

Clinical Trial Landscape of CAR-engineered Cell Therapies in Renal Cell Carcinoma: Current Status and Future Directions

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Abstract

Renal cell carcinoma (RCC) is a common urologic malignancy with poor outcomes in metastatic disease, despite advances in targeted therapies and immune checkpoint inhibitors. Chimeric antigen receptor (CAR)-engineered cell therapies, particularly CAR-T and CAR-natural killer (CAR-NK) cells, have revolutionized the treatment of hematologic malignancies, but face unique barriers in solid tumors such as RCC, including tumor heterogeneity and an immunosuppressive microenvironment. Using the Trialstrove database with the keywords "CAR" and "oncology: kidney," we identified 44 eligible interventional trials as of June 10, 2025. Most are early-phase and industry-sponsored, and are conducted primarily in China and the United States. CAR-T studies outnumber CAR-NK trials, with cluster of differentiation 70 as the most common target, followed by estimated glomerular filtration rate and programmed cell death protein 1. Combination regimens frequently incorporate lymphodepletion with cyclophosphamide and fludarabine. Preliminary clinical data indicate that CAR therapies for RCC are generally safe and feasible but show limited durable efficacy. Key obstacles include antigen escape and poor persistence of infused cells within the tumor microenvironment. To overcome these challenges, next-generation strategies—such as dual-target CAR constructs, cytokine co-expression (e.g., interleukin-15), and biomarker-guided patient selection—are actively being explored. Regulatory frameworks in the United States and China increasingly support innovation in cellular therapies. Overall, the evolving clinical landscape highlights both the promise and the ongoing challenges of CAR-engineered therapies for RCC, underscoring the need for optimized designs and rational combination approaches to improve patient outcomes.

Keywords: Renal cell carcinoma, CAR-T therapy, CAR-NK therapy, clinical trials, immunotherapy, targeted antigens

Introduction

Renal cell carcinoma (RCC) is the most common malignant tumor of the kidney, originating from the renal tubular epithelium. It accounts for 85–90% of renal malignancies and approximately 2–3% of all solid tumors, with clear cell carcinoma representing the predominant histological subtype (about 70–80%) (1,2). Epidemiological studies show a steady global increase in RCC incidence. According to GLOBOCAN 2020, there are approximately 430,000 new cases and 180,000 deaths annually worldwide, with the highest incidence reported in North America and Europe. In the United States, approximately 80,000 new cases are diagnosed annually. RCC occurs about twice as often in men as in women, and incidence peaks between the ages of 50 and 70 (3).

In China, the incidence of RCC has also risen markedly, with an estimated 70,000–80,000 new cases and approximately 30,000 deaths annually. Among urinary tract malignancies, it ranks second only to bladder cancer and is more prevalent in urban and economically developed regions (4). Established risk factors include smoking, obesity, hypertension, chronic kidney disease, including dialysis, occupational exposures (e.g., cadmium, asbestos, organic solvents), and hereditary syndromes such as von Hippel-Lindau (VHL) disease (5). The widespread adoption of imaging technologies has resulted in increased incidental detection of RCC at earlier stages. For localized RCC, surgical resection can achieve a 5-year survival rate of 70–90%. However, the prognosis for patients with advanced or metastatic disease remains poor, with 5-year survival below 20%. Historically, surgical resection was the only curative

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option, while radiotherapy and chemotherapy offered minimal benefit (6).

The therapeutic landscape changed with the advent of tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor (VEGF) pathway (6,7), followed by the development of immune checkpoint inhibitors (ICIs) directed at programmed cell death protein 1 (PD-1)/PD-ligand 1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Combination regimens involving ICIs and TKIs have since become the standard of care (8,9). More recently, chimeric antigen receptor (CAR)-engineered cell therapies—particularly CAR-T and CAR-natural killer (CAR-NK) cells—have transformed the treatment paradigm for hematologic malignancies (10). Nonetheless, their application to solid tumors such as RCC is hindered by challenges including tumor heterogeneity, an immunosuppressive microenvironment, and difficulties in antigen selection (11,12).

