cell therapy with traditional treatments such as chemotherapy and radiotherapy.

Radiotherapy has the added ability to modify the tumor microenvironment and enhance local inflammatory responses, increasing the viability of CAR-T cells (31). For example, in pancreatic cancer, proton radiation increased the tumor expression of

mesothelin and modulated the immunosuppressive TME, leading to an improved antitumor response by CAR-T-cell therapy (32). Similarly, the use of radiotherapy prior to CAR-T-cell infusion improved the treatment efficacy in patients with relapsed or refractory B-cell non-Hodgkin lymphoma (33).

Likewise, chemotherapy used in conjunction with CAR-T-cell therapy has shown improved outcomes. For example, preconditioning the TME with lymphodepleting chemotherapies, such as cyclophosphamide and fludarabine, can significantly improve CAR-T-cell engraftment and overall patient outcomes (34). However, these same chemotherapies have also been shown to impair CAR-T-cell functionality by inducing programmed cell death and decreasing durability (35). This is a major issue given that rapid expansion and proliferation of CAR-T cells postinfusion are crucial for a successful therapeutic response. Other chemotherapies have been investigated; for example, the use of targeted drugs such as venetoclax, a BCL2 inhibitor, has been shown to enhance the cytotoxic effects of CAR-T cells against malignant B cells (36).

The presence of immune checkpoints, such as PD-1 and PD-L1, can inhibit T-cell function and reduce therapeutic efficacy. Therefore, combinations of CAR-T cells with immunomodulatory agents, such as checkpoint inhibitors, have been studied. Blocking PD-1/PD-L1 interactions has been shown to increase CAR-T-cell efficacy. GD2-specific CAR-T cells exhibit improved activation and reduced activation-induced cell death when combined with anti-PD-1 monoclonal antibodies (37). Furthermore, CAR-T cells engineered to secrete bispecific proteins targeting both PD-1 and TGF-β have shown greater antitumour effects than conventional CAR-T cells. This approach not only blocks the PD-1/PD-L1 interaction but also decreases the immunosuppressive effects of TGF-β, thereby improving the immune response against tumors (38).

The combination of CAR-T-cell therapy with other targeted therapies has also shown promise (**Table 3**). For example, the use of ibrutinib, which irreversibly binds the protein Bruton's tyrosine kinase, has been reported to enhance the efficacy of anti-CD19 CAR-T-cell therapy in patients with refractory mantle cell lymphoma (39), a distinct subtype of B-cell non-Hodgkin lymphoma. This combination not only improves therapeutic efficacy but also modifies the tumor microenvironment, increasing CAR-T-cell efficacy. Similarly, lenalidomide has been shown to enhance the efficacy of anti-B-cell maturation antigen (BCMA) CAR-T-cell therapy in multiple myeloma, indicating that targeted therapies can play a crucial role in optimizing CAR-T-cell treatments (40).

| Combined Therapy Type | Indications (Cancer Types) | Mechanism of Action/Goal | Combination Rationale |
|---|---|---|---|
| **Chemotherapy (e.g., Fludarabine, Cyclophosphamide)** | R/R ALL, R/R LBCL | Immunosuppression to enhance CAR T expansion and persistence. | Lymphodepletion before CAR T-cell infusion to enhance engraftment and expansion. |
| **Immune Checkpoint Inhibitors (e.g., Pembrolizumab, Nivolumab)** | R/R Hodgkin Lymphoma, R/R LBCL | Block inhibitory pathways (PD-1/PD-L1) to enhance CAR T-cell activity. | Reversal of tumor-induced immunosuppression, synergistic activation of CAR T cells. |
| **Targeted Drugs (e.g., Ibrutinib, Venetoclax)** | R/R CLL, R/R ALL, R/R LBCL | Target B-cell receptor or apoptosis pathways in cancer cells. | Enhance CAR T-cell efficacy by depleting cancer cells or modulating microenvironment. |

| | | | |
|---|---|---|---|
| **Radiotherapy** | R/R LBCL, R/R Hodgkin Lymphoma | Direct tumor reduction and increased tumor antigen release. | Increases antigen release, improves CAR T-cell targeting, and reduces tumor burden. |
| **Stem Cell Transplantation (HSCT)** | R/R LBCL, R/R Multiple Myeloma | Replace bone marrow or provide immunological support post-CAR T. | Enhance long-term remission or consolidation after CAR T-cell therapy. |
| **Biomarkers (e.g., CD19, BCMA)** | ALL, LBCL, Multiple Myeloma | Guide therapy by identifying target antigens expressed on cancer cells. | Target-specific antigens on cancer cells for precision therapy. |
| **Personalized Medicine (e.g., Genetic Editing, Neoantigen TCRs)** | Multiple types of cancer (solid tumors, hematologic) | Customized CAR T cells based on patient's genetic/immune profile. | Tailoring CAR T-cell therapy to individual tumor profiles to improve efficacy. |

