

CAR-T Cell Therapy Combined with PD-1 Inhibitors in Cancer: Synergistic Antitumor Mechanisms, Clinical Progress, and Future Perspective

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Abstract. Among the most transformative advances in cancer immunotherapy, chimeric antigen receptor (CAR)-T cell therapy and inhibitors of programmed cell death protein 1 (PD-1) stand out, yet each approach carries its own weaknesses. CAR-T therapy produces dramatic responses in hematologic malignancies, although T-cell exhaustion, antigen escape, and an immunosuppressive tumor microenvironment (TME) frequently curtail its durability. In contrast, PD-1 monotherapy acts across a broad range of tumors and can yield long-lasting responses, but primary and acquired resistance leave most patients without benefit. Here we examine the mechanistic basis and potential synergy of pairing CAR-T cells with PD-1 blockade. Data from preclinical models and clinical trials indicate that PD-1 inhibition helps exhausted CAR-T cells recover function, shifts the TME away from an immunosuppressive state, and supports epitope spreading; together these effects strengthen antitumor activity and may lower relapse rates. Feasibility and encouraging responses have been reported in both blood cancers and solid tumors, but several obstacles persist: treatment schedules are not standardized, toxicities may overlap, solid-tumor responses remain modest because resistance is multifactorial, and outcomes vary markedly from one patient to another. This review concludes by outlining the current evidence, dissecting the synergistic mechanisms, and highlighting the challenges ahead, and argues that refined regimens, validated predictive biomarkers, and individualized strategies will be essential before this combination can reach its full potential.

Keywords: CAR-T cell therapy, PD-1 inhibitor, combination therapy, cancer immunotherapy, immune-related adverse events

1. Introduction

1.1. Development background and clinical value of cancer immunotherapy

Cancer immunotherapy, spanning both investigational and established regimens, has matured into a powerful strategy that enlists the immune system against tumors. Rather than attacking malignant cells directly as chemotherapy and radiation do, these treatments work chiefly by reprogramming or bolstering the patient's own defenses so that they recognize and destroy cancer cells [1]. Because the

action relies on the immune system rather than on cytotoxic drugs, immunotherapy offers distinctive clinical benefits, notably the possibility of durable remission and a comparatively milder side-effect profile.

1.2. Advantages and current limitations of CAR-T and PD-1 monotherapy

The strongest argument for CAR-T therapy is its striking activity against hematologic malignancies [2]. T cells drawn from the patient are genetically reprogrammed to display chimeric antigen receptors that bind tumor-surface antigens, after which the engineered cells expand rapidly in vivo and lyse target cells with high efficiency. The approach is not without serious drawbacks, however. Its toxicities can be severe—above all cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which in extreme cases prove fatal. In addition, a subset of patients fail initially or relapse later, a problem linked to antigen loss, exhaustion of the transferred T cells, and an immunosuppressive tumor microenvironment.

PD-1 monotherapy, on the other hand, is valued for acting across many tumor types and for responses that often prove durable. Tumor cells frequently exploit the PD-1/PD-L1 axis to evade immune surveillance, and interrupting this pathway can reinvigorate antitumor T-cell responses [3]. Even so, the shortcomings of single-agent checkpoint blockade are substantial. Objective response rates hover around only 20%-40%, meaning that most patients are primarily resistant, while some who initially respond later acquire resistance. Checkpoint inhibition can also break self-tolerance, provoking immune-related adverse events (irAEs) that affect the skin, gut, liver, endocrine organs, and lungs; severe episodes may force treatment to stop and occasionally endanger life [4]. Compounding these issues, the absence of dependable predictive biomarkers makes it difficult to target the therapy to the patients most likely to respond.

2. Antitumor mechanisms and current research status of CAR-T Cell therapy

2.1. Construction principles and structural characteristics of CAR-T cells

At its core, CAR-T therapy works by inserting the gene for a chimeric antigen receptor into a patient's T cells, equipping them to recognize and eliminate tumor cells without needing major histocompatibility complex (MHC) presentation. The procedure follows a set sequence: T cells are collected, the CAR gene is delivered with viral or non-viral vectors, the modified cells are expanded in vitro, and the finished product is infused back into the patient.