To better define current progress and unmet needs, we analyzed the clinical trial landscape of CAR-engineered therapies in RCC. A comprehensive review was conducted using the *Trialtrove* clinical trial database—the world's largest curated trial repository, encompassing more than 450,000 data sources and over 350,000 global studies. The search strategy used the keywords "chimeric antigen receptor" and "oncology: kidney", with a cut-off date of June 10, 2025. Eligible studies were interventional trials explicitly investigating CAR-T or CAR-NK cell therapies for RCC. Trials without explicit CAR engineering or those with non-interventional designs were excluded. Parameters assessed included temporal trends, trial phase and status, targeted antigens, therapy type (CAR-T vs. CAR-NK), combination regimens, sponsorship, and geographic distribution. Data extraction accuracy was independently validated by multiple reviewers.

1. Treatment Landscape of RCC and Rationale for CAR-based Immunotherapy

RCC is traditionally managed with surgery. Partial nephrectomy is preferred for small, localized tumors to preserve renal function, while radical nephrectomy is reserved for larger or more complex tumors. For frail patients or patients with very small lesions, active surveillance or minimally invasive ablation (cryoablation, radiofrequency ablation) is appropriate. According to the 2025 European Association of Urology guidelines, surgery remains the mainstay in localized disease, with nephron-sparing approaches prioritized when feasible (13).

The advent of systemic therapy has reshaped the management of advanced and metastatic RCC. ICIs—alone or combined with VEGF/TKIs—are now first-line standards of care, exemplified by nivolumab plus ipilimumab or pembrolizumab plus axitinib, which have shown superior survival compared with sunitinib in randomized trials (9,14). Targeted VEGF and mechanistic

target of rapamycin inhibitors remain options for selected patients. Nevertheless, many individuals experience primary resistance or eventual relapse, highlighting the limits of current immunotherapy.

VHL-associated RCC follows a similar paradigm: surveillance and nephron-sparing surgery remain key, and the hypoxia-inducible factor-2 α inhibitor belzutifan offers a new systemic option, showing durable responses in VHL-associated RCC, including tumor shrinkage in early clinical studies (15). Yet, even with these advances, durable control of progressive disease remains uncommon, underscoring the need for novel immunotherapeutic approaches.

CAR-engineered cell therapies—including CAR-T and CAR-NK cells—directly redirect lymphocytes to tumor-associated antigens, potentially overcoming checkpoint resistance and the immunosuppressive tumor microenvironment (TME). Recent preclinical and early clinical evidence shows promise: cluster of differentiation 70 (CD70) is highly expressed in many RCC tumors and has been targeted successfully by novel CAR-T constructs, with CTX130 (allogeneic CD70-targeting CAR-T) achieving disease control in the majority of advanced/refractory clear cell RCC (ccRCC) patients and at least one durable complete response lasting 3 years (16). Early work has also explored dual-targeted CARs [e.g., carbonic anhydrase IX (CAIX) + CD70] to address antigen heterogeneity. These next-generation, highly personalized therapies aim to address the central challenge of immune evasion in RCC and represent a logical extension of current immunotherapy strategies.

2. Principles of CAR-T and CAR-NK Therapies

2.1. Principles of CAR-T Therapy

CAR-T therapy is a novel form of adoptive cell transfer that involves genetically modifying autologous T-cells to express CARs. These synthetic receptors enable T-cells to recognize and eliminate tumor-associated antigens independently of the major histocompatibility complex (11).

2.1.1. CAR Structure and Design

A CAR comprises several modular domains: an extracellular single-chain variable fragment (scFv) for antigen recognition; a hinge region linking the scFv to the transmembrane domain; a transmembrane domain anchoring the receptor to the T-cell membrane; and intracellular signaling domains. The latter include co-stimulatory domains [e.g., CD28, CD137 (4-1BB)] and the CD3 zeta (CD3 ζ) activation domain, which together transmit signals that drive T-cell proliferation and cytotoxic function (Figure 1A) (17). First-generation CARs contained only the CD3 ζ signaling domain. These receptors showed limited T-cell activation and persistence due to the absence of co-stimulation. Second-

generation CARs added a single co-stimulatory domain (e.g., CD28 or 4-1BB), which significantly enhanced T-cell activation, persistence, and antitumor activity (10). Third-generation CARs incorporated two co-stimulatory domains, further improving T-cell function and durability. Fourth-generation CARs ("armored" CARs) engineered to secrete cytokines [e.g., interleukin (IL)-12, IL-15] or express chemokine receptors, thereby enhancing persistence, infiltration, and independence from host immune support (Figure 1B) (11).