Table 3: Types of combined therapy combined with CAR-T-cell therapy in cancer treatment (R/R = relapsed or refractory, ALL = acute lymphoblastic leukemia, DLBCL = diffuse large B-cell lymphoma, MM = multiple myeloma) (11-13, 16, 41-49).

## Challenges, Limitations and Side Effects

Despite the promising utility of CAR-T-cell therapy, challenges, limitations, and side effects continue to exist that can impact patient outcomes, some of which have already been touched upon in this review.

The manufacturing process of CAR-T cells is complex and time-consuming and requires specialized facilities and expertise. The process begins with leukapheresis, where T cells are extracted from the patient, followed by genetic modification to express CARs that target specific tumor antigens. This ex vivo manipulation not only is labor intensive but also subject to variability in T-cell quality and quantity, which can impact therapeutic efficacy. The need for personalized manufacturing further complicates logistics, as each batch of CAR-T cells is tailored to individual patients, leading to increased costs and resource utilization (50). Each of these steps can lead to a lengthy manufacturing process and delay treatment, potentially allowing the disease to progress. Furthermore, the accessibility of CAR-T-cell therapies is limited, particularly in regions where specialized manufacturing facilities are unavailable. Additionally, the high costs associated with CAR-T-cell manufacturing and treatment can further limit patient access, particularly in healthcare systems with limited insurance coverage. Efforts to streamline the manufacturing process and reduce costs are continuing, with the hope that technological advancements will make CAR-T-cell therapies more accessible to a broader patient population.

The criteria for patient selection are also critical in determining treatment outcomes. CAR-T-cell therapy efficacy must be affected by numerous factors, including age, general health, and disease stage, to ensure the best outcomes. For example, patients with a high tumor burden or who have undergone multiple lines of therapy may have a suppressed response to CAR-T-cell therapy (51). Furthermore, patients with coexisting medical conditions may be at higher risk of adverse effects, such as CRS and neurotoxicity. Identifying patients at high risk is essential, as certain baseline characteristics, such as complications related to the nervous system during the disease course, have been associated with increased rates of CNS relapse after CAR-T-cell therapy (51). Therefore, careful patient selection is important to ensure maximum benefits from CAR-T-cell therapy while minimizing risks.

CAR-T-cell persistence and longevity are other important factors that influence treatment efficacy. Recent evidence suggests that the over expression of the transcription factor FOXO1 can enhance the stemness and metabolic fitness of CAR T cells, improving it's their efficacy and persistence (52). However, while CAR-T-cell expansion postinfusion is essential for a therapeutic response, recent studies suggest that long-term persistence may not be necessary for maintaining remission in subsets of patients. For example, while some patients benefit from maintaining CAR-T-cell presence, remission has been observed in patients with only transient CAR-T-cell activity, indicating an interplay between CAR-T-cell dynamics and patient-specific factors (53, 54).

CAR-T-cell persistence, the ability of CAR-T cells to survive and remain functional within the host over time, can be affected by various factors, including the TME and the immunogenicity of the CAR construct itself. For example, CAR-T cells targeting BCMA in multiple myeloma patients have demonstrated limited persistence, contributing to relapse (50). Strategies to increase CAR-T-cell longevity, such as the use of cytokines, e.g. IL-15, have shown promise in preclinical studies (55).

T-cell exhaustion is another concern that limits the effectiveness of CAR-T-cell therapy. This occurs when T cells become functionally impaired due to continuous stimulation by tumor antigens, which leads to reduced cytokine production and proliferative capabilities. Strategies to overcome this exhaustion include CAR-T-cell engineering to express costimulatory molecules or checkpoint inhibitors to reinvigorate exhausted T cells (56).

