KOWALCZUK, Dmytro, KASIANIK, Viktoryia, LAZITSKAYA, Darya, TURLEJ, Kamil, SOBCHYNSKYI, Mykola, MILASHEUSKAYA, Valeryia, MYRNYI, Andrii, KIEŁBASZEWSKA, Iga, SUROSZ, Natalia and MIRANIUK, Katsiaryna. Effectiveness, Limitations, and Future Perspectives of CAR-T Cell Therapy in Solid Tumor Treatment: A Narrative Review. Quality in Sport. 2025;41:60162. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.41.60162
https://apcz.umk.pl/QS/article/view/60162

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 08.04.2025. Revised: 30.04.2025. Accepted: 12.05.2025. Published: 16.05.2025.

Effectiveness, Limitations, and Future Perspectives of CAR-T Cell Therapy in Solid Tumor Treatment: A Narrative Review

Dmytro Kowalczuk* [DK], MD

Międzyleski Specialist Hospital in Warsaw, Bursztynowa 2, 04-749 Warsaw, Poland

dmytro.kovalchuk1999@gmail.com

https://orcid.org/0009-0004-1433-5052

Viktoryia Kasianik* [VK], MD

Mazovian Rehabilitation Center STOCER Ltd. Saint Anna Trauma Surgery Hospital, Barska 16/20, 02-315 Warsaw, Poland

wiktoriakasianik@gmail.com

https://orcid.org/0009-0004-1540-5227

Darya Lazitskaya [DL], MD

Międzyleski Specialist Hospital in Warsaw, Bursztynowa 2, 04-749 Warsaw, Poland

datskayalo@gmail.com

https://orcid.org/0009-0007-8680-8826

Kamil Turlej [KT], MD
University Clinical Center of the Medical University of Warsaw, Banacha 1A, 02-097 Warsaw, Poland
kturlej99@gmail.com
https://orcid.org/0009-0008-2919-284X

Mykola Sobchynskyi [MS], MD
Międzyleski Specialist Hospital in Warsaw, Bursztynowa 2, 04-749 Warsaw, Poland
sobczynski0@gmail.com
https://orcid.org/0009-0008-1804-1114

Valeryia Milasheuskaya [VM], MD
Wroclaw Medical University, wyb.Ludwika Pasteura 1, 50-367 Wroclaw, Poland
valeryiamilasheuskaya@gmail.com
https://orcid.org/0009-0006-4126-2375

Andrii Myrnyi [AM], MD
University Clinical Center of the Medical University of Warsaw, Banacha 1A, 02-097 Warsaw, Poland
andmyrnyi@gmail.com
https://orcid.org/0009-0006-5592-259X

Iga Kiełbaszewska [IK], MD
Independent Public Healthcare Centre in Hajnówka, Doc. Adama Dowgirda 9, 17-200 Hajnówka, Poland
kielbaszewska.i@gmail.com
https://orcid.org/0009-0004-9892-4769

Natalia Surosz [NS], MD
Międzyleski Specialist Hospital in Warsaw, Bursztynowa 2, 04-749 Warsaw, Poland
natalia.surosz@gmail.com
https://orcid.org/0009-0005-1939-151X

Katsiaryna Miraniuk [KM], student
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
mironk2711@gmail.com
https://orcid.org/0009-0006-1406-9756

*These two authors are equal contributors to this work and designated as co-first authors
Corresponding author: Dmytro Kowalczuk, MD, dmytro.kovalchuk1999@gmail.com

Abstract

Introduction: In recent years, immunotherapy has revolutionized therapeutic approaches to cancer treatment. Chimeric Antigen Receptor T-cell (CAR-T) immunotherapy has achieved significant success in the treatment of hematological cancers; however, its effectiveness in solid tumors remains limited.

Aim of Study: To analyze and summarize the current knowledge on the effectiveness, limitations, development prospects, and improvements of CAR-T cells in the treatment of solid tumors.

Brief Description of the State of Knowledge: Despite promising results in hematologic malignancies, the application of CAR-T in solid tumors faces numerous challenges. Key obstacles include the lack of tumor-specific antigens, ineffective targeting and infiltration of CAR-T cells into tumor sites, the immunosuppressive tumor microenvironment (TME), treatment-related toxicity, and antigen escape. The future directions for CAR-T therapy development in solid tumors are the identification of new antigens, optimization of CAR constructs, modification of the TME, and potential combination therapies.

Conclusions: CAR-T therapy represents a promising and personalized approach to cancer treatment, with the potential for durable responses and applications in solid tumors, although further improvements are necessary to overcome existing limitations and enhance the effectiveness and safety of this therapy.

Keywords: CAR-T cells, solid tumors, tumor microenvironment, cancer immunotherapy.

1. Introduction

In recent years, immunotherapy has revolutionized therapeutic approaches to cancer treatment, currently constituting the fourth pillar of oncological therapy alongside surgery, radiotherapy, and chemotherapy. Particularly promising have been strategies utilizing modified T lymphocytes, including Chimeric Antigen Receptor T (CAR-T) cell therapy. CAR-T therapy, which involves the genetic reprogramming of a patient's T lymphocytes to recognize and destroy cancer cells, has yielded unprecedented results in the treatment of treatment-resistant and relapsed hematologic cancers [1]. A prime example of this is therapies targeting the CD19 antigen in various types of B-cell leukemias and lymphomas, where high remission rates have been achieved, reaching up to 85% in acute lymphoblastic leukemia (ALL) [2] and up to 100% in patients with refractory or relapsed B-cell acute lymphoblastic leukemia (B-ALL) [3]. Similarly, CAR-T therapies targeting the BCMA antigen have shown efficacy in the treatment of multiple myeloma, with complete remission rates ranging from 29 to 60% in patients with relapsed/refractory multiple myeloma [4].

Despite these spectacular successes in hematologic oncology, the application of CAR-T therapy in the treatment of solid tumors faces several significant challenges. Major limitations include difficulties in tumor infiltration by T lymphocytes, insufficient recruitment of T cells to the tumor site due to abnormal chemokines secreted by solid tumor cells, and the immunosuppressive tumor microenvironment (TME) [5]. Moreover, in solid tumors, there is limited availability of suitable antigens, tumor heterogeneity, and physical barriers such as desmoplastic stroma

and abnormal vasculature, leading to hypoxia and impaired nutrient availability. Therefore, intensive research is being conducted to improve the efficacy and safety of CAR-T therapy with regard to solid tumors [6].

This scientific article aims to analyze and summarize the current knowledge regarding the effectiveness, limitations, and prospects of CAR-T therapy in the treatment of solid tumors. Both the promising clinical outcomes to date and the main challenges that must be overcome to fully exploit the potential of this innovative immunotherapy method in the fight against solid tumors will be discussed. Additionally, future research directions and strategies aimed at increasing the efficacy, safety, and durability of therapeutic responses in this patient group will be presented.

2. Materials and Methods

A search of the PubMed and Google Scholar databases was conducted using relevant keywords to find available studies published up to March 18, 2025. Only articles written in English were included. A preliminary selection of titles and abstracts was made, followed by a full-text review of the relevant publications.

3. Results

3.1. Studies on the Effectiveness of CAR-T Cell Therapy in Solid Tumor Treatment

3.1.1. Colorectal Cancer (CRC)

Various targets have been studied for CAR-T therapy in colorectal cancer (CRC). The carcinoembryonic antigen (CEA) is one of the main targets, and clinical trials using CAR-T cells targeting CEA have shown some effectiveness [7]. In a phase I study, one of three CRC patients had a partial response, although all patients experienced adverse events, such as severe colitis [8]. Another phase I dose-escalation study of CAR-T therapy targeting CEA in metastatic CRC showed disease stabilization in 7 of 10 patients and tumor reduction in 2 patients [9]. Other targets are also being investigated, such as CD133, which in clinical trials for pancreatic cancer and hepatocellular carcinoma has demonstrated an inhibitory effect on the metastatic potential of tumors [10].

