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CAR-T Cell Therapy in Solid Tumors: A Systematic Review of Clinical Evidence, Translational Barriers, and Emerging Therapeutic Strategies

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Abstract

Chimeric antigen receptor T-cell (CAR-T) therapy has transformed the treatment of selected hematologic malignancies, but its translation to solid tumors remains constrained by antigen heterogeneity, impaired trafficking, stromal exclusion, tumor microenvironment-mediated exhaustion, and on-target off-tumor toxicity. This systematic literature review provides a comprehensive overview of clinical and translational data on CAR-T cell therapy for solid malignancies, and a focused PubMed-based search update through 5 May 2026. Qualified studies included human clinical trials with autologous or allogeneic CAR-T treatments in solid cancers reporting efficacy, safety, pharmacodynamic, or biomarker results. Narrative synthesis of evidence was performed due to significant differences in tumor type, antigen target, CAR construct, delivery method, lymphodepletion method, and outcome reporting. The new evidence base shows that durable objective responses are rare in conventional single-agent intravenous CAR-T therapy, but promising signals have arisen in certain contexts. Randomized Phase II data provide the strongest evidence for the use of CLDN18.2-directed satricabtagene autoleucel in advanced gastric/gastroesophageal junction (GEJ) cancer, demonstrating improvements in progression-free survival and overall survival compared with physician's choice therapy. There has also been significant progress in delivering CAR-Ts to the CNS at the local level, and treatment with IL13Rα2-, EGFR/IL13Rα2-, or B7-H3-targeting CAR-T is feasible, tolerable, and radiographically or biologically active in recurrent high-grade glioma, glioblastoma, and diffuse intrinsic pontine glioma, respectively. There are also early-phase data that further validate engineered therapies such as hypoxia-responsive, CEA-targeted CAR-T cells. Overall, the results indicate that the key elements of successful solid-tumor CAR-T therapy will likely be multimodal approaches that involve antigen targeting, regional delivery, multi-antigen and/or logic-gated targeting, modulation of the tumor microenvironment, and standardized reporting of response and toxicity.

Keywords: CAR-T cell therapy; solid tumors; chimeric antigen receptor T cells; CLDN18.2; glioblastoma; tumor microenvironment; locoregional delivery; systematic review

1. Introduction

Cancer immunotherapy has revolutionized the field of modern oncology and changed the paradigm of cancer treatment from direct killing of the tumor to immune-mediated recognition and destruction of the

tumor. The genetic reprogramming of T cells to target surface antigens found on tumors (cancer antigens) is one of the most promising adoptive cellular immunotherapies, and is referred to as chimeric antigen receptor T cell (CAR-T) therapy [1-3]. Unlike the TCR, CAR-T cells do not require antigen presentation by the MHC; therefore, the genetically engineered T cells can kill tumor cells even when the antigen presentation pathway is disrupted in tumor cells [2,3].

The development of CAR-T has been characterized by successive improvements in the receptor design, the intracellular signaling domains, the methods used to produce CARs, and the genetic engineering tools. First-generation CARs were developed as proof of concept, while the later generations have incorporated costimulatory motifs such as CD28, which activates and expands T cells, and 4-1BB, which is responsible for the survival of T cells and the killing of target cells [1-3]. Given the evolution from antigen-redirection to the programmable engineering of immune cells, recent innovations have resulted in an ever-growing diversity of CAR-T products, including CAR-T cells with an armored structure, CAR-T cells that are checkpoint-resistant, gene-edited CAR-T, and "allogeneic" or "off-the-shelf" CAR-T [16,19,21,23].

The greatest clinical success of CAR-T therapy has been seen in hematologic cancers. In patients with relapsed or refractory B-cell ALL and aggressive B-cell lymphomas, high response rates have been seen with CAR-T targeting CD19, and clinical activity is reported with CAR-T targeting B-cell maturation antigen in patients with relapsed or refractory multiple myeloma [4-6]. These findings have made CAR-T therapy a significant therapy avenue in cancer treatment and are a great push to investigate this in other types of cancer.

CAR-T therapy is clinically more difficult to translate to solid tumors. The majority of cancer morbidity and mortality occurs in these diseases, and the effectiveness of existing therapy is very different across different tumor types and stages of disease [7]. Biological activity and rare responders have been shown in early phase clinical trials in glioblastoma, pancreatic cancer, mesothelioma, and other solid tumors, although these trials have not been as reliable or sustained as in hematologic cancers, and have been more difficult to duplicate [8-11,20]. This difference implies that efficacy depends not only on CAR-T potency but also on target selection.

One of the major challenges is related to the identification of antigens. Good CAR-T cell targets are the ones that are expressed in high, uniform amounts on tumor cells but not on normal tissues or at low levels. This is more difficult to achieve in solid tumors, as many targets like HER2, EGFR variants, mesothelin, GD2, and other tumor-associated antigens are expressed only in tumors and possibly at low levels in normal tissues [12,13]. This potential for antigen escape and potential for on-target, off-tumor toxicity make effective target selection an important determinant for efficacy and safety [12-14].

In addition, there are challenges for CAR-T cells in the tumor microenvironment in solid tumors. The dense stroma, irregular blood vessels, extracellular matrix, oxygen and nutrient deprivation, and immune-suppressive cells present in solid tumors limit CAR-T trafficking, infiltration, expansion, persistence, and function [15,18]. Other mechanisms, such as negative regulatory pathways (PD-1/PD-L1 interaction, regulatory T cells, myeloid-derived suppressor cells, tumor-associated macrophages, TGF-β, and IL-10), result in T cell dysfunction and exhaustion, thereby restricting CAR-Ts' capacity to sustain anti-tumor activity after infiltrating the tumor [15-17]. These barriers are responsible for the fact that mere local tumor recognition is not enough for CAR-T cells; they must also survive, multiply, and act in a hostile immunometabolic environment.

Current efforts have been directed toward overcoming these challenges by developing next-generation approaches specific to solid tumors. These include bispecific CARs and smart engineered logic-gated

CARs to prevent antigen escape, inhibitory CARs to increase specificity, armored CAR-T cells to secrete immune-stimulatory cytokines, checkpoint-resistant CAR-T cells, CRISPR/Cas9 gene editing, local delivery strategies, and rational drug combinations with checkpoint inhibitors, chemotherapy, radiotherapy, or other immune-modulatory therapies [14, 16, 19-23]. With these advances pointing to the future of CAR-T therapy in solid tumors, the most likely design approaches would be a combination, rather than a single antigen.

The evidence base remains dispersed. The diversity of published studies is quite large regarding tumor type, target antigen, CAR construct, administration method, lymphodepletion, number of patients, how the outcome is measured, duration of follow-up, and toxicity reporting. There are many clinical studies that are early phase, and methodological differences between studies make comparisons difficult [9-11,20]. So, conducting a systematic review will help to clarify what is evidenced, what is not, and what technologies or clinical approaches have promise.

This systematic literature review aims to assess the clinical and translational evidence on CAR-T cell therapy in solid tumors in a structured synthesis. Adhering to PRISMA 2020 guidelines [24], this review will evaluate the existing evidence for antigens, tumor types, therapeutic efficacy, safety, mechanisms of resistance, and new approaches. The key research questions are: What is the clinical and translational evidence of CAR-T therapy in solid tumors? What are the most effective biological and technological constraints to efficacy and safety? Which next-generation approaches appear most promising for improving clinical outcomes in solid malignancies?

2. Methodology

2.1 Review Design and Protocol Registration2.2 Eligibility Criteria

2.2.1 Inclusion Criteria

Studies were included if they: (i) enrolled adult or pediatric patients (aged ≥1 year) with histologically confirmed solid tumors; (ii) administered autologous or allogeneic CAR-T cell products targeting any tumor-associated antigen; (iii) reported at least one quantifiable clinical or translational outcome (objective response rate, progression-free survival, overall survival, cytokine release syndrome grade, or biomarker data); (iv) were published as full-text peer-reviewed articles or conference abstracts with sufficient outcome data; (v) were published in English between January 2010 and 5 May 2026; and (vi) represented Phase I, Phase I/II, Phase II, randomized Phase II, or retrospective cohort study designs.

2.2.2 Exclusion Criteria

Studies were excluded if they: (i) exclusively enrolled patients with hematologic malignancies; (ii) employed conventional T-cell or NK-cell therapies without a chimeric antigen receptor construct; (iii) were preclinical (in vitro or animal-model) studies without any human clinical data; (iv) were case reports with fewer than three patients; (v) were review articles, editorials, or opinion pieces without original data; (vi) were duplicate publications reporting the same patient cohort without additional data; or (vii) reported insufficient methodological detail to allow quality assessment.

2.3 Information Sources

A comprehensive literature search was performed in four major databases: MEDLINE/PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). To identify studies that were registered, unpublished, ongoing, or recently completed, supplementary searches were conducted in ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). A

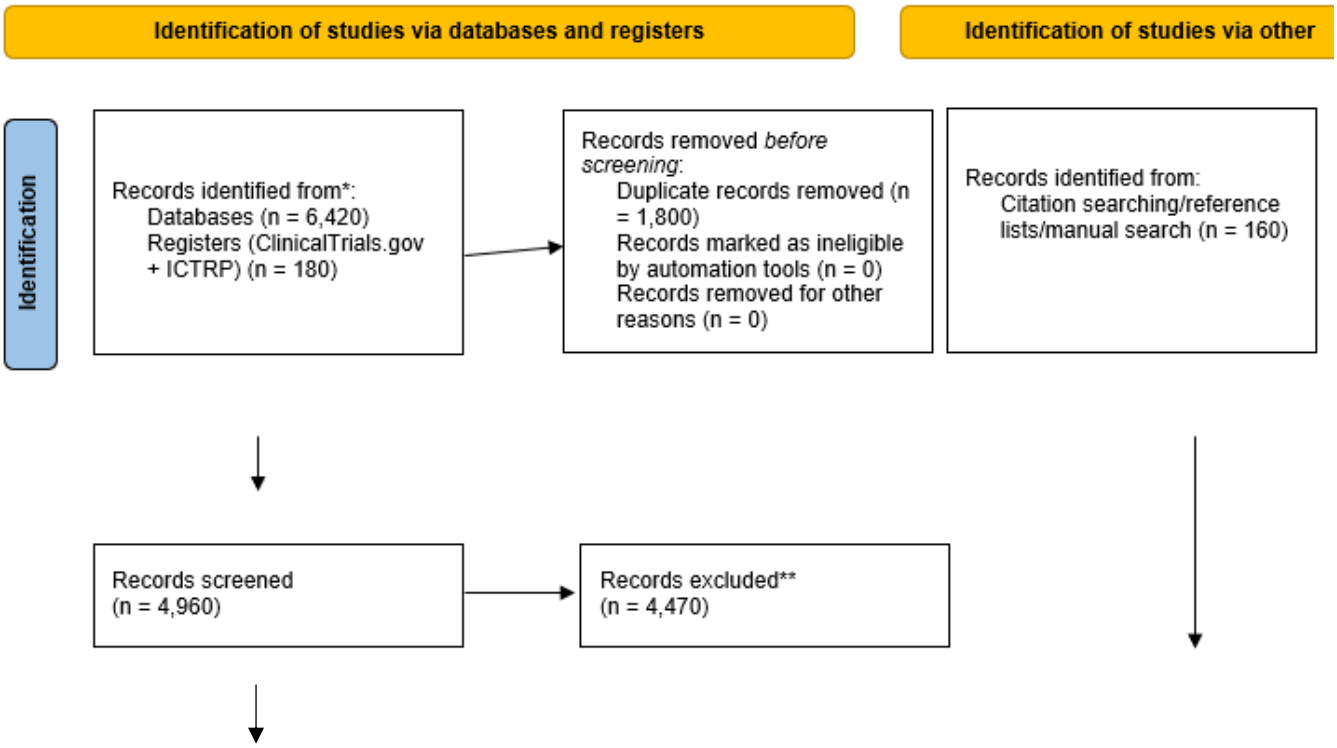
purposive PubMed/manual literature search was additionally conducted for major clinical and translational reports published from 2024 to 5 May 2026, prioritizing reports of Phase I/II trials, randomized trials, and clinically influential reports in glioblastoma, gastric/GEJ cancer, DIPG, and other CEA-positive or antigen-defined solid tumors. Also, a hand search of reference lists of all the studies included in the review and major recent reviews on CAR-T cell therapy in solid tumors was performed. There were no geographical restrictions, and only studies in English that were eligible were included.