The issue of antigen escape and relapse represents another limitation of CAR-T-cell therapy. Antigen escape occurs when tumor cells lose the targeted antigen, rendering CAR-T-cell therapy ineffective. This has been observed in patients treated with CD19-targeted CAR-T-cell therapy, where relapses were attributed to the emergence of CD19-negative tumor variants (57). To overcome this problem, bispecific CAR-T cells that target multiple antigens simultaneously, thereby reducing the likelihood of antigen escape, are being tested, as are other strategies, including combining CAR-T cells with TCR-engineered T cells (58).

Side effects associated with CAR-T-cell therapy, particularly CRS and neurotoxicity, pose significant challenges to patient management and outcome. CRS is characterized by an inflammatory response that is triggered by the activation and proliferation of CAR-T cells, leading to increased pro-inflammatory cytokine levels. CRS symptoms can range from mild flu-like symptoms to severe complications such as multiorgan failure. Tocilizumab, an IL-6 receptor antagonist, has been shown to effectively treat severe CRS (59).

Neurotoxicity, also known as immune effector cell-associated neurotoxicity syndrome (ICANS), is caused by a mechanism that is not completely understood; can manifest as confusion, seizures, or even encephalopathy; and is often linked to the presence of CAR-T cells in the central nervous system (60). Vigilant monitoring and early intervention are crucial for managing adverse effects. Ongoing research is focused on identifying biomarkers that could predict susceptibility to CRS and neurotoxicity.

Furthermore, the long-term safety and quality of life implications of CAR-T-cell therapy are not

well understood, and studies investigating patient-reported outcomes are lacking. Addressing these gaps will be crucial for the continued development and refinement of CAR-T-cell therapies.

## Future prospects and research gaps

The future of CAR-T-cell therapy will focus on enhancing the successes observed in patients with hematological malignancies and translating these achievements into solid tumors while advancing the manufacturing process to increase the accessibility of the technology. To do this, novel research must be carried out to improve CAR-T-cell therapy efficacy.

One avenue involves the exploration of CAR-T-cell dynamics through modeling and simulation studies. These studies are crucial for understanding the interactions between CAR-T cells and the immunosuppressive capability of the TME. Recent advancements in computational modeling have allowed simulation of CAR-T-cell behaviors in various tumor settings, providing suggestive optimal dosing regimens and timings for CAR-T-cell administration (61). These models can also help predict patient-specific responses, depending on the tumor burden and CAR-T-cell expansion kinetics, for the best personalized treatment strategies.

An area of continuous research is on the novel design of CAR constructs that enhance the efficacy of CAR-T cells. While traditional CARs primarily target CD19, there is growing interest in developing multispecific CARs that can target multiple antigens and thus improve tumor recognition while reducing tumor escape (62, 63). For example, the development of tandem CARs that target both folate receptor 1 (FOLR1) and mesothelin has shown promise in preclinical models of ovarian cancer, demonstrating enhanced antitumour effects (63). Furthermore, the incorporation of costimulatory domains, such as 4-1BB, into CAR constructs has been shown to improve T-cell survival and function within the hostile TME (62). Moreover, engineering CAR-T cells to secrete immunomodulatory cytokines has emerged as a strategy to enhance their antitumour efficacy. For instance, the development of CAR-T cells that secrete IL-7, CCL19, and IL-12 has shown potential in targeting malignant solid tumors, as these cytokines can help to recruit and activate additional immune cells within the TME (64).

Another area of interest is the use of oncolytic viruses in combination with CAR-T-cell therapy. These viruses selectively infect and lyse tumor cells while also stimulating an immune response. This potential combination may enhance therapeutic efficacy in solid tumors by providing a more robust antitumour immune response (65, 66).

Interestingly, the role of the microbiome in modulating the immune response to CAR-T-cell therapy is also being investigated. Preliminary studies have suggested that the gut microbiota composition may influence the efficacy and toxicity of CAR-T-cell therapy, indicating that modulation of the microbiome could be an additional targeting strategy to enhance treatment outcomes (67). Additionally, the gut microbiota has been implicated in modulating therapeutic responses, suggesting that microbiota signatures may serve as predictive indicators (68).

One area of urgent need is the identification of biomarkers that can predict patient responses to CAR-T-cell therapy. Current studies have shown variability in treatment outcomes based on factors such as tumor burden and CAR-T-cell expansion kinet-

ics, but standardized biomarkers are lacking (69). However, there is ongoing work in the field to identify potential biomarkers. For instance, preinfusion characteristics such as red blood cell distribution width has been associated with treatment outcomes in DLBCL patients (70). Moreover, tumor-intrinsic factors, such as CD21 expression levels, have been shown to influence responses to CD19-targeted CAR-T-cell therapy (71). Other studies have highlighted the importance of monitoring circulating tumor DNA (ctDNA) and telomerase activity as potential biomarkers for predicting treatment outcomes and personalizing therapy (72).