3.1.2. Sarcomas

A phase I/II clinical trial (NCT00902044) using CAR-T cells targeting the human epidermal growth factor receptor-2 (HER2) in 19 patients with HER2-positive sarcomas (mainly osteosarcomas) showed disease stabilization in 4 of 17 evaluable patients for 3 to 14 months, with one patient having ≥90% tumor necrosis after tumor resection. The median overall survival in this group was 10.3 months. No serious adverse events were observed other than high fever in one patient [11]. A phase II study (SPEARHEAD-1) with TCR-T cells targeting MAGE-A4 showed promising results. In the evaluated population of 33 patients with synovial sarcoma and 4 with myxoid/round-cell liposarcoma, the overall response rate (ORR) was 39.4%, and the disease control rate was 84.8%. Two complete responses were observed in patients with synovial sarcoma [12,13].

3.1.3. Glioblastoma (GBM)

Several targets have been studied for CAR-T therapy in glioblastoma multiforme (GBM). HER2-targeted CAR-T cells in a phase I study (NCT01109095) in 17 GBM patients were well tolerated, and the median overall survival for 8 patients after treatment was 11.1 months (24.5 months from diagnosis), with 3 patients remaining progression-free at the last follow-up [14]. Another phase I study (NCT03500991) with local CAR-T administration targeting HER2 in central nervous system (CNS) tumors in children showed increased chemokine secretion without CAR-T dose-related toxicity. IL-13Rα2 is a promising target [15], and a study (NCT02208362) with multiple administrations of CAR-T cells targeting IL-13Rα2 resulted in complete tumor regression in a patient with disseminated GBM for nearly 8 months [16]. Another study (NCT00730613) with the same target showed good tolerance of therapy with controlled encephalitis, and one patient had a short-term remission [17]. GD2 is also being considered as a target in GBM, and a phase I study (NCT04196413) showed clinical and radiological improvement in patients with H3K27M-mutant DIPG or spinal DMG treated with GD2-targeted CAR-T cells [18]. CAR-T cells targeting EGFRvIII in recurrent GBM (NCT02209376) showed anti-tumor effects, with a median overall survival of approximately 8 months in all patients [19]. Other antigens, such as EphA2 (NCT02575261) and MUC1 (NCT02839954, NCT02617134), are also being investigated [20].

3.1.4. Pancreatic Cancer and Advanced Biliary Tract Cancers (BTC)

In a phase I study (NCT01935843) of CAR-T cells targeting HER2 in patients with pancreatic cancer (PC) and advanced biliary tract cancers (BTC), the median overall survival was 4.8 months (range 1.5–8.3 months), with minimal and reversible toxic effects observed [21]. In pancreatic cancer, other targets, such as CD133 [22], MUC-1 [23], PSCA [24], mesothelin [25], and FAP [26], are also being studied. CAR-T cells with CXCR2 expression may migrate more effectively towards IL-8 in animal models of pancreatic cancer [27].

3.1.5. Neuroblastoma

In a phase I study (NCT00085930) evaluating the effect of CAR-T cells targeting GD2 in 11 patients with neuroblastoma, complete remission was observed in 3 patients [18]. Another study (NCT02107963) with GD2 CAR-T cells showed that they were well tolerated, and in 16.7% of evaluated patients, disease progression was noted after 28 days, while 83.3% had disease stabilization [28].

3.1.6. Metastatic Melanoma

The GD2 ligand was also targeted in a phase I study (ACTRN12613000198729) for patients with GD2-positive metastatic melanoma treated with CAR-T cells. The data showed increased expression of LAG-3 and PD-1 in the administered CAR-T cells. Therefore, combining CAR-T cells with PD-1 checkpoint blockade may enhance the effectiveness of CAR-T therapy [29]. CAR-T cells targeting MART-1 and gp100 were also studied in melanoma. MART-1 studies showed an objective response rate (ORR) not exceeding 12% in one trial [30]. TCRs recognizing MART-1 in other studies showed a slightly better clinical response in one of the studies (ORR 30%), but were associated with skin, eye, and auditory toxicities. Similarly, CAR-T cells targeting gp100 showed

an ORR of 16% in melanoma, but also with skin, eye, and auditory side effects [31]. CAR-T cells targeting NY-ESO-1 showed promising results in clinical trials, with a mean response rate of 47% (ORR ranging from 20 to 67%), 8 complete remissions, and 40 partial remissions, without severe toxicities [32].

3.1.7. Lung Cancer and Breast Cancer

In a phase I study (NCT02706392) evaluating CAR-T cells targeting the receptor tyrosine kinase ROR1 found in lung and breast cancers, 4 out of 5 patients experienced a mixed response with tumor mass reduction in some metastatic sites [33]. In non-small cell lung cancer (NSCLC), CAR-T cells targeting EGFR were studied (NCT01869166), showing partial response in 2 patients and disease stabilization in 5 patients without severe toxicity [34]. EGFR-CAR-T therapy with the piggyBac transposon system in NSCLC (NCT03182816) showed a durable response in 1 patient (over 13 months) and disease stabilization in 6 patients [20]. CEA is also a target in lung and breast cancer. A phase I study of P-MUC1C-ALLO1 (allogenic CAR-T therapy) in advanced or metastatic solid tumors (including breast cancer) showed partial response in a patient with HR+, Her2- breast cancer [35].

3.1.8. Ovarian Cancer

In ovarian cancer, CAR-T cells targeting various antigens, including MUC-1, mucin-16 (MUC-16) [36], and TAG72 [37], have been studied. Cytotoxicity of CAR-T cells targeting these antigens has been demonstrated both in vitro and in vivo. 5T4, an oncofetal TAA, is also considered as a target, with preclinical studies showing its potential [38]. Clinical studies have evaluated CAR-T cells targeting mesothelin (MSLN) in ovarian cancer. One phase I/II study showed partial remission in a patient with recurrent epithelial ovarian cancer treated with MSLN-targeted CAR-T cells and PD-1 blockade combined with an angiogenesis inhibitor [39].

3.1.9. Pleural Mesothelioma

CAR-T cells targeting mesothelin were administered to patients with pleural mesothelioma in a phase I study, showing good expansion but limited durability. Preliminary results from a study with CAR-T cells targeting mesothelin in combination with anti-PD-1 antibody in patients with pleural mesothelioma showed a 72% response rate [40].

3.1.10. Thyroid Cancer

CAR-T cells targeting ICAM-1 are being studied in advanced thyroid cancer [41]. However, challenges exist related to potential targeting of activated T lymphocytes and neutralization by soluble ICAM-1 [42]. Medullary thyroid cancer (MTC) may be a good target due to the expression of CEA and GFRA4, and CAR-T strategies targeting GFRA4 are in the preclinical phase [43].

3.2. Limitations of CAR-T Cell Therapy in Solid Tumors

3.2.1. Difficulties in Tumor Trafficking and Infiltration: This is one of the biggest challenges because, unlike hematologic tumors, T cells must overcome multiple barriers to reach their target site in solid tumors [44]. These barriers include:

1. Immunosuppressive tumor microenvironment (TME), which inhibits T cell activity [45].
2. Physical barriers in the tumor, such as the tumor stroma, which limits the diffusion and mobility of CAR-T cells. The stroma mainly consists of the extracellular matrix, with heparan sulfate proteoglycan (HSPG) being a major component that impedes CAR-T cell infiltration [46].
3. Abnormal tumor vasculature, including distorted high endothelial venules, which normally facilitate T cell entry [47].
4. Lack of an appropriate chemotactic gradient, where T cells may not reach the target if they do not express the correct chemokine receptor [48].

3.2.2. Antigen Heterogeneity and Antigen Loss (Tumor-Antigen Escape): Solid tumors often exhibit heterogeneous expression of tumor-associated antigens (TAAs), and tumor cells may lose expression of the targeted antigen over time, leading to escape from CAR-T therapy. Antigen escape is a significant limitation of CAR-T therapy, especially when targeting a single antigen. Tumor cells can evolve under the immune pressure exerted by CAR-T cells, leading to a reduction or complete loss of target antigen expression. This allows them to evade recognition and destruction by CAR-T cells, resulting in disease relapse. Antigen heterogeneity in solid tumors further complicates this issue, as not all cancer cells within the tumor may express the target antigen. [49].