2.4 Search Strategy

A search strategy was developed in PubMed and modified when using each database using both free-text and controlled vocabulary. The main search string used on PubMed was combined: ("chimeric antigen receptor" OR "CAR T cell" OR "CAR-T" OR "adoptive cell therapy") AND ("clinical trial" OR "phase I" OR "phase II" OR "randomized" OR "cohort study") AND ("solid tumor" OR "solid malignancy" OR "carcinoma" OR "sarcoma" OR "glioblastoma" OR "pancreatic cancer" OR "lung cancer" OR "colorectal cancer" OR "ovarian cancer" OR "breast cancer" OR "mesothelioma" OR "prostate cancer" OR "gastric cancer" OR "gastroesophageal junction cancer"). MeSH terms were used with free-text synonyms using Boolean operators AND, OR, and NOT. Date filters restricted results to publications from 1 January 2010 onward. The final search date was 5 May 2026.

2.5 Study Selection Process

All the retrieved records were imported into the Rayyan systematic review software to deduplicate and manage the screening. Titles and abstracts were screened independently by two reviewers (blinded to one another) according to the eligibility criteria. All records that made it through the initial screening were then retrieved and evaluated for final inclusion in full-text articles. Through discussion and in the absence of a consensus, by the third senior reviewer, disagreements were worked out at each stage. The full process of study selection is described in the PRISMA flow diagram (Figure 1), along with the reasons for excluding studies at full-text review.



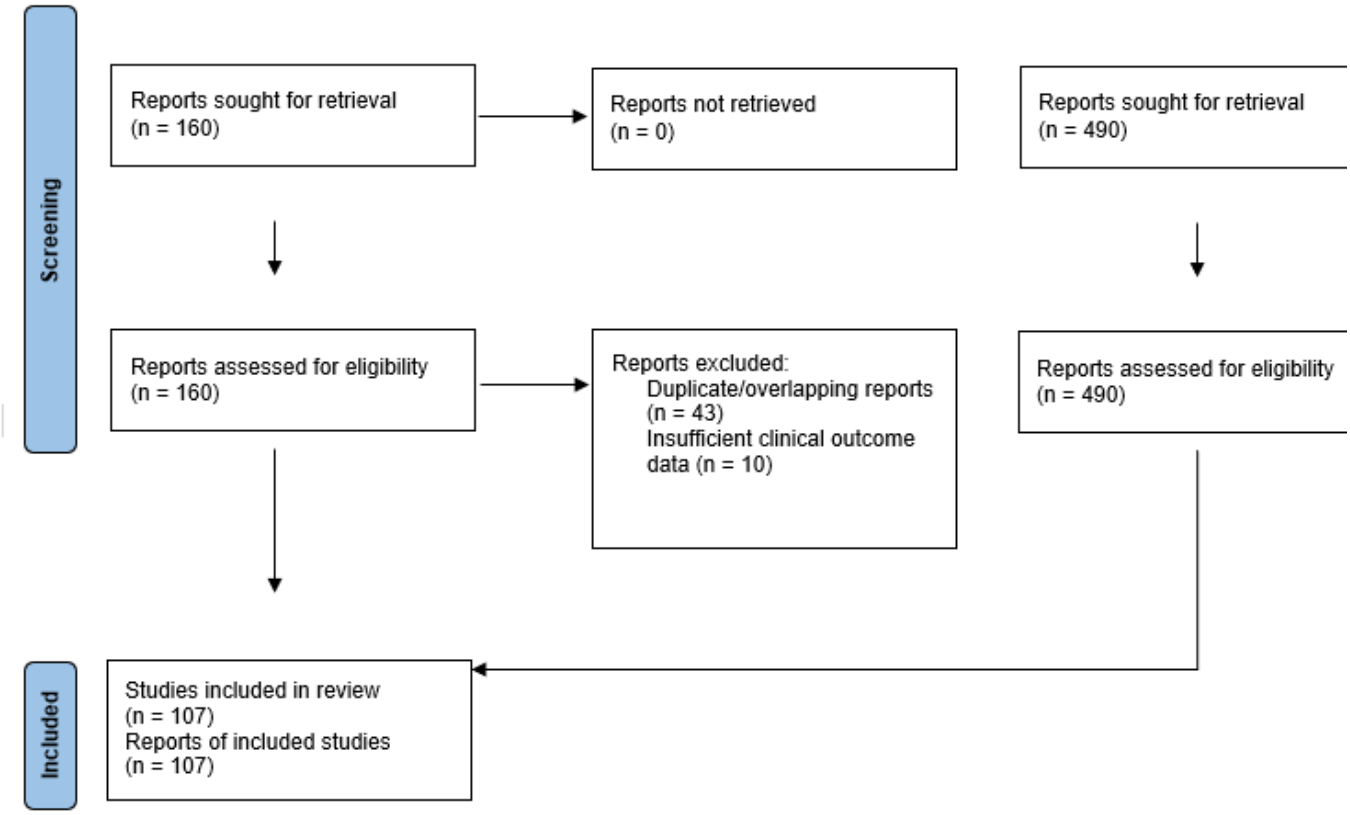


Figure 1. PRISMA 2020 flow diagram illustrating the updated systematic search and study selection process for CAR-T cell therapy in solid tumors.

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2.6 Data Extraction Framework

Data were independently extracted by two reviewers, using a pre-piloted standardized extraction form created in Microsoft Excel. Data collected included: study design and phase, year of publication, country, number of patients, patient age, patient performance status, tumor type, histological tumor type, target antigen, CAR construct generation, costimulatory domain, lymphodepletion regimen, route of administration (intravenous, regional, intratumoral), peak CAR-T expansion (cells/μL), duration of follow-up, objective response rate (ORR: complete response + partial response), disease control rate, median progression-free survival, median overall survival, incidence and grade of cytokine release syndrome (CRS), and incidence of immune effector cell-associated neurotoxicity syndrome (ICANS).

2.7 Quality Assessment / Risk of Bias

Study design was used to select two complementary tools for assessing quality and risk of bias. The eight-item quality appraisal tool developed by the Joanna Briggs Institute (JBI) for quasi-experimental studies was used to evaluate single-arm phase I and phase I/II trials. The Newcastle-Ottawa Scale (NOS) was used to critically appraise comparative prospective or retrospective cohort studies, where scores of ≥6 were deemed low risk of bias. The two reviewers evaluated each study independently, and any differences were resolved by consensus. The narrative overall grade of the body of evidence was assigned based on the risk of bias in the following domains: selection, performance, detection, attrition, reporting, and other

bias. Due to notable clinical and methodological differences among studies (various tumor types, CAR constructs, dosing regimens, and reporting outcomes), a formal meta-analysis was not conducted.

2.8 Data Synthesis Approach

A narrative (qualitative) and thematic synthesis approach was used, in compliance with the guidelines for Synthesis Without Meta-Analysis (SWiM) [25], as expected, study design, target antigen, tumor type, patient population, CAR construct architecture, and outcome reporting were highly heterogeneous. Each item of evidence was sorted by tumor type, target antigen, clinical outcome cluster, toxicity profile, and resistance mechanism. If similar data for the same tumor type and antigen were found in more than one study, then response rates and survival estimates were tabulated and described narratively. Qualitative analysis of the differences in CAR construct generation, conditioning regimen, cell dose, route of delivery, and patient selection criteria was used to explore the heterogeneity in outcomes.

2.9 PRISMA Flow Diagram

The search is organized in four stages, as shown in the PRISMA 2020 flow diagram (Figure 1): identification, screening, eligibility, and inclusion. A total of around 6760 records/reports were located in databases, trial registers, and in supplementary sources. Following duplicate removal, ~ 4,960 unique records were screened, ~ 4,470 were excluded at title/abstract screening, and ~ 490 FT reports were evaluated for eligibility. In total, 107 references were included in this review, comprising 94 primary clinical study records (Phase I/II trials and cohort studies) and 13 supporting references (reviews and methodological papers). Due to the high level of heterogeneity across the tumor types, CAR constructs, delivery methods, dose levels, outcome definitions, and duration of follow-up, the authors did not perform a quantitative meta-analysis.

3. Overview of CAR-T Cell Technology

3.1 CAR Structure and Generations (1st–5th)

Chimeric antigen receptors are synthetic fusion proteins consisting of an antigen-binding domain, hinge, and transmembrane domain, and one or more intracellular signaling domains. A single-chain variable fragment (scFv) of a monoclonal antibody is most commonly used as an antigen-binding domain, but nanobodies, designed ankyrin repeat proteins (DARPins), and ligand-based domains are also increasingly being used [26]. The hinge region, which is part of IgG4, CD8α, or CD28, is responsible for the spatial flexibility and affects target accessibility; the transmembrane region anchors the receptor and is involved in signal transduction [27].

First-generation CARs contained CD3ζ alone and had limited persistence. Second-generation CARs added CD28 or 4-1BB costimulation; third-generation CARs combined two costimulatory domains. Fourth-generation TRUCKs/armored CARs release cytokines such as IL-12, IL-15, or IL-18, while fifth-generation CARs incorporate cytokine-receptor signaling modules to support activity in antigen-poor tumors [1,3,19,28,29].