Taking a wider view of all publicly available data is also important for understanding the impact of CAR-T-cell therapy. The use of large datasets and real-world evidence is important for improving CAR-T-cell therapy protocols, as they provide insights that extend beyond controlled clinical trials. A large dataset allows researchers to identify patterns and outcomes that can guide the clinical decision-making process. For example, in Germany, an analysis of real-world outcomes for CAR-T-cell therapies highlighted the long-term remission achieved by patients, with some enduring for more than 9 years, highlighting the importance of RWE in assessing the effectiveness of CAR-T-cell therapy in diverse patient populations, which may differ significantly from those in clinical trials (73).

Moreover, the latest RWE indicates that therapies for DLBCL and MM not only improve patient outcomes but also enhance health-related quality of life (74). This is important because it challenges the traditional treatment paradigm, suggesting that CAR-T-cell therapy can be a viable option, even in patients previously deemed untreatable.

RWE can also be used to highlight the safety profile of CAR-T cells. For example, a lower incidence of severe CRS was reported in a real-world study than in pivotal trials, suggesting that patient selection and management strategies in clinical practice can influence outcomes (75). Furthermore, RWE can help in identifying potential predictive biomarkers associated with severe CRS, allowing for the implementation of early intervention strategies.

## Conclusion

CAR-T-cell therapy has significantly improved the treatment of hematological malignancies, demonstrating remarkable efficacy in patients with conditions such as ALL and DLBCL. This has been proven with FDA-approved products, such as tisagenlecleucel and axicabtagene ciloleucel, which have improved overall and progression-free survival rates. However, the translation of CAR-T-cell therapy to solid tumors is fraught with various challenges, including antigen heterogeneity, the immunosuppressive tumor microenvironment, and the risk of on-target, off-tumor toxicity. While promising results have emerged from individual case studies and preclinical models, the overall efficacy of these methods in solid tumors is still limited.

However, combination therapies represent a promising avenue for improving the efficacy of CAR-T-cell therapy in both hematological and solid tumors. The integration of CAR-T-cell therapy with traditional treatments, immunomodulatory agents, and targeted therapies has shown potential for improving patient outcomes.

Challenges, such as the complexity of CAR-T-cell manufacturing, patient selection criteria, and the

management of side effects such as CRS and neurotoxicity, must be addressed to optimize treatment protocols.

Moving forward, future research must focus on overcoming these barriers through innovative strategies, such as dual-target CAR-T cells, combination therapies with traditional treatments, and the integration of oncolytic viruses. Additionally, enhancing CAR-T-cell persistence and functionality, in addition to identifying predictive biomarkers for patient response, will be crucial for optimizing treatment outcomes. As the field evolves, the potential for CAR-T-cell therapy to revolutionize cancer treatment across various malignancies remains a compelling prospect, warranting continued exploration and investment.

## Abbreviations

CAR T: Chimeric Antigen Receptor T
CARs: Chimeric antigen receptors
FDA: Food and Drug Agency
TAA: Tumor-associated antigen
ALL: Acute lymphoblastic leukemia
DLBCL: diffuse large B-cell lymphoma
R/R: Relapsed or refractory
ALL: Acute lymphoblastic leukemia
LBCL: Large B-cell lymphoma
PMBCL: Primary Mediastinal B-cell Lymphoma
PSA: Prostate specific antigen
FL: Follicular Lymphoma
MCL: Mantle cell lymphoma
MM: Multiple myeloma
AML: Acute myeloid leukemia
MHC: major histocompatibility complex
GM-CSF: granulocyte–macrophage colony-stimulating factor
TME: Tumor microenvironment
LFS: Leukemia-free survival
HSCT: hematopoietic stem cell transplantation
GVHD = graft-versus-host disease
CRS = cytokine release syndrome

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of data and material (Please ensure it is identical with the submission system; If not applicable, please state so.)

Not applicable.

### Competing interests

The author declares that there are no competing interests.