3.2.3. "On-target, off-tumor" Toxicity: Target antigens for CAR-T cells are not always unique to tumor cells and may also be expressed on normal tissues, leading to attacks on healthy cells and organs. An example is the attack on healthy plasma cells in BCMA CAR-T therapy [50].

3.2.4. Immunosuppressive Tumor Microenvironment: The TME in solid tumors contains various immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs), which inhibit CAR-T cell activity. These cells secrete factors that inhibit T cell activity and promote tumor growth. TAMs can exhibit an M2 phenotype, which has a pro-inflammatory role. The TME contains soluble immunosuppressive factors such as transforming growth factor β (TGF-β), prostaglandin E2 (PGE2), reactive oxygen species (ROS), interleukin-6 (IL-6), interleukin-10 (IL-10), and vascular endothelial growth factor (VEGF). These factors can suppress the proliferation and effector functions of CAR-T cells and promote T cell exhaustion. For example, TGF-β can drive T cell differentiation into Tregs, while PGE2 and adenosine can inhibit T cell signaling and activation. Upregulation of immune checkpoint ligands, such as PD-L1 on tumor cells and other TME cells, can lead to CAR-T cell exhaustion and weaken the antitumor response by interacting with receptors like PD-1 on CAR-T cells. Additionally, factors like low oxygen levels (hypoxia) and high levels of reactive oxygen species (ROS) within the TME negatively impact CAR-T cell proliferation and survival [45].

3.2.5. Heterogeneity of CAR-T Cells: Like unmodified T lymphocytes, CAR-T cells exhibit significant heterogeneity, which can be linked to the CAR construct or intrinsic cell features. This heterogeneity impacts the effectiveness and safety of the treatment. CAR-T cells may become exhausted after repeated antigen stimulation [51].

3.2.6. Toxicities Associated with CAR-T Therapy: Despite promising results, CAR-T therapy is associated with the risk of severe toxicities, such as cytokine release syndrome (CRS) [52] and immune effector cell-associated neurotoxicity syndrome (ICANS) [53].

CRS is a common and potentially life-threatening inflammatory syndrome resulting from excessive activation of the immune system. Activation of CAR-T cells upon recognizing the target antigen leads to their proliferation and the release of large amounts of pro-inflammatory cytokines, such as interferon-γ (IFN-γ), IL-1, IL-6, and IL-10. These cytokines can activate other immune cells, including monocytes and macrophages, which further amplify the inflammatory response by producing IL-6 and IL-1. Mild CRS symptoms include fever, fatigue, muscle and joint pain, low blood pressure, nausea, headaches, and skin rashes. In more severe cases, it can lead to hypotension, cardiac dysfunction, shock, respiratory failure, kidney failure, multiple organ failure, and even death. CRS treatment strategies include the administration of cytokine-blocking drugs such as tocilizumab (IL-6 receptor blocker), siltuximab, and sarilumab, as well as corticosteroids. IL-1 receptor antagonists (anakinra) are also used for CRS prevention [52].

ICANS is a serious adverse effect that can occur within days or weeks after CAR-T cell infusion. The exact etiology of ICANS is not fully understood, but it is believed to result from excessive release of cytokines and other pro-inflammatory molecules by CAR-T cells in the central nervous system. This leads to an immune response in the brain and potentially disrupts the blood-brain barrier. ICANS symptoms can vary and include disorientation, agitation, delirium, and, in severe cases, seizures, brain edema, and encephalopathy. ICANS management involves neurological monitoring, supportive care, and the administration of anticonvulsants and anti-inflammatory drugs (corticosteroids). IL-6 inhibitors are often ineffective in treating CAR-T-related neurotoxicity [53].

3.2.7. High Cost, Duration, and Complexity of Implementation: The implementation of CAR-T therapy presents logistical and financial challenges [54].

3.2.8. Limited Effectiveness Compared to Hematologic Tumors: Meta-analyses have shown a lower response rate to CAR-T therapy in solid tumors compared to hematologic cancers [55].

3.2.9. Risk of Inducing Resistance: The mechanisms of resistance in solid tumors to CAR-T therapy are not fully understood. It is important to note that researchers are actively working on various strategies to overcome these limitations and improve the effectiveness and safety of CAR-T therapy for solid tumors [56].

3.3. Perspectives for CAR-T Therapy in Solid Tumors

3.3.1. Improving Targeting of Tumor Antigens

1. Targeting Multiple Antigens: Utilizing combined CAR-T strategies, involving the simultaneous use of two or more CAR-T cells, each targeting a single antigen, may reduce the risk of tumor resistance associated with antigen loss. An example is the combination of CAR-T targeting EGFR and CD133 in the treatment of cholangiocarcinoma [57].
2. Bispecific CAR-T (biCAR-T): BiCAR-T cells are designed to simultaneously recognize two different antigens on the surface of cancer cells. This strategy aims to overcome antigenic heterogeneity in tumors and prevent antigen escape, a common resistance mechanism in CAR-T therapy targeting a single antigen.

   There are several approaches to constructing biCAR-T cells:

   • Co-expression of two separate CAR receptors within a single T cell, each recognizing a different antigen. This strategy follows the "OR logic," where binding to either antigen induces T cell activation.

   • Tandem bispecific CAR constructs (TanCAR), in which two single-chain variable fragments (scFvs) targeting different antigens are linked within a single receptor chain. Studies have shown that this strategy is functionally superior to co-expressing two separate CARs. Examples include CAR-T cells targeting CD19/CD20 and CD19/CD22 for treating B-cell malignancies.

   • Bispecific CAR-T cells with split signaling pathways, where the activation and co-stimulatory signals are divided between two separate CARs, each recognizing a different antigen. T cell activation occurs optimally only when both antigens are recognized simultaneously, implementing "AND logic" to potentially enhance therapy specificity and safety [58].

   Advantages of Bispecific CAR-T Cells:

   • Enhanced Antitumor Efficacy: By targeting cancer cells expressing either of the selected antigens, bispecific CAR-T therapy is particularly beneficial in addressing antigenic heterogeneity in both solid and hematologic tumors.

   • Reduced Risk of Antigen Escape: Since tumor cells would need to lose the expression of both target antigens to evade recognition and destruction, bispecific CAR-T cells help mitigate one of the major resistance mechanisms in CAR-T therapy.

   • Potentially Greater Specificity: Certain designs, such as those using "AND logic," may improve specificity and reduce on-target off-tumor toxicity, thereby enhancing the safety profile of the therapy [58].

   Examples of Bispecific CAR-T Cells Reported in Studies:

   • CD19/CD20 and CD19/CD22 TanCAR in the treatment of B-cell malignancies, currently in clinical trials for lymphomas and acute lymphoblastic leukemia (ALL).

   • Bispecific CAR-T targeting IL13Rα2 and HER2 demonstrated significant potential in eliminating solid tumor cells and reducing antigen escape in a glioblastoma model.

• biCAR-T targeting ErbB2 and MUC1 showed effective antitumor activity in vitro against breast cancer.

• Preclinical studies tested tandem CARs targeting HER2/IL13Rα2 in glioblastoma and HER2/MUC1 in breast cancer, showing improved antitumor responses compared to single-antigen therapies [58].

3. Switch-controlled CAR-T: Developing systems that allow the precise activation and deactivation of CAR-T cells to control toxicity. An example is the use of small molecule "switches" or suicide genes, like iCasp9, which induces apoptosis in CAR-T cells after administration of a specific drug [59].
4. Targeting Glycosylated Antigens: Employing CAR-T cells that target glycosylated antigens present on cancer cells as a means of bypassing immune evasion [60].
5. Selection of More Specific Tumor-Specific Antigens (TSA): Identifying and targeting tumor-specific antigens (TSA), which are ideal targets but rarely present in solid tumors. Most antigens in solid tumor therapies are tumor-associated antigens (TAA) that are also found in normal tissues [61].