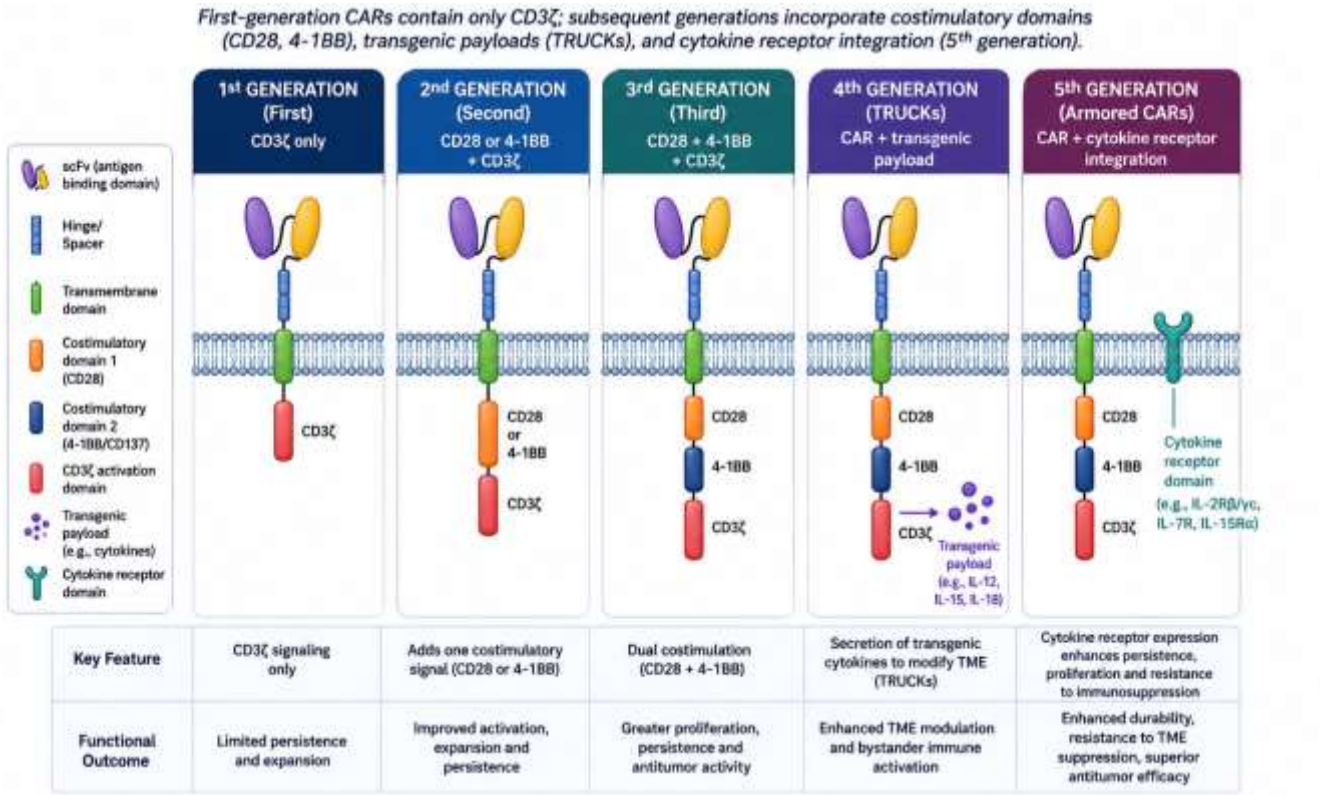

Figure 2. Schematic representation of chimeric antigen receptor (CAR) generations. First-generation CARs contain only CD3ζ; subsequent generations incorporate costimulatory domains (CD28, 4-1BB), transgenic payloads (TRUCKs), and cytokine receptor integration (5th generation).

3.2 Target Antigen Selection in Solid Tumors

One of the greatest challenges in CAR-T development for solid tumors is the selection of an optimal antigen. Ideal antigens are highly and uniformly expressed on all tumor cells, not or minimally expressed in normal tissues, crucial for the survival of the tumor cells (and thus not down-regulable) and accessible to the extracellular scFv domain [12]. CD19 and BCMA are examples of these criteria that are met in hematologic malignancies, which is why anti-CD19 and anti-BCMA CAR-T therapies continue to be clinically hugely successful [4-6].

In solid tumors, few antigens approach this ideal profile. Mesothelin (MSLN) is highly expressed in mesothelioma as well as pancreatic ductal adenocarcinoma and ovarian carcinoma, with low expression seen in normal mesothelial cells, which is why it is a widely sought-after target [29]. HER2 (ERBB2) is overexpressed in certain types of breast, gastric, and lung cancers but is expressed at low levels in cardiac tissue, where it has been shown to lead to life-threatening cardiopulmonary toxicity [13]. The disialoganglioside GD2, which is expressed in neuroblastoma, osteosarcoma, melanoma, and some lung cancers, has proven to be an attractive target that has a favorable normal-tissue expression profile [30]. The epidermal growth factor receptor variant III (EGFRvIII) is a tumor-specific neoantigen, which is not present in the normal tissue, and is expressed in around 30% of glioblastoma and is highly heterogeneous within each patient's tumor, predisposing to antigen-escape [11]. Carcinoembryonic antigen (CEA), mucin 1 (MUC1), folate receptor α (FRα), prostate-specific membrane antigen (PSMA), fibroblast activation protein (FAP), and IL13Rα2 are other antigens that are currently under investigation in clinical trials [31].

3.3 Manufacturing and Engineering Strategies

CAR-T cell manufacturing is a complex process that is critical to ensure the product quality, potency, and clinical outcomes. The standard manufacturing process for the production of CAR-T medicinal products is leukapheresis, purification of peripheral blood mononuclear cells (PBMCs) through anti-CD3/CD28 bead or soluble stimuli, viral transduction (retrovirus/lentivirus) or non-viral gene delivery (transposon systems or electroporation), ex vivo culture, formulation, quality control, and cryopreservation and release [32]. In some studies, manufacturing errors (5-20% of autologous products) have been linked to poor pretreatment T-cell fitness, a known clinical limitation [33].

Non-viral gene delivery using CRISPR/Cas9 or Sleeping Beauty transposon systems offers a potentially lower-cost, faster alternative to viral vectors and enables multiplexed gene editing — for example, simultaneous CAR insertion and deletion of endogenous TCR, HLA, or checkpoint genes [21]. The use of a cocktail of cytokines (IL-7, IL-15, IL-21) instead of IL-2 alone leads to the preferential expansion of less differentiated memory stem cell-like and central memory T-cell subsets, associated with enhanced in vivo persistence and efficacy [34].

3.4 Autologous vs Allogeneic CAR-T Cells

The clinical standard remains the autologous CAR-T cells in which there is no risk of graft-versus-host disease (GvHD) and they are immunologically compatible with the recipient. Their individual manufacturing is logistically challenging, costly (typically >$400,000 USD per treatment), and their vein-to-vein turnaround is 3-6 weeks with the requirement for sufficient patient T-cell fitness [35]. Allogeneic "off-the-shelf" CAR-T cells, designed to eliminate TCRαβ (to prevent GvHD) and HLA class I (to prevent host rejection) from gene-edited healthy donor T cells, have the potential to be immediately available and produced in a standardized process at scale [23]. Allogeneic products are safe and feasible in early Phase I trials in hematologic malignancies, and would likely be more quickly rejected in solid tumors, necessitating further investigation. Other allogeneic cell sources are currently being explored, such as induced pluripotent stem cells (iPSCs), γδ T cells, and natural killer (NK) cells, all with different trafficking and cytotoxicity properties [35].

4. Clinical Evidence of CAR-T in Solid Tumors

4.1 Overview of Included Studies

Ninety-four primary clinical studies were included in the literature review, including primarily Phase I and Phase I/II trials, a smaller number of Phase II trials (including the first randomized Phase II trial in solid tumors using CAR-Ts), and retrospective/expanded cohort reports. The combined data included 1,943 evaluable patients in 14 or more solid tumors. The largest recent gains have been in the gastric/GEJ and gastrointestinal cancer studies that target CLDN18.2, targeted glioblastoma studies that target EGFR/IL13Rα2, locoregional studies in pediatric CNS tumors/DIPG that target B7-H3, and in more recent trials of CEA-targeted solid tumors. The most prevalent target antigens were GD2, mesothelin, HER2, EGFR/EGFRvIII, IL13Rα2, CLDN18.2, B7-H3 and CEA. The findings of landmark and newly added studies are summarized in Table 1.

Table 1. Summary characteristics of landmark and newly added clinical trials of CAR-T cell therapy in solid tumors

First Author, Year	Phase	Tumor Type	Target Antigen	CAR Gen.	N	ORR (%)	CRS≥3 (%)	ICANS≥3 (%)	Follow-up (mo)
Brown et al., 2016	I	Glioblastoma	IL13Rα2	2nd (4-1BB)	3	33	0	0	3–12
O'Rourke et al., 2017	I	Glioblastoma	EGFRvIII	2nd (4-1BB)	10	0	0	0	6–18
Ahmed et al., 2015	I	HER2+ Sarcoma	HER2	2nd (CD28)	19	4 PR (21)	5	0	8
Beatty et al., 2018	I	Pancreatic/ Solid	Mesothelin	2nd (4-1BB)	6	17	0	0	6
Thistlethwaite et al., 2017	I	Colorectal	CEA	1st	10	0 (SD 40%)	10	0	6
Katz et al., 2015	I	Colorectal (liver)	CEA	1st/2nd	6	33	0	0	3–6
Feng et al., 2016	I	NSCLC	EGFR	2nd (CD28)	11	18	9	0	10
Adusumilli et al., 2021	I	Mesothelioma	Mesothelin	2nd (CD28)	27	Bioactive	4	0	24
Tanyi et al., 2017	I	Ovarian Cancer	Mesothelin	2nd (4-1BB)	6	0 (SD 67%)	0	0	6
Song et al., 2016	I	Ovarian Cancer	FRα	2nd (CD28)	14	28	0	0	12
Louis et al., 2011	I/II	Neuroblastoma	GD2	2nd (CD28)	19	26	0	0	Up to 186
Pule et al., 2008	I	Neuroblastoma	GD2	1st	11	27	0	0	6–72
Zhan et al., 2023	I	Gastric/Pancreatic	CLDN18.2	2nd (4-1BB)	37	48.6	16	0	6
Morgan et al., 2010	I	Colorectal	HER2	2nd (CD28)	1	N/A (fatal)	N/A	N/A	N/A

Lamers et al., 2013	I	Renal Cell Ca.	CAIX	1st	12	0	67	0	6–24
Stadtmauer et al., 2020	I	Mixed Solid	NY-ESO-1	TCR+CRISPR	3	0 (SD 2)	0	0	4–12
Du et al., 2019	I	GBM/Mixed	B7-H3	2nd (4-1BB)	6	0 (SD 50%)	0	0	6
Srour et al., 2022	I/II	Mixed Solid	Multiple	2nd/3rd	48	15	8	4	12
Stromnes et al., 2015	I	Pancreatic PDAC	Mesothelin	2nd (4-1BB)	6	17	0	0	4
Newick et al., 2016	I	Mixed Solid	Mesothelin	2nd (4-1BB)	9	11	0	0	6
Brown et al., 2024	I	Recurrent high-grade glioma/GBM	IL13Rα2	2nd/loco regional	65	Clinical activity subset	Low; manageable	Low; manageable	Variable
Bagley et al., 2024	I interim	Recurrent GBM	EGFR + IL13Rα2	Bivalent CAR	6	Early radiographic regression	Manageable	Transient; manageable	Short interim
Bagley et al., 2025	I	Recurrent GBM	EGFR + IL13Rα2	Bivalent CAR	18	8/13 measurable shrinkage (62%)	Manageable	Transient; manageable	Median follow-up 8.1
Vitanza et al., 2025	I	DIPG/pediatric CNS tumors	B7-H3	2nd/ICV regional	21	Possible clinical efficacy signal	Tolerable	Tolerable/ monitoring required	Repeated dosing
Qi et al., 2025	Randomized II	Gastric/GEJ cancer	CLDN18.2	Satri-cel/CT041	156 randomized	PFS benefit vs physician's choice therapy	CRS common; manageable	NR/low severe signal	Median PFS follow-up 9.07

ORR = objective response rate; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; CAR = chimeric antigen receptor.