2.1.2. Manufacturing Process

Cell Collection: T-cells are obtained from patients, typically via leukapheresis (18).

Genetic Modification: Genes encoding the CAR construct are introduced using viral vectors (e.g., lentivirus, γ -retrovirus) or non-viral methods such as transposon systems (10).

In Vitro Expansion: The engineered T-cells are stimulated and expanded *ex vivo* to achieve the therapeutic cell dose (18).

Patient Reinfusion: The expanded CAR-T-cells are administered to the patient by intravenous infusion (Figure 2) (18).

2.1.3. Mechanism of Action

Antigen Recognition: CAR-T-cells identify tumor-specific antigens via their scFv domain (17).

T-cell Activation: Antigen binding triggers signaling through the co-stimulatory and CD3 ζ domains, promoting proliferation and cytokine secretion (19).

Tumor Killing: Activated CAR-T-cells destroy tumor cells by releasing perforin and granzymes, while also secreting pro-inflammatory cytokines [e.g., interferon (IFN)- γ , tumor necrosis factor (TNF)- α] that recruit and activate additional immune cells (19).

2.2. Principles of CAR-NK Therapy

CAR-NK therapy applies similar engineering strategies to NK cells, exploiting their intrinsic ability to kill tumor cells via both antigen-dependent and antigen-independent mechanisms (20).

2.2.1. NK Cell Sources

CAR-NK cells can be derived from multiple sources, including peripheral blood, umbilical cord blood, or induced pluripotent stem cells (iPSCs). These diverse origins support the potential for "off-the-shelf" allogeneic applications (21).

2.2.2. CAR Structure and Design

Like CAR-T-cells, CAR-NK constructs feature an antigen-binding domain (scFv), a hinge and a transmembrane domain, and intracellular signaling modules. For NK cells, co-stimulatory

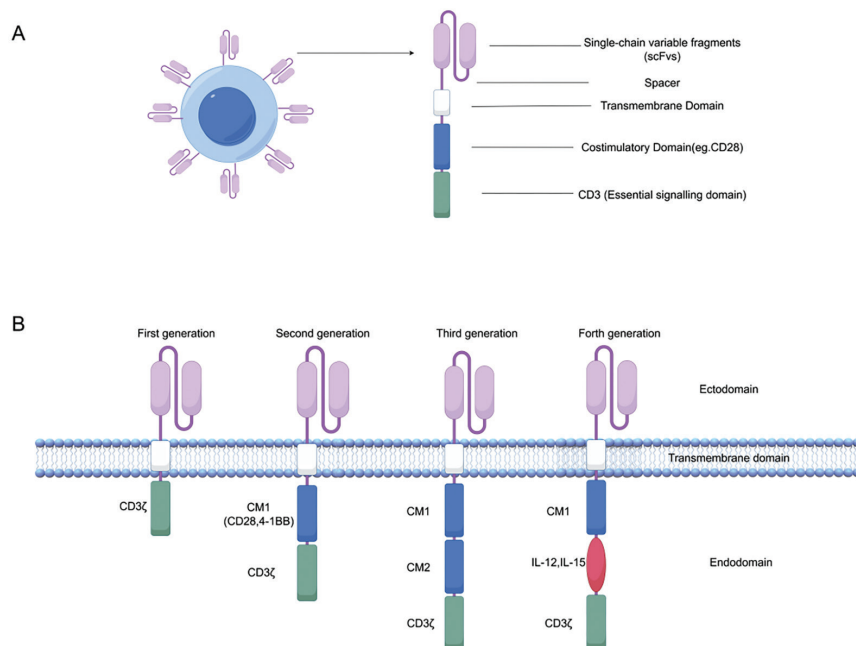


Figure 1. CAR structure domains and generational evolution. (A) The basic structure of a CAR, consisting of an antigen-binding domain (single-chain variable fragment, scFv), a spacer/hinge region, a transmembrane domain, and intracellular signaling domains. (B) The generational evolution of CAR designs: first-generation CARs contain only the CD3 ζ activation domain; second-generation CARs incorporate one costimulatory domain (e.g., CD28 or 4-1BB), enhancing persistence and activity; third-generation CARs combine multiple costimulatory domains for amplified signaling; and fourth-generation CARs (also called "armored" CARs) are based on second-generation constructs and engineered to express cytokines (e.g., IL-12, IL-15) or other molecules to modulate the tumor microenvironment and improve efficacy

CAR: Chimeric antigen receptor, scFv: Single-chain variable fragment, CD: Cluster of differentiation, IL: Interleukin

and activation domains tailored to their biology include DNAX-activating protein 10 (DAP10), DAP12, and CD3 ζ .