3.3.2. Improving Migration and Infiltration of CAR-T Cells into Tumors

1. Chemokine Receptor Expression: Engineering CAR-T cells to express appropriate chemokine receptors (CCR) that bind to chemokines secreted by tumor cells, promoting their infiltration into the tumor microenvironment. For example, T cells with the CXCR2 receptor showed more efficient targeting of melanoma [62].
2. Local Administration of CAR-T: Direct injection of CAR-T cells into the tumor (intra-tumoral) or body cavities (e.g., peritoneal, pleural, or intraventricular) increases their local concentration and reduces systemic toxicity. Delivery systems such as transdermal porous microneedles are also being developed [63].
3. Targeting Tumor Vasculature: Designing CAR-T cells to target antigens associated with tumor blood vessels, such as VEGFR-2 [64], VEGFR-1 [65], or integrins αvβ3 and αvβ6, to improve infiltration and reduce tumor growth [66].
4. Overcoming Physical Barriers: Engineering CAR-T cells to secrete enzymes that degrade the extracellular matrix (ECM), such as heparanase (HPSE), or targeting fibroblast-activating proteins (FAP) to remove stromal cells [67].
5. Armored CAR-T: Equipping CAR-T cells with additional functions, such as chemokine secretion (e.g., CXCL11), to recruit other immune cells [68].

3.3.3. Modulating the Immunosuppressive Tumor Microenvironment (TME)

1. Checkpoint Inhibition: Combining CAR-T therapy with immune checkpoint inhibitors (e.g., anti-PD-1, anti-CTLA-4) to overcome immune suppression within the TME. It is also possible to engineer CAR-T cells to secrete checkpoint inhibitors [69].
2. Engineering CAR-T Cells Resistant to the TME: Modifying CAR-T cells to be less susceptible to immunosuppressive factors in the TME, such as TGF-β (through the expression of dominant-negative TGF-β receptors) or ROS (through the expression of catalase) [70].

3. Reprogramming the TME: Engineering CAR-T cells to secrete cytokines (e.g., IL-12, IL-18) or other factors that can convert the immunosuppressive TME into a more immunogenic one, such as altering macrophage polarization from M2 to M1 and reducing the number of MDSCs and Tregs [71].

3.3.4. Reducing Toxicity

1. Designing CARs with Optimized Affinity: Adjusting the binding strength of the antigen-recognition domain in CAR to achieve therapeutic efficacy with minimal toxicity [72].
2. Incorporating Co-stimulatory Domains Influencing Toxicity: Selecting appropriate co-stimulatory domains (e.g., CD28 vs. 4-1BB) can affect the cytokine profile and the risk of cytokine release syndrome (CRS) [73].
3. Utilizing Suicide Genes and "Switches": As previously mentioned, systems such as iCasp9 or tyrosine kinase inhibitors (e.g., dasatinib) allow for controlled deactivation of CAR-T activity in case of toxicity [59].
4. Blocking Pro-inflammatory Cytokines: Using drugs to block cytokines involved in CRS (e.g., tocilizumab blocking IL-6) [74]. CAR-T cells that secrete antagonists of cytokine receptors (e.g., IL-1R antagonist) are also being developed. Neutralizing GM-CSF may be another approach to managing CRS and neurotoxicity [75].

3.3.5. Utilizing Other Effector Cells

1. CAR-Macrophages (CAR-M): CAR-M cells are genetically modified macrophages engineered to express a chimeric antigen receptor (CAR) on their surface. The CAR recognizes tumor-associated antigens (TAA) in an MHC-independent manner. Upon binding to TAA, CAR-M cells become activated, leading to the phagocytosis of cancer cells, the release of pro-inflammatory cytokines (such as IL-8, IL-6, and TNF-α), and the activation of T cell-dependent antitumor immunity. M1 macrophages, which are promoted by CAR-M modifications, contribute to tumor cell killing through phagocytosis and the release of reactive oxygen and nitrogen species (ROS/iNOS). They can also present tumor antigens, inducing an adaptive immune response.CAR-M cells have unique properties such as phagocytosis, migration, and infiltration of the tumor microenvironment (TME), along with a low risk of graft-versus-host disease (GvHD), making them an attractive allogeneic option. Clinical trials are ongoing with CAR-M cells targeting various antigens in solid tumors [76, 77].
2. CAR-Natural Killer (NK) Cells: CAR-NK cells are genetically modified natural killer (NK) cells engineered to express a chimeric antigen receptor (CAR). Similar to CAR-T cells, the CAR on NK cells recognizes tumor-associated antigens (TAA) in an MHC-independent manner. CAR-NK activation leads to the release of cytotoxic proteins such as perforins and granzymes, which induce apoptosis and necrosis of cancer cells. NK cells also possess natural cytotoxic mechanisms, including target cell recognition through activating and inhibitory receptors (KIR) and antibody-dependent cellular cytotoxicity (ADCC) via the CD16 receptor. Additionally, activated CAR-NK cells secrete cytokines such as IFN-γ and TNF-α, which enhance their own activation and stimulate other immune cells. NK cells modified with CAR are a promising alternative to CAR-T due to their lower risk of CRS and

neurotoxicity, potential for "off-the-shelf" products, and their ability to act both in a CAR-dependent and CAR-independent manner [78].

3.3.6. Utilizing Artificial Intelligence (AI) and Biomarkers

1. Identification of Predictive Biomarkers: Using AI to analyze data (e.g., tumor mutations, signaling pathways, gene expression, radiological imaging) to identify biomarkers that predict response to CAR-T therapy, disease progression, and survival [79].
2. Radiomics: The analysis of medical imaging patterns using AI to predict therapy outcomes:
   • Identification of Predictive Biomarkers: AI-based prognostic tools can utilize radiomic data (from CT, PET, and MRI scans) to identify biomarkers or signatures that predict the outcomes of CAR-T therapy. AI algorithms are capable of analyzing subtle and complex image patterns that are imperceptible to the naked eye, distinguishing patients who will respond to therapy from those who will not.
   • Improvement of Therapeutic Interventions: Accurate prediction of aggressive imaging features through non-invasive methods can be used to refine CAR-T cell-based therapeutic interventions, allowing for better treatment planning.
   • Building Predictive Models: Advanced AI models that predict CAR-T therapy response, disease progression, and survival can be built using radiomic data along with other multi-omics and clinical data.
   • Identification of Imaging Signatures: There is a need to generate radiomic data and other tumor imaging data to predict imaging signatures associated with response to CAR-T therapy using various machine learning techniques.
   • Prediction of New Antigens and Molecules: Radiomics could potentially be used to predict new cancer-associated antigens and novel molecules in immune cells, providing insights for the development of future therapies. [80].

3.3.7. Combination Therapy

Combining CAR-T therapy with other treatment modalities such as chemotherapy (at low doses with immunomodulatory effects), radiotherapy (local tumor ablation releasing antigens), and other immunotherapies (e.g., checkpoint inhibitors, cancer vaccines) to synergistically enhance efficacy [81].

4. Discussion

CAR-T therapy has already shown promising results in some solid tumors, including cancers that poorly respond to current immunotherapies, such as sarcomas. However, compared to the significant progress made in the treatment of hematologic cancers, the application of CAR-T therapy in solid tumors faces considerable challenges.

The main limitations include: the lack of specific tumor antigens, low efficiency in targeting and migration of CAR-T cells to tumor sites, the immunosuppressive tumor microenvironment (TME), and the toxicity associated with CAR-T cells themselves, such as "on-target, off-tumor" toxicity, cytokine release syndrome (CRS), and

neurotoxicity. Furthermore, tumor cells can develop escape mechanisms by downregulating antigen expression. The process of manufacturing CAR-T cells is complex, time-consuming, and costly.