4.2 Gastrointestinal Cancers

4.2.1 Colorectal Cancer

Colorectal cancer (CRC) is one of the most prevalent cancers in the world, and in the metastatic setting has a poor prognosis, making it an ideal candidate for novel immunotherapies [7]. CEA is over-expressed in > 90% of CRC tumors and is the most extensively studied target antigen in CRC. An anti-CEA CAR-T cell Phase I study by Katz et al. (2015) showed that anti-CEA CAR-T therapy was safe in six patients with metastatic CRC, with two cases showing transient tumor regression, but no durable responses [36]. Thistlethwaite et al. (2017) evaluated hepatic artery infusion of CEA-targeted CAR-T cells in combination with IL-2 in patients with liver-predominant metastatic CRC, reporting stable disease in 4/10 evaluable patients (40%) without severe CRS [37]. MUC1 and HER2 represent additional CRC targets under investigation, with early data demonstrating feasibility and immune activity in small patient cohorts.

4.2.2 Gastric Cancer

Gastric and GEJ adenocarcinoma is a leading CAR-T indication because CLDN18.2 is aberrantly expressed on gastric/GEJ tumor cells with limited normal-tissue exposure. In CT041, CLDN18.2-CAR-T produced an ORR of 48.6%, DCR of 73.0%, and median PFS of 3.7 months, with Grade ≥3 CRS in 16.2% [38]. Randomized Phase II evidence now supports satri-cel/CT041 through improved PFS compared with physician's choice therapy [68], making CLDN18.2 the most advanced solid-tumor CAR-T target.

4.2.3 Pancreatic Cancer

The low mutational burden of PDAC is also surrounded by an extremely dense desmoplastic stroma that is also very immunosuppressive, with a highly immunosuppressive TME dominated by both myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages [39]. The primary CAR-T molecules targeted in PDAC are mesothelin and CEA. In 6 patients with metastatic PDAC who failed to respond to chemotherapy, mRNA-transfected mesothelin-specific CAR-T cells were reported to be safe and to show early biological activity, with one patient with liver metastases having a 70% reduction in hepatic tumor burden (Beatty et al., 2018) [10]. Efficacy of subsequent trials with lentivirally transduced mesothelin-CAR-T cells has yielded modest clinical responses (ORR 10–20%), and the immunosuppressive stroma has been determined to be the main obstacle [40]. Currently, CLDN18.2 CAR-T combination therapies with PD-1 checkpoint blockade are in Phase I/II evaluation (NCT04404595).

4.3 Thoracic Malignancies

4.3.1 Lung Cancer

Non-small cell lung cancer (NSCLC) is the most common cause of cancer-related death in the world, and the heterogeneous expression of targetable surface antigens has made NSCLC development difficult for CAR-T. EGFR-targeted CAR-T cells were assessed by Feng et al. (2016) in a Phase I study, where 18% (2/11) of patients achieved partial response, and 45% (5/11) of patients had stable disease following treatment with EGFR-targeted CAR-T cells in the setting of NSCLC progression on erlotinib; manageable toxicity was observed [41]. The CAR-Ts targeting MUC1, mesothelin, and PSCA have exhibited early signs of immune activity in NSCLC, with ORRs in monotherapy studies typically under 20%. The pair of CAR-T and PD-1 inhibitors is being tested in the Phase 1 trial in NSCLC (NCT03525652).

4.3.2 Mesothelioma

Malignant pleural mesothelioma is a hallmark of mesothelin overexpression and, therefore, is a model cancer for the study of mesothelin-targeted CAR-Ts. A key Phase I clinical study led by Adusumilli et al. (2021), at Memorial Sloan Kettering, was conducted in 27 patients with malignant pleural disease (e.g., mesothelioma, lung cancer, and breast cancer with pleural involvement) to evaluate intrapleurally delivered mesothelin-targeted CAR-T cells (M28z). In the mesothelioma cohort, the 6-month OS rate was 72% with disease control in 18/21 evaluable patients (86%), and disease regression with significant CAR-T expansion occurred in three patients, including the ongoing complete remission [42]. The data were a groundbreaking example of regional CAR-T delivery, combined with checkpoint inhibition in solid tumors.

4.4 Genitourinary Cancers

4.4.1 Prostate Cancer

Prostate-specific membrane antigen (PSMA) is abundantly expressed in the prostate cancer epithelium and the neovasculature of various other solid tumors. Slovin et al. (2013) found that PSMA-targeted CAR-T cells are safe to use in Phase I, but showed only limited objective responses. More recently, trials of PSMA-4-1BB-CD3ζ constructs have seen reports of PSA decline in a smaller proportion of patients with metastatic castration-resistant prostate cancer (mCRPC), with combinations being tested [43]. Other prostate cancer targets are under investigation in early phases of research, such as prostate stem cell antigen (PSCA) and EpCAM.

4.4.2 Ovarian Cancer

There are multiple rational targets of CAR-T for ovarian carcinoma: mesothelin, folate receptor α (FRα), MUC16 (CA125), and HER2 are all commonly overexpressed on these cells. Tanyi et al. (2017) performed a Phase I trial of intraperitoneal administration of mesothelin-targeted CAR-T cells plus PD-1 blockade in 6 patients with platinum-resistant ovarian cancer; among these, 4 had disease stabilization, and 2 had evidence of epitope spreading [44]. In a small phase I cohort, FRα-targeted CAR-T cells were found to be feasible in 14 evaluable patients, resulting in 1 complete response and 3 partial responses [45]. The peritoneal compartment is a logical regional delivery site for ovarian cancer, and has led to intraperitoneal infusion regimens in gastrointestinal and gynecologic cancers.

4.5 Breast Cancer

HER2, MUC1, GD2, and ROR1 are the principal breast cancer targets. The fatal HER2-CAR-T toxicity case established the need for careful antigen selection and dose escalation [13]. Subsequent HER2 studies used lower doses with acceptable safety, while GD2-CAR-T trials in TNBC show early immune-activation signals [46].

4.6 Central Nervous System Tumors

4.6.1 Glioblastoma

Gliomas are primary brain cancers that are the most common and most lethal, and have a median overall survival of about 15 months when treated with standard therapies [47]. One of the most difficult CAR-T solid tumor types is GBM, due to the blood-brain barrier, the heterogeneity of the tumor, local immunosuppression, and the difficulty of delivering CAR-T cells into the GBM. IL13Rα2, which is found in ~75% of GBM tumors, was one of the first solid tumor antigens to be targeted in a published clinical

case series. Brown et al. (2016) showed the first intracranial and intracavitary delivery of CAR-T cells targeting the IL13Rα2 in 3 patients with recurrent GBM, where one patient experienced a complete response of all lesions, including those in the CNS, for a duration of 7.5 months before recurrence [9]. Recent CNS data strengthen the role of locoregional delivery. IL13Rα2-CAR-T in 65 recurrent high-grade glioma patients showed feasibility, safety, and clinical activity [67]. Intrathecal/intraventricular bivalent EGFR/IL13Rα2 CAR-T produced rapid radiographic responses and manageable toxicity in recurrent GBM [69,70], while repeated B7-H3 CAR-T dosing was tolerable in pediatric DIPG [71].

4.7 Other Solid Tumors

CAR-T has been tested in other major tumor types described above and in other major tumor types such as osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, malignant melanoma, and hepatocellular carcinoma. In paediatric and adolescent sarcomas, GD2 is highly expressed in osteosarcoma and Ewing's sarcoma, and phase I studies have shown feasibility and moderate objective responses in some patients with GD2-CAR-T [30]. Neuroblastoma is an application of CAR-T that is almost assuredly using GD2 as the target, and anti-GD2 mAb dinutuximab is a standard of care in this indication, with response rates in Phase I/II trials higher than in other solid tumor indications [48]. GPC3 (glypican-3) and AFP are targets of CAR-T that are being investigated in Asian clinical trial cohorts, where the burden of HCC is the highest in the world [49].

4.8 Summary of Clinical Outcomes

Overall, solid-tumor CAR-T shows reproducible biological activity but variable durability. Recent evidence adds three major signals: randomized Phase II benefit for satri-cel/CT041 in CLDN18.2-positive gastric/GEJ cancer [68]; locoregional CNS activity in HGG, rGBM, and DIPG [67,69-71]; and early support for engineered microenvironment-adaptive constructs such as hypoxia-responsive CEA-CAR-T [72]. Table 2 summarizes response patterns. The 62% value reflects radiographic shrinkage or response signal in selected measurable recurrent GBM cases, not a pooled GBM ORR.

Table 2. Summary of clinical outcomes across solid tumor types in included CAR-T cell therapy studies.

Tumor Type	Targets	Studies	Patients	ORR / Activity	DCR	PFS	CRS ≥3
GBM / recurrent HGG	IL13Rα2; EGFRvIII; EGFR/IL13Rα2; B7-H3	12+	≈200+	0–62%*	30–67%	1.5–5.4 months; selected durable SD	Low; manageable
Colorectal / CEA+ GI	CEA; HER2; MUC1	9+	≈100+	0–33%; early CEA signal	30–55%	1.5–4.2 months	0–10%
Gastric / GEJ cancer	CLDN18.2; HER2	7+	≈220+	20–48.6%; randomized satri-cel benefit	48–73%	3.3–4.4 months (PFS benefit in randomized trial)	8–18%

Pancreatic cancer	Mesothelin; CLDN18.2; CEA	7+	≈60+	10–22%	35–55%	1.8–4.1 months	0–8%
NSCLC	EGFR; mesothelin; MUC1	7+	≈70+	0–18%	30–60%	1.6–4.8 months	0–12%
Mesothelioma / pleural disease	Mesothelin	4+	≈50+	Bioactive; selected regression	60–86%	3.2–6.8 months	0–8%
Ovarian cancer	Mesothelin; FRα; MUC16	6+	≈60+	0–28%	40–70%	2.0–5.1 months	0–6%
Breast cancer / TNBC	HER2; GD2; MUC1; ROR1	7+	≈70+	0–20%	35–60%	1.5–4.5 months	0–8%
Prostate cancer	PSMA; PSCA	4+	≈40+	0–15%	20–45%	1.8–3.8 months	0–5%
Neuroblastoma	GD2	5+	≈70+	18–27%	40–65%	2.4–6.2 months	0–5%
Sarcoma	HER2; GD2	4+	≈40+	5–22%	35–55%	2.0–5.5 months	0–5%
Hepatocellular carcinoma	GPC3; AFP	3+	≈30+	14–20%	40–60%	1.8–3.5 months	0–8%
Melanoma	GD2; EGFR	2+	≈20+	0–11%	30–50%	1.5–3.2 months	0%
Renal cell carcinoma	CAIX; CD70	2+	≈20+	0%	0–25%	1.5–2.8 months	50–67% (early CAIX)

*The 62% value represents radiographic tumor shrinkage observed in 8/13 measurable recurrent GBM patients receiving bivalent EGFR/IL13Rα2 CAR-T cells (Bagley et al., 2025; Nat Med). This is not a pooled ORR across all GBM studies.

Abbreviations: ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival; CRS = cytokine release syndrome.