2.2.3. Manufacturing Process

Cell Collection and Isolation: NK cells are isolated from peripheral blood, cord blood, or iPSCs (22).

Genetic Modification: CAR genes are introduced using viral vectors or non-viral approaches such as transposons (20).

In Vitro Expansion: Modified NK cells are expanded *ex vivo* to reach therapeutic numbers (22).

Patient Reinfusion: Expanded CAR-NK cells are infused intravenously (22).

2.2.4. Mechanism of Action

Antigen Recognition: CAR-NK cells engage tumor-specific antigens via the scFv domain.

NK Cell Activation: Signal transduction through co-stimulatory and activation domains promotes NK cell proliferation and cytokine secretion (21).

Tumor Killing: Activated CAR-NK cells eliminate tumor cells through perforin- and granzyme-mediated cytotoxicity, cytokine release (e.g., IFN- γ , TNF- α), and apoptosis-inducing pathways via death receptor ligands such as Fas ligand and

tumor necrosis factor-related apoptosis-inducing ligand (Figure 2) (23).

3. CAR-T and CAR-NK Therapies in RCC

3.1. Current Status of CAR-engineered Cell Therapy Clinical Studies in RCC

A systematic review of the Trialtrave database was conducted on June 10, 2025, using search terms related to CAR-engineered cell therapies and RCC. This search identified 44 interventional trials meeting the inclusion criteria. Studies lacking CAR engineering or employing non-interventional designs were excluded. Temporal analysis revealed a steady increase in the number of trial initiations from 2010 (n=1) to a peak in 2023 (n=9), followed by a modest decline (Figure 3A).

3.2. Trial Phases and Design

Most trials are early-phase (Phase I or Phase I/II) (Figure 3B), reflecting the exploratory nature of CAR-based therapy in solid tumors. These studies primarily evaluate safety, tolerability, and dose escalation to define the maximum tolerated dose and recommended Phase II dose, and collect preliminary efficacy signals such as objective response rate (ORR), duration of response, and progression-free survival. No Phase III trials