Despite these challenges, there has been an intense clinical development of CAR-T therapy against solid tumors, with numerous strategies aimed at improving its efficacy and safety. Prospects include: better selection of tumor-specific antigens (TSA) and optimization of T cell engineering to reduce toxicity and enhance anti-tumor effectiveness. Combining CAR-T therapy with other methods, such as oncolytic viruses and radiotherapy (improving T cell targeting), as well as immune checkpoint inhibitors, cytokines, and cancer vaccines (enhancing T cell activity and survival), is also under consideration.

Alternative strategies are also being explored, such as CAR-NK cells and CAR-macrophages, which show certain advantages over CAR-T therapy, particularly regarding toxicity and the potential for "off-the-shelf" product production. Additionally, combining different therapies based on modified cells, such as CAR-M with CAR-NK or CAR-T, may enhance anti-tumor effects by engaging both the innate and adaptive immune systems and targeting different antigens simultaneously.

The future also lies in the use of artificial intelligence (AI) to overcome many obstacles associated with CAR-T therapy, including predicting new antigens, analyzing safety and efficacy, and automating the production process. The development of fourth- and fifth-generation CAR receptors and the use of CRISPR/Cas9 gene-editing technology are also promising directions for development. There is also the potential for the development of more cost-effective methods, such as universal CAR-T cells derived from healthy donors.

5. Conclusions

In summary, CAR-T cell therapy is revolutionizing cancer treatment, demonstrating remarkable efficacy in hematologic malignancies. However, its application in treating solid tumors faces significant challenges that limit its effectiveness. Key obstacles include limited penetration and migration of CAR-T cells into the tumor, the immunosuppressive tumor microenvironment, lack of specific tumor antigens, antigen escape, and therapy-related toxicities. Future research directions focus on developing innovative CAR-T cell engineering strategies to enhance their antitumor activity and reduce toxicity, identifying reliable tumor-associated antigens, overcoming tumor microenvironment barriers, and exploring alternative CAR-based therapies, such as CAR-NK and CAR-macrophages. The use of combination therapy and artificial intelligence may contribute to optimizing the clinical applications of CAR-T therapy in solid tumors.

Disclosure

Author's Contribution:

Conceptualization: DK, VK

Methodology: NS, KM

Formal analysis: DL, KT, MS

Investigation: VM, AM, KT

Writing-rough preparation: IK, DL, MS

Writing-review and editing: DK, VK

Supervision: DK, VK

All authors have read and agreed with the published version of the manuscript.

Funding Statement: The authors did not receive special funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: The authors declare no conflict of interest.

References

1. Pan C, Liu H, Robins E, Song W,Liu D, Li Z, Zheng L. Next-generation immuno-oncology agents: current momentum shifts in cancer immunotherapy. J Hematol Oncol. 2020;13(1):29.
2. Pasquini MC, Hu ZH, Curran K, Laetsch T, Locke F, Rouce R, Pulsipher MA, Phillips CL, Keating A, Frigault MJ, Salzberg D, Jaglowski S, Sasine JP, Rosenthal J, Ghosh M, Landsburg D, Margossian S, Martin PL, Kamdar MK, Hematti P, Nikiforow S, Turtle C, Perales MA, Steinert P, Horowitz MM, Moskop A, Pacaud L, Yi L, Chawla R, Bleickardt E, Grupp S. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Adv. 2020;4:5414–24.
3. Pan J, Zuo S, Deng B, Xu X, Li C, Zheng Q, Ling Z, Song W, Xu J, Duan J, Wang Z, Yu X, Chang A H, Feng X, Tong C. Sequential CD19–22 CAR T therapy induces sustained remission in children with r/r B-ALL. Blood. 2020;135:387–91.
4. Que Y, Xu M, Xu Y, Almeida VDF, Zhu L, Wang Z, Wang Y, Liu X, Jiang L, Di Wang Di, Li C, Zhou J. Anti-BCMA CAR-T Cell Therapy in Relapsed/Refractory Multiple Myeloma Patients With Extramedullary Disease: A Single Center Analysis of Two Clinical Trials. Front Immunol. 2021;12:755866.
5. Liu Z, Zhou Z, Dang Q, Xu H, Lv J, Li H, Han X. Immunosuppression in tumor immune microenvironment and its optimization from CAR-T cell therapy. Theranostics. 2022;12:6273–90.
6. Liu G, Rui W, Zhao X, Lin X. Enhancing CAR-T cell efficacy in solid tumors by targeting the tumor microenvironment. Cell Mol Immunol. 2021;18:1085–95.
7. Zhang Q, Zhang Z, Peng M, Fu S, Xue Z, Zhang R. CAR-T cell therapy in gastrointestinal tumors and hepatic carcinoma: From bench to bedside. Oncoimmunology. 2016;5:e1251539.
8. Lazaro-Gorines R, Ruiz-de-la-Herran J, Navarro R, Sanz L, Alvarez-Vallina L, Martinez-Del-Pozo A, J G Gavilanes, J Lacadena. A novel Carcinoembryonic Antigen (CEA)-Targeted Trimeric Immunotoxin shows significantly enhanced Antitumor Activity in Human Colorectal Cancer Xenografts. Sci Rep. 2019;9:11680.
9. Zhang C, Wang Z, Yang Z, Wang M, Li S, Li Y, Zhang R, Xiong Z, Wei Z, Shen J, Luo Y, Zhang Q, Liu L, Qin H, Liu W, Wu F, Chen W, Pan F, Zhang X, Bie P, Liang H, Pecher G, Qian C. Phase I Escalating-Dose Trial of CAR-T Therapy Targeting CEA(+) Metastatic Colorectal Cancers. Mol Ther. 2017;25:1248–58.

10. Dai H, Tong C, Shi D, Chen M, Guo Y, Chen D, Han X, Wang H, Wang Y, Shen P . Efficacy and biomarker analysis of CD133-directed CAR T cells in advanced hepatocellular carcinoma: a single-arm, open-label, phase II trial. Oncoimmunology. 2020;9:1846926.
11. Ahmed N, Brawley VS, Hegde M, Robertson C, Ghazi A, Gerken C, Liu E, Dakhova O, Ashoori A, Corder A, Gray T, Wu M, Liu H, Hicks J, Rainusso N, Dotti G, Mei Z, Grilley B, Gee A, Rooney C, Brenner M K, Heslop H E, Wels W S, Wang L L, Anderson P, Gottschalk S. Human Epidermal Growth Factor Receptor 2 (HER2) –Specific Chimeric Antigen Receptor–Modified T Cells for the Immunotherapy of HER2-Positive Sarcoma. J Clin Oncol. 2015;33:1688–96.
12. P. F. Robbins, R. A. Morgan, S. A. Feldman, J. C. Yang, R. M. Sherry, M. E. Dudley, J. R. Wunderlich, A. V. Nahvi, L. J. Helman, C. L. Mackall, U. S. Kammula, M. S. Hughes, N. P. Restifo, M. Raffeld, C.-C. R. Lee, C. L. Levy, Y. F. Li, M. El-Gamil, S. L. Schwarz, C. Laurencot, S. A. Rosenberg, Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. J. Clin. Oncol. 29, 917–924 (2011).
13. S. P. D'Angelo, B. A. Van Tine, S. Attia, J.-Y. Blay, S. J. Strauss, C. M. Valverde Morales, A. R. Abdul Razak, E. Van Winkle, T. Trivedi, S. Biswas, D. Williams, E. Norry, D. M. Araujo, SPEARHEAD-1: A phase 2 trial of afamitresgene autoleucel (formerly ADP-A2M4) in patients with advanced synovial sarcoma or myxoid/round cell liposarcoma. J. Clin. Oncol. 39, 11504 (2021).
14. Ahmed N, Brawley V, Hegde M, Bielamowicz K, Kalra M, Landi D, Robertson C, Gray T L, Diouf O, Wakefield A, Ghazi A, Gerken C, Yi Z, Ashoori A, Wu M, Liu H, Rooney C, Dotti G, Gee A, Su J, Kew Y, Baskin D, Zhang Y J, New P, Grilley B, Stojakovic M, Hicks J, Powell S Z, Brenner M K, Heslop H E, Robert Grossman R, Wels W S, Gottschalk S. HER2-Specific Chimeric Antigen Receptor–Modified Virus-Specific T Cells for Progressive Glioblastoma: A Phase 1 Dose-Escalation Trial. JAMA Oncol. 2017;3:1094.
15. Vitanza NA, Johnson AJ, Wilson AL, Brown C, Yokoyama JK, Kunkele A, Chang C A, Rawlings-Rhea S, Huang W, Seidel K, Albert C M, Pinto N, Gust J, Finn L S, Ojemann J G, Wright J, Orentas R J, Baldwin M, Gardner R A, Michael C Jensen M C, Park J R. Locoregional infusion of HER2-specific CAR T cells in children and young adults with recurrent or refractory CNS tumors: an interim analysis. Nat Med. 2021;27:1544–52.
16. Brown CE, Alizadeh D, Starr R, Weng L, Wagner JR, Naranjo A, Ostberg J R, Blanchard M S, Kilpatrick J, Simpson J, Kurien A, Priceman S J, Wang X, Harshbarger T L, D'Apuzzo M, Ressler J A, Jensen M C, Barish M E, Chen M, Portnow J, Forman S J, Badie B. Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy. New England J Med. 2016;375:2561–9.
17. Brown CE, Badie B, Barish ME, Weng L, Ostberg JR, Chang WC, Naranjo A, Starr R, Wagner J, Wright C, Zhai Y, Bading J R, Ressler J A, Portnow J, D'Apuzzo M, Stephen J Forman S J, Jensen M C. Bioactivity and Safety of IL13Ralpha2-Redirected Chimeric Antigen Receptor CD8+ T Cells in Patients with Recurrent Glioblastoma. Clin Cancer Res. 2015;21:4062–72.
18. Louis CU, Savoldo B, Dotti G, Pule M, Yvon E, Myers GD, Rossig C, Russell H V, Diouf O, Liu E, Liu H, Wu M-F, Gee A P, Mei Z, Rooney C M, Heslop H E, Brenner M K. Antitumor activity and long-term fate of chimeric antigen receptor–positive T cells in patients with neuroblastoma. Blood. 2011;118:6050–6.