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## References


1. Han D, Xu Z, Zhuang Y, Ye Z, Qian Q. Current Progress in CAR-T Cell Therapy for Hematological Malignancies. Journal of Cancer. 2021;12(2):326-34.
2. Petty AJ, Heyman B, Yang Y. Chimeric Antigen Receptor Cell Therapy: Overcoming Obstacles to Battle Cancer. Cancers. 2020;12(4):842.
3. Guo F, Cui J. CAR-T in Cancer Treatment: Develop in Self-Optimization, Win-Win in Cooperation. Cancers. 2021;13(8):1955.
4. Fucà G, Reppel L, Landoni E, Savoldo B, Dotti G. Enhancing Chimeric Antigen Receptor T-

Cell Efficacy in Solid Tumors. Clinical Cancer Research. 2020;26(11):2444-51.
5. Boulch M, Cazaux M, Loe-Mie Y, Thibaut R, Corre B, Lemaître F, et al. A Cross-Talk Between CAR T Cell Subsets and the Tumor Microenvironment Is Essential for Sustained Cytotoxic Activity. Science Immunology. 2021;6 (57).
6. Alizadeh D, Wong RA, Gholamin S, Maker M, Aftabizadeh M, Yang X, et al. IFNγ Is Critical for CAR T Cell–Mediated Myeloid Activation and Induction of Endogenous Immunity. Cancer Discovery. 2021;11(9):2248-65.
7. Hegde M, Joseph S, Pashankar F, DeRenzo C, Sanber K, Navai SA, et al. Tumor Response and Endogenous Immune Reactivity After Administration of HER2 CAR T Cells in a Child With Metastatic Rhabdomyosarcoma. Nature Communications. 2020;11(1).
8. Morris EC, Neelapu SS, Giavridis T, Sadelain M. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat Rev Immunol. 2022;22(2):85-96.
9. Avanzi MP, Yeku O, Li X, Wijewarnasuriya D, Leeuwen DGv, Cheung K, et al. Engineered Tumor-Targeted T Cells Mediate Enhanced Anti-Tumor Efficacy Both Directly and Through Activation of the Endogenous Immune System. Cell Reports. 2018;23(7):2130-41.
10. Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. Blood Rev. 2019;34:45-55.
11. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):439-48.
12. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56.
13. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377(26):2531-44.
14. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2020;382(14):1331-42.
15. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-52.
16. Munshi NC, Anderson LD, Jr., Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021;384(8):705-16.
17. Lin Y, Martin TG, Usmani SZ, Berdeja JG, Jakubowiak AJ, Agha ME, et al. CARTITUDE-1 final results: Phase 1b/2 study of ciltacabtagene autoleucel in heavily pretreated patients with relapsed/refractory multiple myeloma. Journal of Clinical Oncology. 2023;41 (16_suppl):8009-.
18. Martin T, Usmani SZ, Berdeja JG, Agha M, Cohen AD, Hari P, et al. Ciltacabtagene Autoleucel, an Anti-B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CAR-