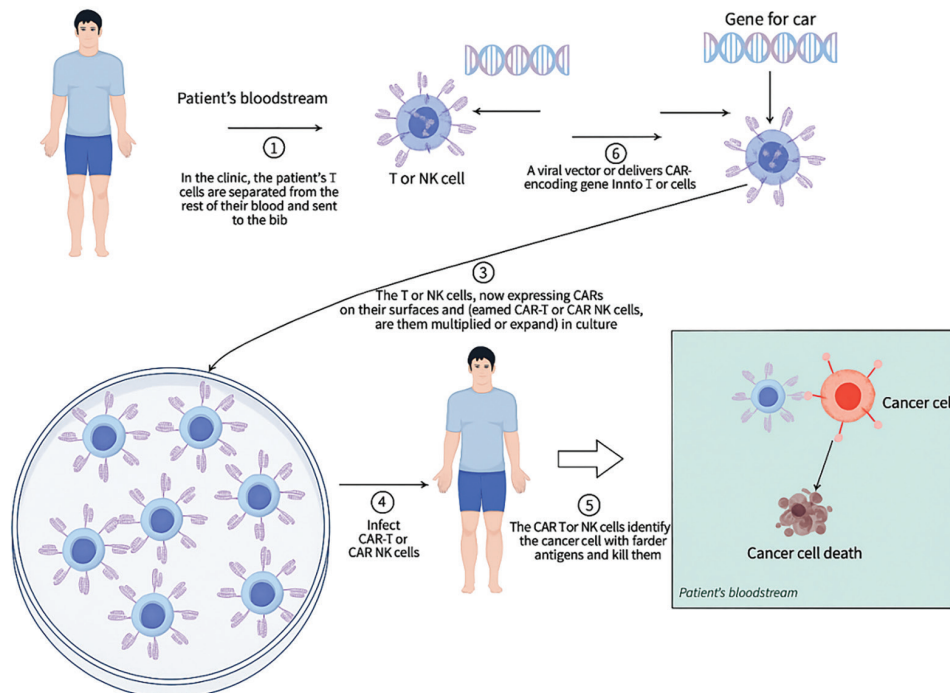


Figure 2. Schematic diagram of the CAR-T or CAR-NK cell therapy process. This figure outlines the key steps of CAR-T or CAR-NK cell therapy: (1) T or NK cells are isolated from the patient's blood; (2) a viral vector is used to deliver the chimeric antigen receptor (CAR) gene into the T or NK cells in the laboratory; (3) CAR-expressing T or NK cells are expanded in culture; (4) CAR-T or CAR-NK cells are infused into the patient; (5) CAR-expressing cells recognize and kill cancer cells by binding to target antigens; (6) cancer cell death subsequently occurs

CAR: Chimeric antigen receptor, NK: Natural killer

have yet been initiated, underscoring the need to demonstrate superiority over current standards—TKIs and ICI—before large-scale randomized evaluation.

A representative example is the multicenter TRAVERSE phase 1a/b trial (NCT04696731), which is testing the allogeneic anti-CD70 CAR-T product ALLO-316 in advanced ccRCC after failure of ICI and VEGF inhibitor therapy (24). At a median follow-up of 6.8 months, the ORR was 20% in CD70-positive patients and 25% in patients with $\geq 50\%$ CD70 expression; all confirmed responses were ongoing at data cut-off. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were mostly mild, and no Graft-versus-host disease (GvHD) occurred, underscoring a manageable safety profile. Other early-phase candidates include CTX-131 and ADI-

270 (CD70-directed), IOMX-0675 (anti-LILRB1/2), and next-generation constructs targeting PD-1, VEGF receptor (VEGFR), CAIX, and c-mesenchymal-epithelial transition factor (c-MET).

3.3. Integration of CAR-NK Platforms

Alongside CAR-T, CAR-NK therapies are emerging as a complementary approach, combining innate cytotoxicity with reduced risk of GvHD. Nearly all ongoing CAR-NK trials are Phase I or I/II and are primarily led by academic centers in China (Figure 3C). Platforms include umbilical cord blood-derived CAR-NK cells (CB-NK), CAR-NKT cells, and the NK-92 cell line, with targets mirroring CAR-T efforts, notably CD70, and extending to NKG2D ligands. Despite small sample sizes and occasional program discontinuations (e.g., fate therapeutics' FT-536), these