19. O'Rourke DM, Nasrallah MP, Desai A, Melenhorst JJ, Mansfield K, Morrissette JJD, Martinez-Lage M, Brem S, Maloney E, Shen A, Isaacs R, Mohan S, Plesa G, Lacey S F, Navenot J-M, Zheng Z, Levine B L, Okada H, June C H, Brogdon J L, Maus M V. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. Sci Transl Med. 2017;9:eaaa0984.
20. Zhang Y, Zhang Z, Ding Y, Fang Y, Wang P, Chu W, Jin Z, Yang X, Wang J, Lou J, Qian Q. Phase I clinical trial of EGFR-specific CAR-T cells generated by the piggyBac transposon system in advanced relapsed/refractory non-small cell lung cancer patients. J Cancer Res Clin Oncol. 2021;147:3725–34.
21. Feng K, Liu Y, Guo Y, Qiu J, Wu Z, Dai H, Yang Q, Wang Y, Han W. Phase I study of chimeric antigen receptor modified T cells in treating HER2-positive advanced biliary tract cancers and pancreatic cancers. Protein Cell. 2018;9:838–47.
22. Wang Y, Chen M, Wu Z, Tong C, Dai H, Guo Y, Liu Y, Huang J, Lv H, Luo C, Feng K-C, Yang Q-M, Li X-L, Han W . CD133-directed car T cells for advanced metastasis malignancies: a phase i trial. Oncoimmunology (2018) 7:e1440169. doi: 10.1080/2162402X.2018.1440169
23. Qu CF, Li Y, Song YJ, Rizvi SMA, Raja C, Zhang D, J Samra, R Smith, A C Perkins, C Apostolidis, B J Allen. MUC1 expression in primary and metastatic pancreatic cancer cells for in vitro treatment by (213)bi-c595 radioimmunoconjugate. Br J Cancer (2004) 91:2086–93. doi: 10.1038/sj.bjc.6602232
24. Argani P, Rosty C, Reiter RE, Wilentz RE, Murugesan SR, Leach SD, B Ryu, H G Skinner, M Goggins, E M Jaffee, C J Yeo, J L Cameron, S E Kern, R H Hruban. Discovery of new markers of cancer through serial analysis of gene expression: prostate stem cell antigen is overexpressed in pancreatic adenocarcinoma. Cancer Res (2001) 61:4320–4.
25. Argani P, Iacobuzio-Donahue C, Ryu B, Rosty C, Goggins M, Wilentz RE, S R Murugesan, S D Leach, E Jaffee, C J Yeo, J L Cameron, S E Kern, R H Hruban. Mesothelin is overexpressed in the vast majority of ductal adenocarcinomas of the pancreas: identification of a new pancreatic cancer marker by serial analysis of gene expression (SAGE). Clin Cancer Res (2001) 7:3862–8.
26. Tran E, Chinnasamy D, Yu Z, Morgan RA, Lee C-CR, Restifo NP, Rosenberg S A. Immune targeting of fibroblast activation protein triggers recognition of multipotent bone marrow stromal cells and cachexia. J Exp Med (2013) 210:1125–35. doi: 10.1084/jem.20130110
27. Whilding LM, Halim L, Draper B, Parente-Pereira AC, Zabinski T, Davies DM, Maher J. Car T-cells targeting the integrin αvβ6 and co-expressing the chemokine receptor cxcr2 demonstrate enhanced homing and efficacy against several solid malignancies. Cancers (Basel) (2019) 11:E674. doi: 10.3390/cancers11050674
28. Stroncek DF, Lee DW, Ren J, Sabatino M, Highfill S, Khuu H, Shah N N , Kaplan R N, Fry T J, Mackal C L. Elutriated lymphocytes for manufacturing chimeric antigen receptor T cells J. Transl. Med. 2017; 15:59
29. Gargett T, Yu W, Dotti G, Yvon ES, Christo SN, Hayball JD, Lewis I D, Brenner M K, Brown M P. 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. Mol Ther. 2016;24:1135–49.
30. T. Chodon, B. Comin-Anduix, B. Chmielowski, R. C. Koya, Z. Wu, M. Auerbach, C. Ng, E. Avramis, E. Seja, A. Villanueva, T. A. McCannel, A. Ishiyama, J. Czernin, C. G. Radu, X. Wang, D. W. Gjertson,

A. J. Cochran, K. Cornetta, D. J. L. Wong, P. Kaplan-Lefko, O. Hamid, W. Samlowski, P. A. Cohen, G. A. Daniels, B. Mukherji, L. Yang, J. A. Zack, D. B. Kohn, J. R. Heath, J. A. Glaspy, O. N. Witte, D. Baltimore, J. S. Economou, A. Ribas, Adoptive transfer of MART-1 T-cell receptor transgenic lymphocytes and dendritic cell vaccination in patients with metastatic melanoma. Clin. Cancer Res. 20, 2457–2465 (2014).