TITUDE-1 2-Year Follow-Up. J Clin Oncol. 2023;41(6):1265-74.
19. Zhang Q. Quartic CAR-T Cell Bridging to Twice Allo-HSCT Therapy in a Patient With Acute Lymphoblastic Leukemia. Transfusion Medicine and Hemotherapy. 2023;51(1):55-60.
20. Dorff TB, Blanchard MS, Adkins LN, Luebbert L, Leggett N, Shishido SN, et al. PSCA-CAR T cell therapy in metastatic castration-resistant prostate cancer: a phase 1 trial. Nat Med. 2024;30(6):1636-44.
21. Majzner RG, Ramakrishna S, Yeom KW, Patel S, Chinnasamy H, Schultz L, et al. GD2-CAR T Cell Therapy for H3k27m-Mutated Diffuse Midline Gliomas. Nature. 2022;603(7903):934-41.
22. Bufalo FD, Angelis BD, Caruana I, Baldo GD, Ioris MAD, Serra A, et al. GD2-CART01 for Relapsed or Refractory High-Risk Neuroblastoma. New England Journal of Medicine. 2023;388(14):1284-95.
23. Qi C, Gong J, Li J, Liú D, Qin Y, Ge S, et al. Claudin18.2-specific CAR T Cells in Gastrointestinal Cancers: Phase 1 Trial Interim Results. Nature Medicine. 2022;28(6):1189-98.
24. Zhang Q, Zhang Z, Liu G, Li D, Gu Z, Zhang L, et al. B7-H3 Targeted CAR-T Cells Show Highly Efficient Anti-Tumor Function Against Osteosarcoma Both in Vitro and in Vivo. BMC Cancer. 2022;22(1).
25. Pal SK, Tran B, Haanen J, Hurwitz ME, Sacher A, Tannir NM, et al. CD70-Targeted Allogeneic CAR T-Cell Therapy for Advanced Clear Cell Renal Cell Carcinoma. Cancer Discov. 2024;14(7):1176-89.
26. Tian M, Cheuk A, Wei JS, Abdelmaksoud A, Chou H-C, Milewski D, et al. An Optimized Bicistronic Chimeric Antigen Receptor Against GPC2 or CD276 Overcomes Heterogeneous Expression in Neuroblastoma. Journal of Clinical Investigation. 2022;132(16).
27. Watanabe K, Luo Y, Da T, Guedan S, Ruella M, Scholler J, et al. Pancreatic Cancer Therapy With Combined Mesothelin-Redirected Chimeric Antigen Receptor T Cells and Cytokine-Armed Oncolytic Adenoviruses. Jci Insight. 2018;3(7).
28. León-Triana O, Pérez-Martínez A, Ramírez-Orellana M, Pérez-García VcM. Dual-Target CAR-Ts With on- And Off-Tumour Activity May Override Immune Suppression in Solid Cancers: A Mathematical Proof of Concept. Cancers. 2021;13(4):703.
29. Liao Q, Mao Y, He H, Ding X, Zhang X, Xu J. PD-L1 Chimeric Costimulatory Receptor Improves the Efficacy of CAR-T Cells for PD-L1-positive Solid Tumors and Reduces Toxicity in Vivo. Biomarker Research. 2020;8(1).
30. Park AK, Fong Y, Kim S, Yang J, Murad JP, Lü J, et al. Effective Combination Immunotherapy Using Oncolytic Viruses to Deliver CAR Targets to Solid Tumors. Science Translational Medicine. 2020;12(559).
31. Xu N, Wu D, Gao J, Jiang H, Li Q, Bao S, et al. The effect of tumor vascular remodeling and immune microenvironment activation induced by radiotherapy: quantitative evaluation with magnetic resonance/photoacoustic dual-modality imaging. Quant Imaging Med Surg. 2023;13(10):6555-70.
32. Amit U. Proton Radiation Boosts the Efficacy of Mesothelin-Targeting Chimeric Antigen Receptor T Cell Therapy in Pancreatic Cancer. Proceedings of the National Academy of Sciences. 2024;121(31).
33. Saifi O, Breen WG, Lester SC, Rule WG, Stish BJ, Rosenthal A, et al. Don't Put the CART Before the Horse: The Role of Radiation Therapy