Four building blocks make up a chimeric antigen receptor (CAR): an extracellular antigen-recognition domain, typically a single-chain variable fragment (scFv); a hinge region; a transmembrane domain; and an intracellular signaling domain. The scFv carries out MHC-independent antigen binding, the hinge modulates how readily the receptor reaches its target, the transmembrane segment is usually sourced from cluster of differentiation 8 (CD8) alpha or cluster of differentiation 28 (CD28), and the intracellular domain governs how strongly the T cell is activated.

CAR architecture has evolved across generations. First-generation constructs carried cluster of differentiation 3 (CD3) zeta alone and generated activation signals too weak to sustain responses. Adding a single costimulatory module, either CD28 or tumor necrosis factor receptor superfamily member 9 (CD137), produced the second-generation designs that dominate the clinic today; third-generation CARs stack two costimulatory domains, while fourth-generation versions incorporate extra elements such as cytokine cassettes aimed at reshaping the tumor microenvironment. Affinity of the scFv remains a central design variable.

2.2. Antitumor mechanisms of CAR-T monotherapy

Through their extracellular recognition domain, CAR-T cells bind tumor-surface antigens independently of MHC, assemble an immunological synapse, and trigger T-cell activation. Once activated, they attack tumors through several routes. They kill directly by releasing perforin and granzyme: perforin pores open in the target membrane and granzyme activates the caspase cascade, driving apoptosis, which the tumor necrosis factor (TNF) receptor superfamily member 6 pathway can also initiate. They also act at a distance through cytokines, secreting large quantities of interferon-gamma (IFN- γ) and TNF-alpha that slow tumor growth directly and, at the same time, recruit and stimulate innate effectors such as macrophages and natural killer cells, magnifying the overall response. The killing of tumor cells further promotes immunogenic cell death and epitope spreading, because released tumor antigens are captured and cross-presented by endogenous antigen-presenting cells, which then license T cells against additional tumor antigens and broaden the response beyond the original target—an effect that helps counter tumor heterogeneity [5]. Finally, a fraction of CAR-T cells settles into a memory compartment, persisting long-term and maintaining immune surveillance that guards against late recurrence.

2.3. Major limitations of CAR-T monotherapy

Impressive as CAR-T monotherapy is in blood cancers, it still runs into several recurring limitations. Antigen escape is one: under treatment pressure, tumors may downregulate or shed the target altogether, as seen in cluster of differentiation 19 (CD19)-negative relapse, and disease returns [4]. Exhaustion and poor persistence are equally problematic, since continuous antigen exposure together with inhibitory surroundings push CAR-T cells into a dysfunctional state marked by feeble proliferation, blunted effector activity, and rising expression of inhibitory receptors such as PD-1 and lymphocyte activation gene 3 (LAG-3). The tumor microenvironment poses yet another barrier, especially in solid tumors, where regulatory T cells, myeloid-derived suppressor cells, suppressive cytokines, and abundant PD-L1 blunt infiltration and function, while a dense extracellular matrix and mismatched chemokines frustrate homing. Toxicity adds to the burden: cytokine release syndrome and ICANS are frequent and occasionally fatal, and on-target/off-tumor damage can arise when healthy tissue expresses the antigen [6]. Manufacturing is also complex and hard to access, because individualized collection, gene editing, expansion, and quality control make for a slow, expensive process that patients with rapidly advancing disease may not be able to wait for. Finally, immunogenicity is a concern, as murine-derived scFv can elicit anti-CAR antibodies that shorten persistence and weaken efficacy.