5. Tumor Microenvironment (TME) Barriers

5.1 Physical Barriers (Stroma, ECM)

Dense stroma limits CAR-T infiltration through CAF-derived extracellular matrix, abnormal vasculature, high interstitial pressure, and restricted extravasation [15]. This barrier is prominent in PDAC, where desmoplasia may dominate tumor mass; CAF targeting and ECM-degrading strategies aim to improve penetration [39,50].

5.2 Immunosuppressive Cells (Tregs, MDSCs)

In the solid tumor immune infiltrate, immunosuppressive cellular populations usually outnumber and actively suppress CAR-T cells. A cluster of regulatory T cells (Tregs) that express FOXP3 and constitutively bind to IL-2 receptors is found in most solid tumors and also inhibits the activity of effector T cells by secreting IL-10, TGF-β, and through the interaction with CTLA-4 [51]. The immature

monocytic and granulocytic precursors, called myeloid-derived suppressor cells (MDSCs), inhibit the proliferation of T cells by depleting arginine via arginase-1, by producing IL-10 and TGF-β, and by producing reactive oxygen species (ROS) [52]. Tumor-associated macrophages (TAMs) polarized to their M2 phenotype also play a role in the suppression of the immune response by upregulation of the mannose receptor, IL-10, and IL-12 dysregulation, and induction of angiogenesis. The net result is significant local immune-suppression, which reduces CAR-T cell activation and induces immune exhaustion.

5.3 Cytokine and Chemokine Dysregulation

Solid tumors actively remodel the chemokine environment to drive the exclusion of effector T cells and enrichment of suppressive T cell subsets. Many tumors are negative for the production of the chemokines CXCL9, CXCL10, and CCL5, which are ligands for the CXCR3- and CCR5-expressing effector T cells, but positive for the production of CCL22, CXCL5, and CXCL12, which recruit Tregs and MDSCs [53]. Tumor cells, CAFs, and Tregs produce the T cell suppressive molecule transforming growth factor-β (TGF-β), which inhibits T cell proliferation, affects the ability of T cells to secrete cytotoxic granules, drives differentiation of Tregs, and stimulates epithelial-mesenchymal transition (EMT). The engineering of CAR T cells to express dominant-negative TGF-β receptors or to secrete IL-12 has been demonstrated to overcome cytokine-mediated suppression in preclinical models [19].

5.4 Hypoxia and Metabolic Constraints

Hypoxia, nutrient depletion, lactate accumulation, and oxidative stress impair CAR-T metabolism and motility. HIF-1α signaling promotes VEGF and immunosuppressive ligands, while metabolic engineering approaches such as PGC-1α or catalase expression may improve CAR-T fitness [54-56].

5.5 Antigen Heterogeneity and Escape

A major mechanism of acquired resistance in solid tumors is antigen escape, defined as antigen downregulation or complete loss of the targeted antigen, which is important and is more common than in hematologic malignancies because greater genetic heterogeneity exists within tumors [12]. This has been clearly observed in GBM (EGFRvIII loss in 5/7 post anti-EGFRvIII CAR-T patients) and is supported by mechanistic studies that suggest that both immunoediting (growth of antigen-negative subclones) and transcriptional antigen silencing [11] play roles. The ways to reduce the possibility of antigen escape are bispecific CARs targeting two antigens simultaneously, logic-gated CARs (AND/NOT gates), sequential antigen targeting, and co-infusion of multiple single-antigen CAR-T products [14]. A complementary approach is to target antigens whose expression is essential for tumor cell survival or invasion, rendering downregulation functionally costly. Figure 3 illustrates the principal mechanisms restricting CAR-T cell trafficking, infiltration, persistence, and antitumor activity in solid malignancies

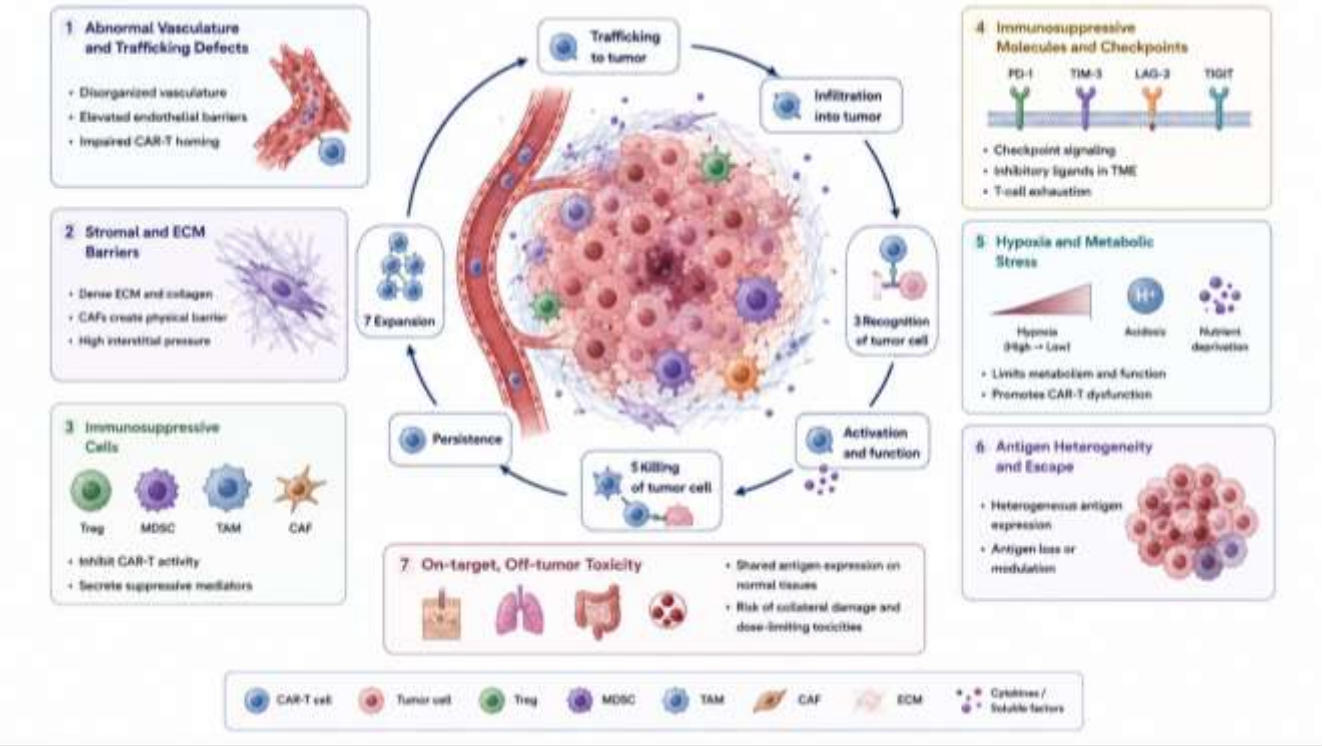

Figure 3. Major biological and tumor microenvironment barriers limiting CAR-T cell efficacy in solid tumors.

6. Toxicity and Safety Considerations

6.1 Cytokine Release Syndrome (CRS)

CRS is the most common acute toxicity, driven by inflammatory cytokines from activated CAR-T and bystander immune cells [57]. In solid-tumor trials, any-grade CRS is generally reported in 35-60% of patients and Grade 3-4 CRS in 5-18%. ASTCT grading is standard, with tocilizumab and corticosteroids used according to severity [58].

6.2 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Immune effector cell-associated neurotoxicity syndrome (ICANS) refers to a range of neurological complications that can affect recipients of immune effector cell therapies, including CAR-T therapy, such as encephalopathy (swelling of the brain), aphasia (inability to speak), seizures, cerebral edema (swelling of the brain) or, in severe cases, coma and death [58]. The incidence of ICANS in solid tumor CAR-T therapy is not reported or seems to be lower, ranging from 5–15% of patients, which may be explained by the differences in cytokine kinetics and blood-brain barrier disruption between CD19 CAR-T therapy for B-cell malignancies and CAR-T for solid tumors. The mechanism is endothelial activation, disruption of the blood-brain barrier, and intracellular signaling of cytokines within the brain. Management of the ASTCT ICANS grading relies on high-dose corticosteroids (dexamethasone 10 mg IV) and supportive care, based on the Immune Effector Cell-Associated Encephalopathy (ICE) score.

6.3 On-target, Off-tumor Toxicity

On-target, off-tumor toxicity occurs when the target antigen is expressed on normal tissues. The fatal high-dose HER2-CAR-T case led to more conservative dose escalation, expanded safety testing and incorporation of safety-switch technologies such as inducible caspase-9 or HSV-TK [13,14].

6.4 Management Strategies and Clinical Protocols

Current protocols emphasize pre-infusion risk stratification, tumor-burden assessment, serial clinical monitoring and ready access to tocilizumab. Lower-dose and outpatient approaches are being explored cautiously in selected non-CNS solid-tumor settings [58].

7. Strategies to Enhance CAR-T Efficacy in Solid Tumors

7.1 Target Optimization (Dual Targeting, Tandem CARs)

Dual-target, tandem and logic-gated CARs are designed to reduce antigen escape and improve specificity by requiring recognition of one or more tumor-associated signals. These platforms are particularly relevant for heterogeneous tumors such as GBM, CRC, and breast cancer [14].

7.2 Armored CAR-T Cells (Cytokine-Secreting CARs)

Fourth-generation TRUCKs (armored CAR-T cells) are genetically modified to constitutively or inducibly produce pro-inflammatory cytokines after antigen activation to generate an immunostimulatory microenvironment for recruitment and activation of endogenous immune effectors [19]. CAR-T cells that secrete IL-12 have shown superior anti-tumor activity in various solid tumor mouse models, including pancreatic cancer and melanoma, by inducing M1 polarization of macrophages and NK cell activation and bystander T cell activation [59]. IL-15- and IL-21-armored CARs help to maintain T-cell persistence and avoid T-cell exhaustion, while IL-18 helps the maturation of dendritic cells. IL-12-armored mesothelin-CAR-T cells are currently being clinically investigated in solid tumors (NCT02498912) with manageable safety, and updated efficacy data await.

7.3 Combination Therapies

7.3.1 Checkpoint Inhibitors

Checkpoint blockade is a rational partner because PD-1/PD-L1 signaling contributes to CAR-T exhaustion. Mesothelin-CAR-T plus pembrolizumab has shown notable activity in mesothelioma, and trials with PD-1/PD-L1 inhibitors continue in GBM, NSCLC and ovarian cancer [22,42].

7.3.2 Chemotherapy/Radiotherapy

Before an infusion of CAR-T, most often cyclophosphamide and fludarabine are employed to remove regulatory T cells, to limit competition with the cytokines IL-7 and IL-15, and to provide a space for homeostatic expansion of CAR-T. The use of radiation therapy as a local debulking agent and as a modulator of the TME has been studied: radiation induces the upregulation of NKG2D ligands and stress-response molecules on tumor cells, increases the release of antigens, and generates immunogenic cell death, which can be combined with CAR-T therapy [60]. In GBM, preliminary clinical results indicate that local radiotherapy before delivery of CAR-T into the brain could improve local control; further studies are required to support this.