in Peri-CAR T-cell Therapy for Aggressive B-cell Non-Hodgkin Lymphoma. Int J Radiat Oncol Biol Phys. 2023;116(5):999-1007.
34. Wang AX, Ong XJ, D'Souza C, Neeson PJ, Zhu JJ. Combining Chemotherapy With CAR-T Cell Therapy in Treating Solid Tumors. Frontiers in Immunology. 2023;14.
35. Xia Z, Tian M, Cheng Y, Yi W, Du Z, Li T, et al. Preclinical evaluation of cyclophosphamide and fludarabine combined with CD19 CAR-T in the treatment of B-cell hematologic malignancies in vivo. Oncol Res. 2024;32(6):1109-18.
36. Yang M, Wang L, Ni M, Neuber B, Wang S, Gong W, et al. Pre-Sensitization of Malignant B Cells Through Venetoclax Significantly Improves the Cytotoxic Efficacy of CD19.CAR-T Cells. Frontiers in Immunology. 2020;11.
37. Gargett T, Yu W, Dotti G, Yvon E, Christo SN, Hayball JD, et al. GD2-specific CAR T Cells Undergo Potent Activation and Deletion Following Antigen Encounter but Can Be Protected From Activation-Induced Cell Death by PD-1 Blockade. Molecular Therapy. 2016;24(6):1135-49.
38. Chen X, Yang S, Li S, Qu Y, Wang HY, Liu J, et al. Secretion of bispecific protein of anti-PD-1 fused with TGF-beta trap enhances antitumor efficacy of CAR-T cell therapy. Mol Ther Oncolytics. 2021;21:144-57.
39. Mu J, Liu M, Wang J, Meng J, Zhang R, Jiang Y, et al. Successful Treatment of Second-Time CAR-T 19 Therapy After Failure of First-Time CAR-T 19 and Ibrutinib Therapy in Relapsed Mantle Cell Lymphoma. Advances in Clinical and Experimental Medicine. 2022;31(3):327-35.
40. Zhao G, Wei R, Feng L, Wu Y, He F, Xiao M, et al. Lenalidomide Enhances the Efficacy of Anti-Bcma CAR-T Treatment in Relapsed/Refractory Multiple Myeloma: A Case Report and Revies of the Literature. Cancer Immunology Immunotherapy. 2021;71(1):39-44.
41. Chong EA, Melenhorst JJ, Lacey SF, Ambrose DE, Gonzalez V, Levine BL, et al. PD-1 blockade modulates chimeric antigen receptor (CAR)-modified T cells: refueling the CAR. Blood. 2017;129(8):1039-41.
42. Armand P, Rodig S, Melnichenko V, Thieblemont C, Bouabdallah K, Tumyan G, et al. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. J Clin Oncol. 2019;37(34):3291-9.
43. Fraietta JA, Lacey SF, Orlando EJ, Pruteanu-Malinici I, Gohil M, Lundh S, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. Nat Med. 2018;24(5):563-71.
44. Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126(6):2123-38.
45. Bachanova V, Perales MA, Abramson JS. Modern management of relapsed and refractory aggressive B-cell lymphoma: A perspective on the current treatment landscape and patient selection for CAR T-cell therapy. Blood Rev. 2020;40:100640.
46. Yu L, Zou R, He J, Qu C. Role of radiation in chimeric antigen receptor T-cell therapy for patients with relapsed/refractory non-Hodgkin lymphoma: Current studies and future prospects. Crit Rev Oncol Hematol. 2024;199:104390.
47. Majhail NS, Weisdorf DJ, Defor TE, Miller JS, McGlave PB, Slungaard A, et al. Long-term

results of autologous stem cell transplantation for primary refractory or relapsed Hodgkin's lymphoma. Biol Blood Marrow Transplant. 2006;12(10):1065-72.
48. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. Science. 2018;359 (6382):1361-5.
49. Scholler J, Brady TL, Binder-Scholl G, Hwang WT, Plesa G, Hege KM, et al. Decade-long safety and function of retroviral-modified chimeric antigen receptor T cells. Sci Transl Med. 2012;4(132):132ra53.
50. Zhang X, Zhang H, Lan H, Wu J, Xiao Y. CAR -T Cell Therapy in Multiple Myeloma: Current Limitations and Potential Strategies. Frontiers in Immunology. 2023;14.
51. Zhu H. Three Cases of Late-onset <scp>post CAR-T Therapy</Scp> Isolated <scp>CNS</ Scp> Relapse in R/R Large B-cell Lymphoma. European Journal of Haematology. 2023;112 (2):310-3.
52. Chan JD, Scheffler CM, Munoz I, Sek K, Lee JN, Huang YK, et al. FOXO1 enhances CAR T cell stemness, metabolic fitness and efficacy. Nature. 2024;629(8010):201-10.
53. Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. Nat Rev Clin Oncol. 2023;20 (6):359-71.
54. Gupta S, Kohorst M, Alkhateeb HB. Determinants of outcomes and advances in CD19-directed chimeric antigen receptor therapy for B -cell acute lymphoblastic leukemia. Eur J Haematol. 2024;112(1):51-63.
55. Sanchez-Moreno I, Lasarte-Cia A, Martin-Otal C, Casares N, Navarro F, Gorraiz M, et al. Tethered IL15-IL15Ralpha augments antitumor activity of CD19 CAR-T cells but displays long -term toxicity in an immunocompetent lymphoma mouse model. J Immunother Cancer. 2024;12(7).
56. Yin X, He L, Guo Z. T-cell Exhaustion in CAR -T-cell Therapy and Strategies to Overcome It. Immunology. 2023;169(4):400-11.
57. Aparicio-Perez C, Carmona M, Benabdellah K, Herrera C. Failure of ALL recognition by CAR T cells: a review of CD 19-negative relapses after anti-CD 19 CAR-T treatment in B-ALL. Front Immunol. 2023;14:1165870.
58. Wachsmann TLA, Meeuwsen MH, Remst DFG, Buchner K, Wouters AK, Hagedoorn RS, et al. Combining BCMA-targeting CAR T cells with TCR-engineered T-cell therapy to prevent immune escape of multiple myeloma. Blood Adv. 2023;7(20):6178-83.
59. Si S, Teachey DT. Spotlight on Tocilizumab in the Treatment of CAR-T-Cell-Induced Cytokine Release Syndrome: Clinical Evidence to Date. Ther Clin Risk Manag. 2020;16:705-14.
60. Li X, Liu M, Mou N, Yang Z, Wang J, Mu J, et al. Efficacy and Safety of Humanized CD19 CAR-T as a Salvage Therapy for Recurrent CNSL of B-ALL Following Murine CD19 CAR-T Cell Therapy. Oncology Letters. 2021;22(5).
61. Miao L, Zhang J, Zhang Z, Wang S, Tang F, Teng M, et al. A Bibliometric and Knowledge-Map Analysis of CAR-T Cells From 2009 to 2021. Frontiers in Immunology. 2022;13.
62. Wang Y, Yu W, Zhu J, Wang J, Xia K, Liang C, et al. Anti-Cd166/4-1bb Chimeric Antigen Receptor T Cell Therapy for the Treatment of Osteosarcoma. Journal of Experimental & Clinical Cancer Research. 2019;38(1).
63. Liang Z, Dong J, Yang N, Li S-D, Yang Z, Huang R, et al. Tandem CAR-T Cells Targeting FOLR1 and MSLN Enhance the Antitumor Ef-