31. M. W. Rohaan, R. Gomez-Eerland, J. H. van den Berg, M. H. Geukes Foppen, M. van Zon, B. Raud, I. Jedema, S. Scheij, R. de Boer, N. A. M. Bakker, D. van den Broek, L. M. Pronk, L. G. Grijpink-Ongering, A. Sari, R. Kessels, M. van den Haak, H. A. Mallo, M. Karger, B. A. van de Wiel, C. L. Zuur, C. W. Duinkerken, F. Lalezari, J. V. van Thienen, S. Wilgenhof, C. U. Blank, J. H. Beijnen, B. Nuijen, T. N. Schumacher, J. B. A. G. Haanen, MART-1 TCR gene-modified peripheral blood T cells for the treatment of metastatic melanoma: A phase I/IIa clinical trial. Immuno-Oncol. Technol. 15, 100089 (2022).
32. T. S. Nowicki, B. Berent-Maoz, G. Cheung-Lau, R. R. Huang, X. Wang, J. Tsoi, P. Kaplan-Lefko, P. Cabrera, J. Tran, J. Pang, M. Macabali, I. P. Garcilazo, I. B. Carretero, A. Kalbasi, A. J. Cochran, C. S. Grasso, S. Hu-Lieskovan, B. Chmielowski, B. Comin-Anduix, A. Singh, A. Ribas, A pilot trial of the combination of transgenic NY-ESO-1-reactive adoptive cellular therapy with dendritic cell vaccination with or without Ipilimumab. Clin. Cancer Res. 25, 2096–2108 (2019).
33. Specht JM, Lee S, Turtle C, Berger C, Veatch J, Gooley T. Phase I study of immunotherapy for advanced ROR1+ malignancies with autologous ROR1-specific chimeric antigen receptor-modified (CAR)-T cells. Journal of Clinical Oncology. 2018;36:TPS79.
34. Feng K, Guo Y, Dai H, Wang Y, Li X, Jia H, Han W. Chimeric antigen receptor-modified T cells for the immunotherapy of patients with EGFR-expressing advanced relapsed/refractory non-small cell lung cancer. Sci China Life Sci. 2016;59:468–79.
35. Oh DY, Henry JT, Baranda J, Dumbrava EE, Cohen E, Eskew JD, Belani R, McCaigue J, Namini H, Martin C, Murphy A, Ostertag E, Coronella J, Shedlock D, Rodriguez Rivera I I. Poseida therapeutics: development of an allogeneic CAR-T targeting MUC1-C (MUC1, cell surface associated, C-terminal) for epithelial derived tumors - Form 8-K. 2022.
36. Liu J, Li L, Luo N, Liu Q, Liu L, Chen D, Cheng Z, Xi X . Inflammatory signals induce MUC16 expression in ovarian cancer cells via NF-κB activation. Exp Ther Med. 2021;21(2):163.
37. Ponnusamy MP, Venkatraman G, Singh A P, Chauhan S C, Johansson S L, Jain M, Smith L, Davis J S, Remmenga S W, Batra S K. Expression of TAG-72 in ovarian cancer and its correlation with tumor stage and patient prognosis. Cancer Lett. 2007;251(2):247–57.
38. E Wrigley, A T McGown, J Rennison, R Swindell, D Crowther, T Starzynska, P L Stern. 5T4 oncofetal antigen expression in ovarian carcinoma. Int J Gynecol Cancer. 1995;5(4):269–74.
39. Fang J, Ding N, Guo X, Sun Y, Zhang Z, Xie B, Li Z, Wang H, Mao W, Lin Z, Qin F, Yuan M, Chu W, Qin H, Qian Q, Xu Q. alphaPD-1-mesoCAR-T cells partially inhibit the growth of advanced/refractory ovarian cancer in a patient along with daily apatinib. J Immunother Cancer. 2021;9:e001162.
40. Haas AR, Tanyi JL, O'Hara MH, Gladney WL, Lacey SF, Torigian DA, Soulen M C, Tian L, McGarvey M, Nelson A M, Farabaugh C S, Moon E, Levine B L, Melenhorst J J, Plesa G, June C H, Albelda S M,

Beatty G L. Phase I Study of Lentiviral-Transduced Chimeric Antigen Receptor-Modified T Cells Recognizing Mesothelin in Advanced Solid Cancers. Mol Ther. 2019;27:1919–29.

41. Min IM, Shevlin E, Vedvyas Y, Zaman M, Wyrwas B, Scognamiglio T, Moore M D, Wang W, Park S, Park S, Panjwani S, Gray K D, Tassler A B, Zarnegar R, Fahey 3rd T J, Jin M M. CAR T therapy targeting icam-1 eliminates advanced human thyroid tumors. Clin Cancer Res (2017) 23:7569–83. doi: 10.1158/1078-0432.CCR-17-2008
42. Pasieka Z, Kuzdak K, Czyz W, Stepień H, Komorowski J. Soluble intracellular adhesion molecules (sicam-1, svcam-1) in peripheral blood of patients with thyroid cancer. Neoplasma (2004) 51:34–7.
43. Bhoj VG, Li L, Parvathaneni K, Zhang Z, Kacir S, Arhontoulis D, Zhou K, McGettigan-Croce B, Nunez-Cruz S, Gulendran G, Boesteanu A C, Johnson L, Feldman M D, Radaelli E, Mansfield K, Nasrallah M, Goydel R S, Peng H, Rader C, Michael C Milone M C, Siegel D L. Adoptive T cell immunotherapy for medullary thyroid carcinoma targeting gdnf family receptor alpha 4. Mol Ther Oncol (2021) 20:387–98. doi: 10.1016/j.omto.2021.01.012
44. Bhat AA, Nisar S, Maacha S, Carneiro-Lobo T C, Akhtar S, Siveen K S, Wani N A, Rizwan A, Bagga P, Singh M, Reddy R, Uddin S, Grivel J-C, Chand G, Frenneaux M P, Siddiqi M A, Bedognetti D, El-Rifai W, Muzafar A Macha M A, Haris M . Cytokine-chemokine network driven metastasis in esophageal cancer; promising avenue for targeted therapy. Mol Cancer. 2021;20(1):2.
45. Safarzadeh Kozani P, Safarzadeh Kozani P, Rahbarizadeh F. Addressing the obstacles of CAR T cell migration in solid tumors: wishing a heavy traffic. Crit Rev Biotechnol. 2022;42:1079–98.
46. Zhang BL, Qin D-Y, Mo Z-M, Li Y, Wei W, Wang Y-S, Wang W, Wei Y-Q . Hurdles of CAR-T cell-based cancer immunotherapy directed against solid tumors. Sci China Life Sci. 2016;59(4):340–8.
47. Ager A. High endothelial venules and other blood vessels: critical regulators of lymphoid organ development and function. Front Immunol. 2017;8:45.
48. Kershaw MH, Wang G, Westwood JA, Pachynski RK, Tiffany HL, Marincola FM, Wang E, Young H A, Murphy P M, Hwu P. Redirecting migration of T cells to chemokine secreted from tumors by genetic modification with CXCR2. Hum Gene Ther. 2002;13:1971–80.
49. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer J. 2021;11(4):69.
50. Sun S, Hao H, Yang G, Zhang Y, Fu Y. Immunotherapy with CAR-modified T cells: toxicities and overcoming strategies. J Immunol Res. 2018;2018:2386187.
51. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.
52. Norelli M, Camisa B, Barbiera G, Falcone L, Purevdorj A, Genua M, Sanvito F, Ponzoni M, Doglioni C, Cristofori P, Traversari C, Bordignon C, Ciceri F, Ostuni R, Bonini C, Casucci M, Bondanza A . Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. Nat Med. 2018;24(6):739–48.
53. Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, Halton E, Wang X, Senechal B, Purdon T, Cross JR, Liu H, Vachha B, Chen X, DeAngelis LM, Li D, Bernal Y, Gonen M, Wendel HG, Sadelain M, Brentjens RJ. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov. 2018;8(8):958–71.