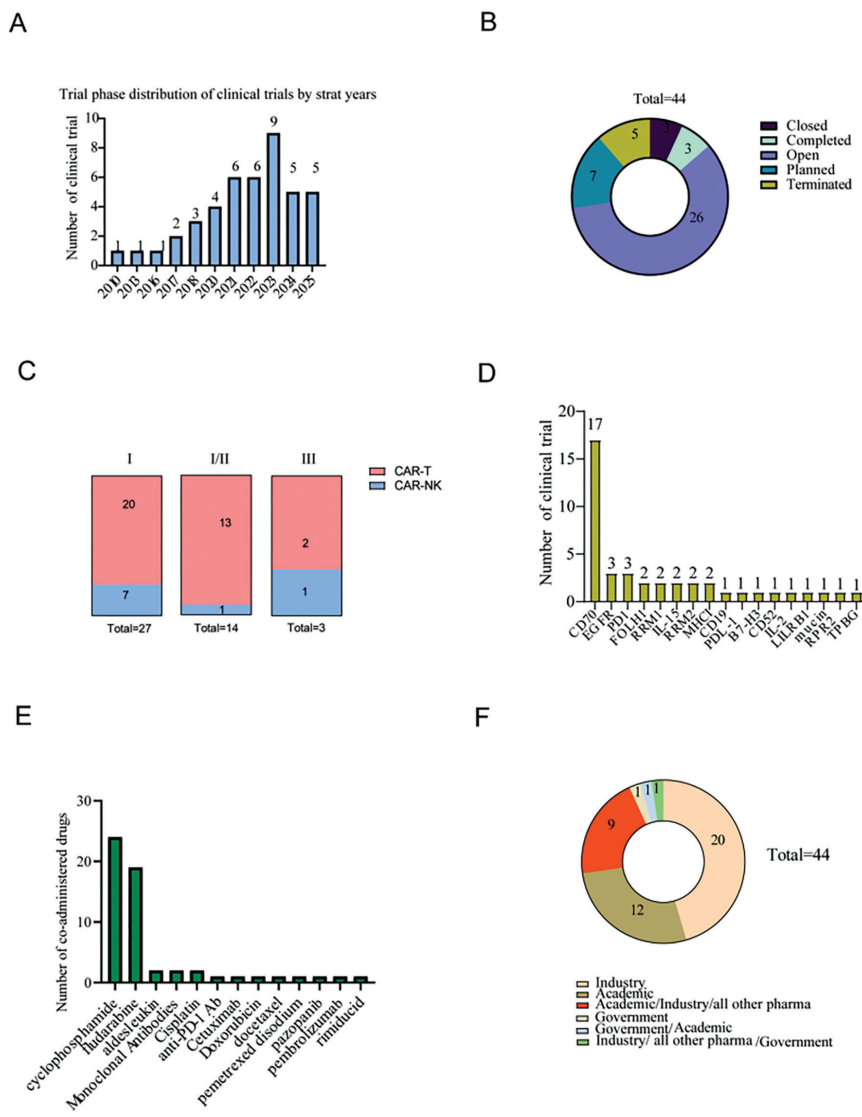


Figure 3. The Clinical Trial landscape of CAR-engineered cell therapies for renal cell carcinoma. (A) Number of trials by start year; (B) trial status distribution; (C) distribution of CAR-T versus CAR-NK trails by clinical phase; (D) number of trials per antigen target; (E) frequency of each co-administered drug with CAR cells; (F) sponsor type distribution

CAR: Chimeric antigen receptor, NK: Natural killer

studies provide important proof-of-concept evidence for NK-based engineering in RCC.

3.4. Antigen Targets and Technological Innovations

Antigen Spectrum (Figure 3D): CD70 is the dominant and most promising antigen (n=17), owing to high expression in ccRCC and minimal expression in normal tissue. Other exploratory targets include B7-H3 (CD276), estimated glomerular filtration rate, prostate-specific membrane antigen, human leukocyte antigen G, VEGFR, CAIX, and c-Met, reflecting diversification beyond CD70.

Technological Platforms: Allogeneic CAR constructs (e.g., ALLO-316, MT-027) shorten manufacturing timelines and reduce cost compared with autologous approaches. Logic-gated CAR designs (for example, A2B-395, which contains a tumor-specific "switch") enhance on-target safety.

Combination Strategies (Figure 3E): Many trials pair CAR cells with checkpoint inhibitors (e.g., pembrolizumab) or with lymphodepleting chemotherapy (cyclophosphamide and fludarabine) to improve CAR-cell persistence and antitumor efficacy.

3.5. Sponsorship and Geographic Landscape

Industry-led trials (n=20) outpace those sponsored by academic institutions (n=12) or mixed collaborations, highlighting robust commercial investment (Figure 3F). China and the United States dominate the global landscape, with Chinese cities such as Shanghai, Chongqing, and Shenzhen emerging as development hubs.

3.6. Key Findings and Challenges

Across both CAR-T and CAR-NK modalities, safety profiles are acceptable, with CRS generally mild; however, efficacy remains modest, with low-to-moderate ORRs and infrequent durable remissions. Major biological barriers include antigen escape, limited CAR-cell tumor infiltration, and a TME.

Overall, CAR-engineered cell therapy in RCC is transitioning from conceptual promise to early clinical reality. While CAR-T trials currently dominate and provide the most robust preliminary efficacy data, CAR-NK programs broaden the therapeutic horizon, potentially offering advantages in off-the-shelf availability, reduced cost, and enhanced safety. Overcoming the hostile TME, improving persistence, and achieving durable responses prior to Phase III validation and eventual clinical adoption.

3.7. Key Clinical Trial Results

Two landmark Phase I trials have defined the current clinical landscape of CD70-targeted CAR therapies in RCC.

The TRAVERSE trial (NCT04696731) evaluated ALLO-316 (allogeneic anti-CD70 CAR-T) in patients with CD70-positive metastatic ccRCC who had progressed on ICI and VEGF inhibitors. At a median follow-up of 6.8 months, an ORR of 33% was achieved in CD70-positive patients, with a disease control rate (DCR) of 100%, and all responses were ongoing. CRS and ICANS were mild, and no GvHD occurred (24).