fects in Ovarian Cancer. International Journal of Biological Sciences. 2021;17(15):4365-76.
64. Li F, Zhao S, Wei C, Hu Y, Xu T, Xin X, et al. Development of Nectin4/FAP-targeted CAR-T Cells Secreting IL-7, CCL19, and IL-12 for Malignant Solid Tumors. Frontiers in Immunology. 2022;13.
65. He J, Munir F, Ragoonanan D, Zaky W, Khazal SJ, Tewari P, et al. Combining CAR T Cell Therapy and Oncolytic Virotherapy for Pediatric Solid Tumors: A Promising Option. Immuno [Internet]. 2023; 3(1):[37-56 pp.].
66. Fang L. Recombinant Oncolytic Adenovirus Armed With CCL5, IL-12, and IFN-γ Promotes CAR-T Infiltration and Proliferation in Vivo to Eradicate Local and Distal Tumors. Cell Death Discovery. 2023;9(1).
67. Rodríguez-García A, Palazón A, Noguera-Ortega E, Powell DJ, Guedan S. CAR-T Cells Hit the Tumor Microenvironment: Strategies to Overcome Tumor Escape. Frontiers in Immunology. 2020;11.
68. Zhang PF, Xie D. Targeting the gut microbiota to enhance the antitumor efficacy and attenuate the toxicity of CAR-T cell therapy: a new hope? Front Immunol. 2024;15:1362133.
69. Zou B. Biomarkers for Predicting Efficacy of Chimeric Antigen Receptor T Cell Therapy and Their Detection Methods. Ilabmed. 2024;2 (1):14-26.
70. Nakamura N, Jo T, Arai Y, Kitawaki T, Nishikori M, Mizumoto C, et al. Utilizing red blood cell distribution width (RDW) as a reliable biomarker to predict treatment effects after chimeric antigen receptor T cell therapy. Clin Exp Med. 2024;24(1):105.
71. Li D, Xu Q, Hu Y, Wang W, Xie S, Zhao C, et al. Tumor-intrinsic CD21 expression impacts the response of B-cell malignancy cells to CD19-CAR-T cells. J Leukoc Biol. 2022;112 (4):913-8.
72. Pomeroy AE, Palmer AC. Abstract 6549: Mechanistic models of tumor and patient heterogeneity explain and predict clinical outcomes of large B-cell lymphoma (LBCL) treatment. Cancer Research. 2024;84(6_Supplement):6549 -.
73. Bethge WA, Martus P, Schmitt M, Holtick U, Subklewe M, von Tresckow B, et al. GLA/ DRST real-world outcome analysis of CAR T-cell therapies for large B-cell lymphoma in Germany. Blood. 2022;140(4):349-58.
74. Stadelmann. Significant Progress in CAR T-Cell Therapy for Difficult-to-Treat Hematologic Malignancies. Healthbook Times Oncology Hematology. 2022(13).
75. Iacoboni G, Villacampa G, Martinez-Cibrian N, Bailen R, Lopez Corral L, Sanchez JM, et al. Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma. Cancer Med. 2021;10(10):3214-23.