54. Naghizadeh A, Tsao W-C, Cho J H, Xu H, Mohamed M, Li D, Xiong W, Metaxas D, Ramos C A, Liu D . In vitro machine learning-based CAR T immunological synapse quality measurements correlate with patient clinical outcomes. PLoS Comput Biol. 2022;18(3):e1009883.
55. Hou B, Tang Y, Li W, Zeng Q, Chang D. Efficiency of CAR-T Therapy for Treatment of Solid Tumor in Clinical Trials: A Meta-Analysis. Disease Markers. 2019;2019:1–11.
56. Majzner RG, Mackall CL. Tumor antigen escape from CAR T-cell therapy. Cancer Discov. 2018;8(10):1219–26.
57. Feng K-c, Guo Y-l, Liu Y, Dai HR, Wang Y, Lv HY, Huang J-H, Yang Q-M, Han W-D. Cocktail treatment with EGFR-specific and CD133-specific chimeric antigen receptor-modified T cells in a patient with advanced cholangiocarcinoma. J Hematol Oncol. 2017;10:4.
58. Hegde M, Corder A, Chow KKH, Mukherjee M, Ashoori A, Kew Y, Zhang Y J, Baskin D S, Merchant F A, Brawley V S, Byrd T T, Krebs S, Wu M F, Liu H, Heslop H E, Gottschalk S, Yvon E, Ahmed N. Combinational Targeting Offsets Antigen Escape and Enhances Effector Functions of Adoptively Transferred T Cells in Glioblastoma. Mol Ther. 2013;21:2087–101.
59. Di Stasi A, Tey SK, Dotti G, Fujita Y, Kennedy-Nasser A, Martinez C, Straathof K, Liu E, Durett AG, Grilley B, Liu H, Cruz CR, Savoldo B, Gee AP, Schindler J, Krance RA, Heslop HE, Spencer DM, Rooney CM, Brenner MK. Inducible apoptosis as a safety switch for adoptive cell therapy N. Engl. J. Med. 2011; 365:1673-1683
60. Meril S, Harush O, Reboh Y, Matikhina T, Barliya T, Cohen CJ. Targeting glycosylated antigens on cancer cells using siglec-7/9-based CAR T-cells. Mol Carcinog. 2020;59:713–23.
61. F Manfredi, B C Cianciotti, A Potenza, E Tassi, M Noviello, A Biondi, F Ciceri, C Bonini, E Ruggiero, TCR redirected T cells for cancer treatment: Achievements, hurdles, and goals. Front. Immunol. 11, 1689 (2020).
62. Tobin RP, Jordan KR, Kapoor P, Spongberg E, Davis D, Vorwald VM, Couts K L, Gao D, Smith D E, Borgers J S W, Robinson S, Amato C, Gonzalez R, Lewis K D, Robinson W A, Borges V F, McCarter M D. IL-6 and IL-8 Are Linked With Myeloid-Derived Suppressor Cell Accumulation and Correlate With Poor Clinical Outcomes in Melanoma Patients. Front Oncol. 2019;9:1223.
63. Thadi A, Khalili M, Morano W, Richard S, Katz S, Bowne W. Early Investigations and Recent Advances in Intraperitoneal Immunotherapy for Peritoneal Metastasis. Vaccines. 2018;6:54.
64. Chinnasamy D, Tran E, Yu Z, Morgan RA, Restifo NP, Rosenberg SA. Simultaneous targeting of tumor antigens and the tumor vasculature using T lymphocyte transfer synergize to induce regression of established tumors in mice. Cancer Res. 2013;73:3371–80.
65. Wang W, Ma Y, Li J, Shi HS, Wang LQ, Guo FC, Zhang J, Li D, Mo B-H, Wen F, Liu T, Liu Y-T, Wang Y-S, Wei Y-Q. Specificity redirection by CAR with human VEGFR-1 affinity endows T lymphocytes with tumor-killing ability and anti-angiogenic potency. Gene Ther. 2013;20:970–8.
66. Phanthaphol N, Somboonpatarakun C, Suwanchiwasiri K, Chieochansin T, Sujjitjoon J, Wongkham S, et al. Chimeric Antigen Receptor T Cells Targeting Integrin alphavbeta6 Expressed on Cholangiocarcinoma Cells. Front Oncol. 2021;11:657868.

67. Ignazio Caruana I, Savoldo B, Hoyos V, Weber G, Liu H, Kim E S, Ittmann M M, Marchetti D, Dotti G. Heparanase promotes tumor infiltration and antitumor activity of CAR-redirected T lymphocytes Nat. Med. 2015; 21:524-529
68. Chmielewski M, Hombach A A, Abken H. Of CARs and TRUCKs: chimeric antigen receptor (CAR) T cells engineered with an inducible cytokine to modulate the tumor stroma Immunol. Rev. 2014; 257:83-90
69. Rafiq S, Yeku O O, Jackson H J, Purdon T J, Leeuwen D G, Drakes D J, Song M, Miele M M, Li Z, Wang P, Yan S, Xiang J, Ma X, Seshan V E, Hendrickson R C, Liu C, Brentjens R J . Targeted delivery of a PD-1-blocking scFv by CAR-T cells enhances anti-tumor efficacy in vivo Nat. Biotechnol. 2018; 36:847-856
70. Chang Z L, Lorenzini M H, Chen X, Tran U, Bangayan N J, Chen Y Y Rewiring T-cell responses to soluble factors with chimeric antigen receptors Nat. Chem. Biol. 2018; 14:317-324
71. Adachi K, Kano Y, Nagai T, Okuyama N, Sakoda Y, Tamada K. IL-7 and CCL19 expression in CAR-T cells improves immune cell infiltration and CAR-T cell survival in the tumor Nat. Biotechnol. 2018; 36:346-351
72. van der Stegen SJ, Hamieh M, Sadelain M. The pharmacology of second-generation chimeric antigen receptors. Nat. Rev. Drug Discov. 14, 499–509 (2015).
73. C Imai, K Mihara, M Andreansky, I C Nicholson, C-H Pui, T L Geiger, D Campana. Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia Leukemia. 2004; 18:676-684
74. Locke F L, Neelapu S S, Bartlett N L, Lekakis L J, Jacobson C A, Braunschweig I, Oluwole O O, Siddiqi T, Lin Y, Timmerman J M, Reagan P M, Bot A, Rossi J M, Sherman M, Navale L, Jiang Y, Aycock J S, Elias M, Wiezorek J S, Go W Y, Miklos D B. Preliminary results of prophylactic tocilizumab after axicabtageneciloleucel (axi-cel; KTE-C19) treatment for patients with refractory, aggressive non-Hodgkin lymphoma (NHL). Blood. 2017;130(Supplement 1):1547–1547.
75. Dinarello CA, Simon A, van der Meer JWM. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Nat Rev Drug Discovery. 2012;11:633–52.
76. Zhou J, Tang Z, Gao S, Li C, Feng Y, Zhou X. Tumor-Associated Macrophages: Recent Insights and Therapies. Front Oncol. 2020;10:188.
77. Pan Y, Yu Y, Wang X, Zhang T. Tumor-Associated Macrophages in Tumor Immunity. Front Immunol. 2020;11:583084.
78. Liu E, Marin D, Banerjee P, Macapinlac H A, Thompson P, Basar R, Kerbauy L N, Overman B, Thall P, Kaplan M, Nandivada V, Kaur I, Cortes A N, Cao K, Daher M, Hosing C, Cohen E N, Kebriaei P, Mehta R, Neelapu S, Nieto Y, Wang M, Wierda W, Keating M, Champlin R, Shpall E J, Rezvani K. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors N. Engl. J. Med. 2020; 382:545-553
79. Hartmann FJ, Babdor J, Gherardini PF, Amir ED, Jones K, Sahaf B, Marquez DM, Krutzik P, O'Donnell E, Sigal N, Maecker HT, Meyer E, Spitzer MH, Bendall SC. Comprehensive immune monitoring of clinical trials to advance human immunotherapy. Cell Rep. 2019;28(3):819-831.e4.

80. P J Hayden, C Roddie, P Bader, G W Basak, H Bonig, C Bonini, C Chabannon, F Ciceri, S Corbacioglu, R Ellard, F Sanchez-Guijo, U Jäger, M Hildebrandt, M Hudecek, M J Kersten, U Köhl, J Kuball, S Mielke, M Mohty, J Murray, A Nagler, J Rees, C Rioufol, R Saccardi, J A Snowden, J Styczynski, M Subklewe, C Thieblemont, M Topp, Á U Ispizua, D Chen, R Vrhovac, J G Gribben, N Kröger, H Einsele, I Yakoub-Agha . Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Ann Oncol. 2022;33(3):259–75.
81. Xu J, Wang Y, Shi J, Liu J, Li Q, Chen L. Combination therapy: A feasibility strategy for CAR-T cell therapy in the treatment of solid tumors. Oncol Lett. 2018;16:2063–70.