The COBALT-RCC trial (NCT04922015) evaluated CTX130 (allogeneic CD70-targeting CAR-T) in patients with advanced ccRCC. It reported a DCR of 81.3%, including one patient achieving complete remission for >3 years with no dose-limiting toxicity (16).

These trials demonstrate the feasibility and preliminary efficacy of CD70-targeted CAR-T therapies in RCC, with acceptable safety profiles. Both studies support the clinical potential of allogeneic platforms to overcome autologous manufacturing limitations and to improve accessibility.

3.8. CAR-Based Therapies in RCC

Emerging CAR-T and CAR-NK therapies show considerable promise for ccRCC. Early clinical studies have shown encouraging activity. Key Phase I trials such as TRAVERSE and COBALT-RCC have demonstrated the feasibility of CD70-targeted CAR-T therapies in RCC, with preliminary efficacy and acceptable safety profiles. Nanobody-based CD70 CAR-T cells effectively eliminated RCC cells *in vitro* and in xenograft models, demonstrating robust expansion and durable antitumor activity (25). CAR-NK therapy is also being investigated in early studies to counteract the TME. Dual-target constructs simultaneously engage CAIX and CD70, thereby enhancing efficacy and safety. Armored CARs incorporate localized release of ICIs (e.g., PD-1/CTLA-4 bispecifics) to remodel the TME. Multi-target and logic-gated designs, as well as allogeneic "off-the-shelf" CAR-NK platforms, aim to overcome antigen heterogeneity, immune escape, and poor cell persistence. Iterative CAR optimization and biomarker-driven patient selection, along with rational combinations with ICIs or TKIs, are key to improving efficacy and long-term survival in RCC.

4. Challenges and Future Directions

The growing body of clinical research on CAR-engineered cell therapies in RCC has established preliminary feasibility and safety, but also highlighted substantial obstacles. CD70-targeted CAR therapies have demonstrated clinical benefit, yet progress is limited by several key issues: antigen heterogeneity and immune escape, the TME, inadequate CAR cell trafficking and persistence, and safety concerns such as CRS and neurotoxicity.

A major obstacle is antigen escape, where tumor cells evade CAR-cell recognition by downregulating or losing expression of

the targeted antigen. This phenomenon, well-documented in hematologic malignancies, also occurs in solid tumors like RCC due to intratumoral heterogeneity and selective pressure from therapy. In RCC, antigen escape contributes to limited long-term efficacy, as observed in early trials in which initial responses were not sustained. Strategies to mitigate this include dual- or multitarget CAR constructs and logic-gated designs that require multiple antigens for activation.

Future efforts should prioritize iterative optimization of CAR designs. Next-generation approaches are justified by the need to address RCC-specific barriers: (1) dual- or multi-target CARs combat antigen heterogeneity and antigen escape, as single-target therapies risk relapse due to antigen loss, (2) Armored CARs secrete cytokines or checkpoint inhibitors to enhance persistence and counteract the immunosuppressive TME, (3) Logic-gated or switchable CARs improve safety by requiring multiple signals for activation, reducing off-tumor toxicity, (4) Allogeneic "off-the-shelf" platforms enable faster access and scalability. These innovations build on promising early data and aim to achieve deeper, more sustained remissions.

In parallel, biomarker-driven patient selection and rational combination approaches with established treatments—such as TKIs and ICI—are expected to play an increasingly important role. Together, these strategies have the potential to improve efficacy, extend the durability of response, and ultimately enhance long-term survival in RCC patients.

Conclusion

CAR-T and CAR-NK therapies represent an emerging frontier in the treatment of RCC, offering potential solutions to the limitations of current targeted and immune checkpoint therapies. While their clinical efficacy remains modest at present, ongoing advances in CAR engineering, dual- and multi-targeting strategies, and rational combination regimens signal that cell-based therapies are poised to assume a meaningful role in future RCC management. Realizing this potential will require sustained innovation, biomarker-driven patient selection, and rigorous validation through well-designed clinical trials. Ultimately, these efforts may translate into durable responses and improved survival for patients with RCC.

Footnotes

Authorship Contributions

Concept: H.L., Design: Z.W., Data Collection or Processing: Y.L., W.C., Analysis or Interpretation: H.L., Literature Search: H.L., Z.W., Y.L., B.H., Writing: H.L., Z.W., Y.L., W.C., B.H.

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