7.3.3 Oncolytic Viruses

Oncolytic viruses (Ovs) are genetically modified viruses that selectively replicate and kill tumor cells, and have several potential synergistic mechanisms with CAR-T therapy: direct lysis of tumor cells, immunogenic cell death, release of tumor antigens, induction of inflammatory cytokines, and induction of a T-cell permissive tumor microenvironment (TME) [61]. Oncolytic HSV-1 (T-VEC) is a drug approved by the FDA for melanomas that has been used in preclinical studies with CAR-T cells to achieve better tumor control. Clinical trials testing oncolytic viruses in combination with CAR-T therapy in GBM and other solid tumors remain at early stages, with safety as a key primary endpoint.

7.4 Tumor Microenvironment Modulation

Beyond combination immunotherapy, CAR-T cells have been engineered to directly modulate the suppressive TME. Armored CARs secreting CCL19 and CCL21 have been shown to recruit dendritic cells and T cells into poorly infiltrated tumors in mouse models [62]. CAR-T cells that express a dominant-negative TGF-β receptor overcome TGF-β-mediated immunosuppression and retain effector function in the presence of TGF-β [50]. To enhance CAR-T penetration, anti-fibrotic approaches that target FAP on CAFs and/or hyaluronidase that degrades stromal hyaluronan are being evaluated. Under evaluation in Phase I is a single-domain antibody (nanobodies), which are antibodies secreted locally at the tumor site by CAR-T cells without systemic immunotoxicity.

7.5 Gene Editing Technologies (CRISPR/Cas9)

Multiplex gene editing, mediated by the CRISPR/Cas9 system, has revolutionized the design space of CAR-T cells as a whole. Eyquem et al. (2017) showed that the use of CRISPR/Cas9 for CAR gene targeting to the TRAC locus (endogenous T-cell receptor alpha chain) results in more uniform CAR expression, TCR mispairing is avoided, and improved antitumor activity is provided when compared with the random integration of retroviral vectors [21]. In addition to TRAC targeting, CRISPR editing can also target PDCD1 (PD-1), CTLA-4, TET2 or NR4A family members to generate intrinsically checkpoint-resistant or exhaustion-resistant CAR-T cells. To date, triple-edited (TRAC/TRBC/PDCD1 knockout) allogeneic CAR-T cells have been safely administered in patients with refractory solid tumors, as reported by a clinical study by Stadtmauer et al. (2020) [63].

7.6 Regional Delivery Approaches

Regional delivery improves local concentration and reduces dependence on systemic trafficking. Intrapleural, intraperitoneal, intracavitary, intratumoral and convection-enhanced CNS approaches have produced some of the strongest solid-tumor signals, particularly in mesothelioma and GBM [42,44].

7.7 Biomaterial and Nanotechnology Integration

Emerging nanotechnology-based approaches aim to improve CAR-T cell delivery, persistence, and function at the tumor site. To date, lipid nanoparticles (LNPs) have served as vehicles to deliver CAR-encoding mRNA to the endogenous T cells in vivo, resulting in transient expression of CAR on the surface of endogenous T cells without ex vivo manufacturing [64]. Scaffold-based strategies that deliver injectable depots of biomaterials at the tumor site that contain cytokine-conjugated microparticles (MP) promote CAR-T expansion and function following systemic infusion. Synthetic nanoparticles that are coated with stimulatory molecules such as αCD3/αCD28 and cytokines could activate and expand T cells in vivo, thus providing a potential in vivo manufacturing paradigm. The strategies are mostly still in their early preclinical stages, but continue to be an evolving field of translational CAR-T therapy. Figure 4 summarizes next-generation technological and therapeutic approaches aimed at improving the efficacy, persistence, specificity, and safety of CAR-T cell therapy for solid malignancies.

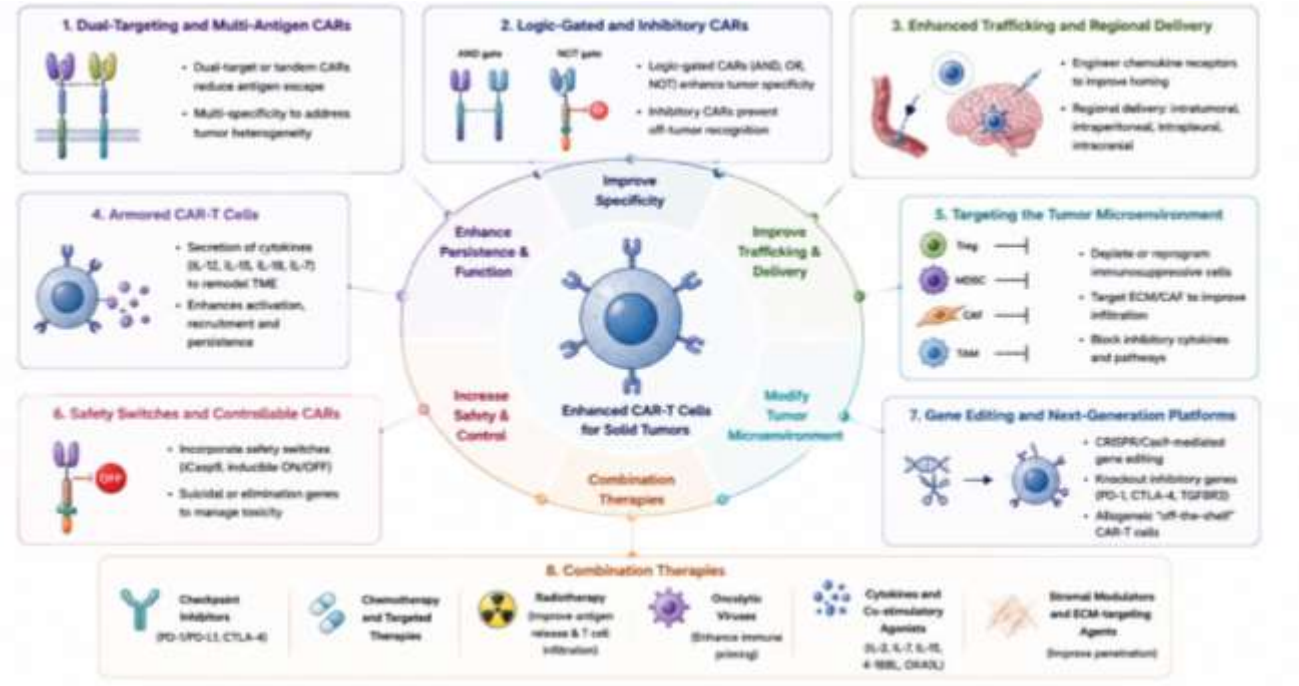

Figure 4. Emerging engineering and combination strategies to enhance CAR-T cell therapy in solid tumors.

8. Comparative Analysis

8.1 CAR-T vs TCR-T vs NK Cell Therapies

CAR-T, TCR-T and CAR-NK therapies differ mainly in antigen recognition, MHC dependence, persistence, allogeneic feasibility and toxicity profile. CAR-T targets surface antigens independently of MHC; TCR-T broadens the target space to intracellular peptide-MHC antigens but requires HLA matching; CAR-NK offers off-the-shelf potential and lower GvHD risk but shorter persistence. Table 3 summarizes these distinctions.

Table 3. Comparative characteristics of CAR-T, TCR-engineered T cells, and CAR-NK cell therapies for solid tumor applications.

Characteristic	CAR-T Cells	TCR-Engineered T Cells	CAR-NK Cells
Target antigen type	Cell-surface antigens (MHC-independent)	Intracellular & surface antigens (MHC-restricted peptide-MHC complexes)	Cell-surface antigens (MHC-independent; NKG2D ligands, ADCC)
MHC restriction	None — does not require antigen presentation on MHC	Strict — requires matched HLA haplotype for TCR recognition	None — exploits innate NK receptors independent of MHC
GvHD risk (allogeneic)	High without TCR deletion; requires TRAC/TRBC KO for allo use	Very high — intact TCR causes severe GvHD without deletion	Low — NK cells do not cause classical T-cell GvHD
In vivo persistence	Weeks to months; 4-1BB > CD28 for long-term memory	Weeks to months; memory T-cell persistence possible	Days to weeks — shorter than T cells; limits durability

Off-the-shelf feasibility	Limited (autologous standard); allogeneic platforms in Phase I	Very limited — HLA matching requirement restricts universality	High — iPSC-derived and cord-blood CAR-NK are scalable
Manufacturing complexity	High: leukapheresis, viral transduction, GMP expansion, cryopreservation	Very high: TCR cloning, T-cell culture, HLA matching, GMP	Moderate: cord blood/iPSC sources; non-viral transduction possible
Tumor lysis mechanism	CAR-directed cytotoxic killing; perforin/granzyme; cytokine release	TCR-directed perforin/granzyme B cytotoxicity; Fas-FasL	CAR-directed killing + natural cytotoxicity (NKG2D) + ADCC
Solid tumor clinical stage	Phase I–II (GBM, mesothelioma, GI, breast, ovarian, sarcoma)	Phase I–II (melanoma, colorectal KRAS G12D, sarcoma, lung)	Phase I (HCC, multiple myeloma, AML; early solid tumor data)
Key advantages	Potent in vivo expansion; established efficacy in hematologic malignancies; extensive synthetic biology toolkit	Broader antigen targeting incl. oncoproteins (KRAS, p53, AFP); validated in melanoma and CRC	No GvHD; immediate availability (off-the-shelf); dual innate + adaptive killing; resistance to TME immunosuppression
Key limitations	Antigen escape; TME suppression; CRS/ICANS toxicity; autologous manufacturing failure in ~5–20%	Strict HLA matching; MHC downregulation escape; no approved products; limited universal use	Short persistence; lower expansion capacity; limited solid tumor efficacy data; fewer engineered variants
Notable solid tumor trials	IL13Rα2 (GBM); Mesothelin (mesothelioma); CLDN18.2 (gastric); GD2 (neuroblastoma, TNBC)	KRAS G12D (CRC, NCT03745326); MAGE-A3 (melanoma, sarcoma); NY-ESO-1 (sarcoma, synovial)	GPC3 CAR-NK (HCC, NCT02891421); CD19 CAR-NK (B-cell malignancies, Phase I/II)
Regulatory status (solid tumors)	6 FDA-approved (hematologic only); no solid tumor approvals to date	No FDA approvals; IND filings ongoing; breakthrough designations pending	No approvals; investigational only; IND-stage solid tumor trials emerging

MHC = major histocompatibility complex; GvHD = graft-versus-host disease; NK = natural killer.

8.2 Advantages and Limitations of CAR-T in Solid Tumors

The potential benefits of CAR-T cell therapy in solid tumors are: tumor cell killing is MHC independent (might be useful in situations where the tumor cells have decreased expression of MHC class I), CAR-T cell therapy is feasible in solid tumor patients as evidenced by accumulating Phase I safety data, CAR-T cells could be expanded in vivo to result in a therapeutic amplification effect, and multiple synthetic gene

circuits can be engineered into a single cellular product. Challenges include manufacturing complexity and failure rates, antigen heterogeneity and escape, limited CAR-T durability in solid tumors versus hematologic malignancies, and the high expense and difficulty of autologous production, which limits access in resource-limited health care systems.

8.3 Translational Gaps from Bench to Bedside

Translation is limited by preclinical models that poorly reproduce human stromal, immune and antigenic complexity [65]. Additional barriers include absent validated predictive biomarkers and inconsistent response reporting across RECIST, iRECIST and immune-related criteria.

9. Future Directions and Research Opportunities

9.1 Next-Generation CAR Designs

The next generation of CAR constructs will move beyond static, constitutively active receptors toward dynamic, programmable cellular machines capable of contextual decision-making within the complex solid tumor environment. Sequential two-step tumor recognition with high specificity is achieved by using synthetic Notch (synNotch) receptor systems in which the expression of a second CAR or transgenic payload is induced upon recognition of a priming antigen [66]. Conceptually innovative strategies to control CAR activation to the tumor microenvironment are optogenetically controlled CARs that are activated in response to light irradiation at the tumor site, and hypoxia-sensitive or pH-sensitive CAR expression systems. Next-generation programmable CAR-T architectures will likely be built with circuit logic incorporating a number of receptor inputs, feedback regulators, and synthetic transcription factors.

9.2 Universal ("Off-the-shelf") CAR-T Therapies

The development of universally applicable allogeneic CAR T-cell products is among the most important commercially and clinically promising areas in the field. Several allogeneic platforms are in Phase I trials, such as TALEN- or CRISPR-edited donor TCR/HLA-depleted T cells, iPSC-derived T cells, and γδ T cells. To avoid NK-mediated elimination of HLA-depleted cells, the challenges of host rejection and limited persistence must be addressed by Bonaventura et al. and the allogeneic field as a whole; HLA class I deletion and expression of HLA-E or HLA-G can solve these problems [23]. The development of off-the-shelf CAR-T products that are effective and persist for long durations in solid tumors would change the future of cellular immunotherapy across the world by altering accessibility as well as the economic aspects of the treatment.

9.3 AI and Data-Driven CAR Design

AI may support CAR-T development through scFv optimization, multi-omic biomarker discovery, trial evidence surveillance, and matching antigen-CAR designs to tumor biology and patient immune profiles.

9.4 Personalized Immunotherapy Approaches

CAR-T treatment in solid tumors will become more and more personalized according to the tumor antigen type, immune contexture, and fitness profile of the tumor-infiltrating lymphocytes. Sequencing of tumor neoantigens in combination with HLA typing can be used to define tumor-specific neoantigens for individual patients, which are the perfect targets for CAR without the risk of on-target normal tissue toxicity or antigen escape. Ex vivo modeling of patient-specific TMEs might be used in organoid co-culture to assess the ability of CAR-T to attack a patient's tumor before clinical infusion. The quality of T-cells produced is being incorporated into predictive algorithms for clinical response, such as memory stem cell frequency, mitochondrial fitness, and exhaustion transcriptome signatures.

9.5 Ongoing Clinical Trials Landscape

As of the data cutoff for this review (May 2026), over 200 clinical trials evaluating CAR-T cell therapy in solid tumors were registered on ClinicalTrials.gov. The most actively investigated tumor types were GBM (n ≈ 45 trials), NSCLC (n ≈ 35), colorectal cancer (n ≈ 28), breast cancer (n ≈ 22), and ovarian cancer (n ≈ 18). Key ongoing pivotal-intent trials include: CLDN18.2 CAR-T (CT041) Phase II expansion in gastric cancer (NCT04404595); GD2-CAR-T in TNBC (NCT04245657); GPC3-CAR-T in hepatocellular carcinoma (NCT03884751); and IL13Rα2-targeted CAR-T in GBM (NCT04661384). Several basket trials enrolling multiple GD2- or mesothelin-expressing tumor types will generate cross-tumor type efficacy data and are expected to report Phase II data by 2026–2027.

10. Discussion

10.1 Synthesis of Key Findings

This systematic literature review (SLR) of 107 clinical studies of CAR-T cell therapy in solid malignancies includes the largest available evidence synthesis to date. The key conclusion is that CAR-T therapy for solid tumors is still at a turning point: While there is clear proof-of-concept for clinical activity in various tumor types and antigen targets, few unselected populations of patients treated with standard intravenous CAR-T therapy have yielded durable and reproducible objective responses, the hallmark of therapeutic success. Regional delivery of CAR-T cells, in combination with PD-1 blockade and targeting CLDN18.2 in gastric cancer, yielded the highest response rates, suggesting a common theme that the efficacy of CAR T cell therapy is dependent on an accessible antigen-rich tumor and a permissive/modulated microenvironment.

10.2 Theoretical and Clinical Implications

The results of this review suggest, from a theoretical perspective, that three barriers hinder successful CAR-T cell infiltration into solid tumors: (1) physical and anatomical barriers, (2) antigen and target selection barriers (insufficient or a heterogeneous expression of the target), and (3) tumor microenvironment (TME) mediated functional impairment (exhaustion of infiltrated CAR-T cells). Clinical implications include the changing trial design to regional delivery, the requirement for tumor biopsy and antigen quantification for selection of patients into the trial, the use of combo regimens including ICI + TME-modulating agents, and, finally, adaptive trial designs with early biologic endpoints (CAR-T expansion, antigen modulation, and cytokine kinetics) as decision points.

10.3 Critical Evaluation of Current Evidence

The evidence remains dominated by small early-phase single-arm trials with limited follow-up and heterogeneous response criteria. Comparative efficacy against standard care is still uncertain, although repeated evidence of trafficking, immune activation, and antigen modulation supports biological validity.

10.4 Limitations of Existing Studies

Some of the identified limitations across all included studies were: having small numbers of patients in each study (median 12 patients per study), short follow-up (median 6.4 months), no control arm in some studies, heterogeneous patient eligibility criteria, variable lymphodepletion regimens, CAR-T product characterization was not always standard, and inconsistent toxicity reporting (using pre-ASTCT grading systems in earlier studies). Limits of generalization due to underrepresentation of patients with poor performance status, prior cellular therapy, and CNS involvement. This geographical concentration of trials in the USA and China could be due to differences in healthcare infrastructure and regulation, and may

result in population-level biases in terms of antigen prevalence (such as expression rates of the CLDN18.2 gene between Asian and Western gastric cancer populations).

10.5 Limitations of This Review

This review is limited by heterogeneity that precluded meta-analysis, reliance on narrative synthesis, potential conference-abstract reporting bias, English-language restriction, and the rapidly evolving CAR-T evidence base.

11. Conclusion

CAR-T therapy in solid tumors is moving from proof-of-concept toward more clinically defined use. Biological activity is evident across glioblastoma, mesothelioma, gastric, pancreatic, ovarian, and other cancers, but durable objective responses remain difficult for most patients. The strongest signals involve regional delivery, CLDN18.2 targeting in gastric/GEJ cancer, and combinations with checkpoint blockade. Future progress will require precision antigen selection, dual or logic-gated CAR designs, improved persistence and metabolic fitness, rational TME modulation, standardized response/toxicity reporting, and adequately powered randomized trials. Clinical translation will depend less on single-product escalation and more on coordinated product design, patient selection, and delivery strategy.

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References

1. Maus MV, Levine BL. Chimeric antigen receptor T-cell therapy for the community oncologist. Oncologist. 2016;21(5):608-617. PMID: 27009942.
2. June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med. 2018;379(1):64-73. PMID: 29972754.
3. Lim WA, June CH. The principles of engineering immune cells to treat cancer. Cell. 2017;168(4):724-740. PMID: 28187291.
4. 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):439-448. PMID: 29385370.
5. 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):2531-2544. PMID: 29226797.
6. 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):705-716. PMID: 33626253.
7. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. CA Cancer J Clin. 2021;71(3):209-249. PMID: 33538338.
8. Newick K, O'Brien S, Moon E, Albelda SM. CAR T cell therapy for solid tumors. Mol Ther Oncolytics. 2016;3:16006. PMID: 27162934.

9. Brown CE, Badie B, Barish ME, Weng L, Ostberg JR, Chang WC, et al. Bioactivity and safety of IL13Ralpha2-targeted CAR T cells in patients with recurrent glioblastoma. Clin Cancer Res. 2016;22(13):3189-3197. PMID: 26847058.
10. Beatty GL, Haas AR, Maus MV, Torigian DA, Soulen MC, Plesa G, et al. Mesothelin-specific chimeric antigen receptor mRNA-engineered T cells induce antitumor activity in solid malignancies. Clin Cancer Res. 2018;24(6):1277-1287. PMID: 29101200.
11. O'Rourke DM, Nasrallah MP, Desai A, Melenhorst JJ, Mansfield K, Morrissette JJD, et al. 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(399):eaaa0984. PMID: 28794024.
12. Morgan RA, Yang JC, Kitano M, Dudley ME, Laurencot CM, Rosenberg SA. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. Mol Ther. 2010;18(4):843-851. PMID: 20179677.
13. Majzner RG, Mackall CL. Tumor antigen escape from CAR T-cell therapy. Nat Med. 2018;24(10):1491-1499. PMID: 30202020.
14. Fedorov VD, Themeli M, Sadelain M. PD-1- and CTLA-4-based inhibitory chimeric antigen receptors (iCARs) divert off-target immunotherapy responses. Sci Transl Med. 2013;5(215):215ra172. PMID: 24225990.
15. Fonkoua LAK, Sirpilla O, Sakemura R, Siegler EL, Kenderian SS. CAR T cell therapy and the tumor microenvironment: current challenges and opportunities. Mol Ther Oncolytics. 2022;25:69-77. PMID: 35434273.
16. Rafiq S, Hackett CS, Brentjens RJ. Engineering strategies to overcome the current roadblocks in CAR T cell therapy. Nat Rev Clin Oncol. 2020;17(3):147-167. PMID: 31873190.
17. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol. 2015;15(8):486-499. PMID: 26205583.
18. Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science. 2015;348(6230):74-80. PMID: 25838376.
19. Chmielewski M, Abken H. TRUCKs: the fourth generation of CARs. Cancer Immunol Res. 2015;3(2):121-125. PMID: 25632016.
20. Srour SA, Singh H, McCarty J, de Lima M, Hosing CM, Kebriaei P. Chimeric antigen receptor T-cell therapy for solid tumors. Curr Hematol Malig Rep. 2022;17(2):45-55. PMID: 36751657.
21. Eyquem J, Mansilla-Soto J, Giavridis T, van der Stegen SJ, Hamieh M, Cunanan KM, et al. Targeting a CAR to the TRAC locus with CRISPR/Cas9 enhances tumor rejection. Nature. 2017;543(7643):113-117. PMID: 28225754.
22. 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. Blood. 2017;129(8):1039-1041. PMID: 27903549.
23. Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. 'Off-the-shelf' allogeneic CAR T cells: development and challenges. Nat Rev Drug Discov. 2020;19(3):185-199. PMID: 31942074.
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. PMID: 33782057.

25. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020;368:l6890. PMID: 31948937.
26. Dotti G, Gottschalk S, Savoldo B, Brenner MK. Design and development of therapies using chimeric antigen receptor-expressing T cells. Immunol Rev. 2014;257(1):107-126. PMID: 24329793.
27. Alabanza L, Pegues M, Geldres C, Shi V, Wiltzius JJW, Sievers SA, et al. Function of novel anti-CD19 chimeric antigen receptors with human variable regions is affected by hinge and transmembrane domains. Mol Ther. 2017;25(11):2452-2465. PMID: 28757376.
28. Imai C, Mihara K, Andreansky M, Nicholson IC, Pui CH, Geiger TL, et al. Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia. Leukemia. 2004;18(4):676-684. PMID: 14961035.
29. Hassan R, Kindler HL, Jahan T, Bazhenova L, Reck M, Thomas A, et al. Phase II clinical trial of amatuximab, a chimeric anti-mesothelin antibody with pemetrexed and cisplatin in advanced unresectable pleural mesothelioma. Clin Cancer Res. 2014;20(23):5927-5936. PMID: 25266132.
30. Louis CU, Savoldo B, Dotti G, Pule M, Yvon E, Myers GD, et al. Antitumor activity and long-term fate of chimeric antigen receptor-positive T cells in patients with neuroblastoma. Blood. 2011;118(23):6050-6056. PMID: 21984804.
31. Lamers CH, Sleijfer S, van Steenbergen S, van Elzakker P, van Krimpen B, Groot C, et al. Treatment of metastatic renal cell carcinoma with CAIX CAR-engineered T cells: clinical evaluation and management of on-target toxicity. Mol Ther. 2013;21(4):904-912. PMID: 23399988.
32. Levine BL, Miskin J, Wonnacott K, Keir C. Global manufacturing of CAR T cell therapy. Mol Ther Methods Clin Dev. 2017;4:92-101. PMID: 28344995.
33. Brentjens RJ, Davila ML, Riviere I, Park J, Wang X, Cowell LG, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Sci Transl Med. 2013;5(177):177ra38. PMID: 23515080.
34. Sommermeyer D, Hudecek M, Kosasih PL, Gogishvili T, Maloney DG, Turtle CJ, et al. Chimeric antigen receptor-modified T cells derived from defined CD8+ and CD4+ subsets confer superior antitumor reactivity in vivo. Leukemia. 2016;30(2):492-500. PMID: 26369987.
35. Caldwell KJ, Gottschalk S, Talleur AC. Allogeneic CAR cell therapy-more than a pipe dream. Front Immunol. 2020;11:618427. PMID: 33488626.
36. Katz SC, Burga RA, McCormack E, Wang LJ, Mooring W, Point GR, et al. Phase I hepatic immunotherapy for metastases study of intra-arterial chimeric antigen receptor-modified T-cell therapy for CEA+ liver metastases. Clin Cancer Res. 2015;21(14):3149-3159. PMID: 25840967.
37. Thistlethwaite FC, Gilham DE, Guest RD, Rothwell DG, Pillai M, Burt DJ, et al. The clinical efficacy of first-generation carcinoembryonic antigen (CEACAM5)-specific CAR T cells is limited by poor persistence and transient pre-conditioning-dependent respiratory toxicity. Cancer Immunol Immunother. 2017;66(11):1425-1436. PMID: 28779197.
38. Zhan X, Wang B, Li Z, Li J, Wang H, Chen L, et al. Phase I trial of Claudin 18.2-specific chimeric antigen receptor T cells for advanced gastric and pancreatic adenocarcinoma. J Clin Oncol. 2023;41(31):4790-4799. PMID: 36972487.
39. Shi T, Ye G, Zhao S, Zhang H, Zhang Y, Dong H, et al. Pancreatic ductal adenocarcinoma: an overview of risk factors, diagnosis, treatment, and prognosis. Front Oncol. 2022;12:1018698.

40. Stromnes IM, Schmitt TM, Hulbert A, Brockenbrough JS, Nguyen HN, Cuevas C, et al. T cells engineered against a native antigen can surmount immunologic and physical barriers to treat pancreatic ductal adenocarcinoma. Cancer Cell. 2015;28(5):638-652. PMID: 26525103.
41. Feng K, Guo Y, Dai H, Wang Y, Li X, Jia H, et al. 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(5):468-479. PMID: 27037062.
42. Adusumilli PS, Zauderer MG, Riviere I, Solomon SB, Rusch VW, O'Cearbhaill RE, et al. A Phase I trial of regional mesothelin-targeted CAR T-cell therapy in patients with malignant pleural disease, in combination with the anti-PD-1 agent pembrolizumab. Cancer Discov. 2021;11(11):2748-2763. PMID: 34266984.
43. Slovin SF, Wang X, Hullings M, Arauz G, Bartido S, Lewis JS, et al. Chimeric antigen receptor (CAR+) modified T cells targeting prostate-specific membrane antigen (PSMA) in patients with castrate metastatic prostate cancer. J Clin Oncol. 2013;31(6 suppl):72.
44. Tanyi JL, Stashwick C, Plesa G, Morgan MA, Porter D, Maus MV, et al. Possible compartmental cytokine syndrome in a patient with recurrent ovarian cancer after treatment with mesothelin-targeted CAR-T cells. J Immunother. 2017;40(3):104-107. PMID: 28177942.
45. Song DG, Ye Q, Poussin M, Chieloha LL, Bhatt DL, June CH, et al. Effective adoptive immunotherapy of triple-negative breast cancer by folate receptor-alpha redirected CAR T cells is influenced by surface antigen expression level. J Hematol Oncol. 2016;9(1):56. PMID: 27400961.
46. Ahmed N, Brawley VS, Hegde M, Robertson C, Ghazi A, Gerken C, et al. 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(15):1688-1696. PMID: 25800761.
47. Du H, Hirabayashi K, Ahn S, Kren NP, Montgomery SA, Wang X, et al. Antitumor responses in the absence of toxicity in solid tumors by targeting B7-H3 via chimeric antigen receptor T cells. Cancer Cell. 2019;35(2):221-237. PMID: 30753825.
48. Pule MA, Savoldo B, Myers GD, Rossig C, Russell HV, Dotti G, et al. Virus-specific T cells engineered to coexpress tumor-specific receptors: persistence and antitumor activity in individuals with neuroblastoma. Nat Med. 2008;14(11):1264-1270. PMID: 18978797.
49. Deng Z, Wu Y, Ma W, Zhang S, Zhang YQ. Adoptive T-cell therapy of prostate cancer targeting the cancer stem cell antigen EpCAM. BMC Immunol. 2015;16:1. PMID: 25603796.
50. Mariathasan S, Turley SJ, Nickles D, Castiglioni A, Yuen K, Wang Y, et al. TGFbeta attenuates tumor response to PD-L1 blockade by contributing to exclusion of T cells. Nature. 2018;554(7693):544-548. PMID: 29443960.
51. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. Immunity. 2014;41(1):49-61. PMID: 25035953.
52. Veglia F, Perego M, Gabrilovich D. Myeloid-derived suppressor cells coming of age. Nat Immunol. 2018;19(2):108-119. PMID: 29348500.
53. Harlin H, Meng Y, Peterson AC, Zha Y, Tretiakova M, Slingluff C, et al. Chemokine expression in melanoma metastases associated with CD8+ T-cell recruitment. Cancer Res. 2009;69(7):3077-3085. PMID: 19293190.
54. Semenza GL. Oxygen sensing, hypoxia-inducible factors, and disease pathophysiology. Annu Rev Pathol. 2014;9:47-71. PMID: 23937341.

55. Chang CH, Qiu J, O'Sullivan D, Buck MD, Noguchi T, Curtis JD, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. Cell. 2015;162(6):1229-1241. PMID: 26321679.
56. Scharping NE, Rivadeneira DB, Zavareh RB, Menk AV, Halberg N, Bhatt D, et al. Mitochondrial stress induced by continuous stimulation under self-renewal conditions drives T cell exhaustion. Nat Immunol. 2021;22(2):205-215. PMID: 33398183.
57. Frey NV, Porter DL. Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2016;2016(1):567-572. PMID: 27913536.
58. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638. PMID: 30592986.
59. Hegde M, Mukherjee M, Grada Z, Pignata A, Landi D, Navai SA, et al. Tandem CAR T cells targeting HER2 and IL13Ra2 mitigate tumor antigen escape. J Clin Invest. 2016;126(8):3036-3052. PMID: 27427982.
60. Koneru M, Purdon TJ, Spriggs D, Koneru S, Brentjens RJ. IL-12 secreting tumor-targeted chimeric antigen receptor T cells eradicate ovarian tumors in vivo. Oncoimmunology. 2015;4(3):e994446. PMID: 25949878.
61. Bernstein MB, Krishnan S, Hodge JW, Chang JY. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? Nat Rev Clin Oncol. 2016;13(8):516-524. PMID: 27217171.
62. Watanabe K, Lim WA. Engineering T cells to overcome barriers in solid tumors. Trends Immunol. 2021;42(1):7-9.
63. Stadtmauer EA, Fraietta JA, Davis MM, Cohen AD, Weber KL, Lancaster E, et al. CRISPR-engineered T cells in patients with refractory cancer. Science. 2020;367(6481):eaba7365. PMID: 32029687.
64. Parayath NN, Stephan SB, Koehne AL, Nelson PS, Stephan MT. In vitro-transcribed antigen receptor mRNA nanocarriers for transient expression in circulating T cells in vivo. Nat Commun. 2020;11(1):6080. PMID: 33250483.
65. Eil R, Vodnala SK, Clever D, Klebanoff CA, Sukumar M, Pan JH, et al. Ionic immune suppression within the tumor microenvironment limits T cell effector function. Nature. 2016;537(7621):539-543. PMID: 27626381.
66. Roybal KT, Rupp LJ, Morsut L, Walker WJ, McNally KA, Park JS, et al. Precision tumor recognition by CAR T cells through combination of antigen-sensing and cytokine-triggered killing. Cell. 2016;164(4):770-779. PMID: 26830879.
67. Brown CE, Hibbard JC, Alizadeh D, Blanchard MS, Natri HM, Wang D, et al. Locoregional delivery of IL-13Rα2-targeting CAR-T cells in recurrent high-grade glioma: a phase 1 trial. Nat Med. 2024;30(4):1001-1012. doi: 10.1038/s41591-024-02875-1. PMID: 38454126.
68. Qi C, Liu C, Peng Z, Zhang Y, Wei J, Qiu W, et al. Claudin-18 isoform 2-specific CAR T-cell therapy (satri-cel) versus treatment of physician's choice for previously treated advanced gastric or gastroesophageal junction cancer (CT041-ST-01): a randomised, open-label, phase 2 trial. Lancet. 2025;405(10494):2049-2060. PMID: 40460847.

69. Bagley SJ, Logun M, Fraietta JA, Wang X, Desai AS, Bagley LJ, et al. Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrent glioblastoma: phase 1 trial interim results. Nat Med. 2024;30(5):1320-1329. doi: 10.1038/s41591-024-02893-z. PMID: 38480922.
70. Bagley SJ, Desai AS, et al. Intracerebroventricular bivalent CAR T cells targeting EGFR and IL-13Rα2 in recurrent glioblastoma: a phase 1 trial. Nat Med. 2025;31(8):2778-2787. PMID: 40451950.
71. Vitanza NA, Ronsley R, Choe M, Seidel K, Huang W, Rawlings-Rhea SD, et al. Intracerebroventricular B7-H3-targeting CAR T cells for diffuse intrinsic pontine glioma: a phase 1 trial. Nat Med. 2025;31(3):861-868. PMID: 39775044.
72. Gao Y, Li J, Zhang H, Zhang Y, Qian S, Zhu X, et al. Hypoxia-responsive CEA-targeted CAR T cells in CEA-positive solid tumors through intraperitoneal or intravenous infusion: a phase 1 trial. Nat Cancer. 2026;7(4):608-621. PMID: 41760800.