3. Antitumor mechanisms and clinical characteristics of PD-1/PD-L1 inhibitors

3.1. Physiological and pathological mechanisms of the PD-1/PD-L1 immune evasion pathway

In the tumor microenvironment, this pathway is "hijacked" and becomes a core mechanism of immune evasion: First, tumor cells can constitutively overexpress PD-L1 or upregulate it in response to IFN- γ , and aberrant oncogenic signaling (such as Phosphatidylinositol 3-kinase–Protein Kinase B signaling pathway (PI3K-AKT) and epidermal growth factor receptor (EGFR)) also drives its overexpression. Second, upon PD-1 binding to PD-L1, the intracellular immunoreceptor tyrosine-based switch motif motifs recruit Src homology 2 domain-containing phosphatase 1 and Src homology 2 (SHP-1/SHP-2) phosphatases, which dephosphorylate key molecules in the T cell

receptor (TCR) signaling pathway, thereby inhibiting T cell activation, proliferation, and cytotoxic function. Third, persistent PD-1 signaling drives CD8⁺ T cells into an exhausted state, accompanied by co-expression of other inhibitory receptors such as LAG-3 and T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) and upregulation of the transcription factor thymocyte selection-associated high mobility group box (TOX), leading to loss of effector function. Fourth, PD-1 signaling can also enhance the function of regulatory T cells, further weakening antitumor immunity [7].

3.2. Antitumor pharmacological mechanisms of PD-1 inhibitors

PD-1 inhibitors (such as pembrolizumab and nivolumab) restore antitumor immune responses by blocking the binding of PD-1 to its ligands PD-L1/programmed death-ligand 2 (PD-L2), thereby relieving the immunosuppression imposed on T cells within the tumor microenvironment [8]. The main pharmacological mechanisms include: First, alleviation of T-cell receptor signaling inhibition. Programmed cell death protein 1 inhibitors prevent the recruitment of SHP-1/SHP-2 domain-containing phosphatase 2 by the intracellular immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoreceptor tyrosine-based switch motif (ITSM) of programmed cell death protein 1, restoring the phosphorylation levels of key molecules in the T-cell receptor signaling pathway, such as zeta-chain-associated protein kinase 70 and phosphatidylinositol 3-kinase, and thereby reactivating T cell proliferation, cytokine secretion (e.g., IFN- γ and TNF- α), and cytotoxic function. Second, partial reversal of T cell exhaustion. Under chronic antigen stimulation, CD8⁺ T cells enter an exhausted state. PD-1 inhibitors can partially restore the effector function of exhausted T cells, promoting their proliferation and killing activity; however, due to limited epigenetic remodeling, this reversal is usually incomplete. Third, promotion of memory T cell formation and durable responses. PD-1 blockade can enhance the generation and maintenance of memory precursor T cells, enabling durable remission in a subset of patients, known as the "long-tail effect". Fourth, modulation of the immune cell composition within the tumor microenvironment. PD-1 inhibitors not only act on effector T cells but also influence the suppressive function of regulatory T cells, promote the maturation and antigen-presenting capacity of dendritic cells, and enhance the antitumor activity of natural killer cells, thereby synergistically amplifying the immune response.

3.3. Clinical limitations of PD-1 monotherapy

First, in most solid tumors, the objective response rate to PD-1 monotherapy is only 20%–40%, with mechanisms involving insufficient tumor immunogenicity, defective antigen presentation, and aberrant IFN- γ signaling.

Second, some patients who initially respond may develop acquired resistance, with mechanisms including beta-2-microglobulin (B2M) or Janus kinase 1/2 (JAK1/JAK2) mutations, compensatory upregulation of other checkpoint molecules, and persistent immunosuppressive microenvironment.

Third, PD-1 blockade can disrupt self-tolerance and trigger multi-system irAEs, a minority of which may be life-threatening.

Fourth, the predictive value of PD-L1 expression and tumor mutational burden is limited, making it difficult to precisely identify patients who are likely to benefit.

Fifth, Tumors with low T cell infiltration and poor immunogenicity often respond poorly to PD-1 monotherapy.

4. Synergistic antitumor mechanisms of CAR-T combined with PD-1 inhibitors

4.1. PD-1 blockade reverses CAR-T Cell exhaustion and restores cytotoxic function

When CAR-T cells meet tumor antigen in vivo, sustained stimulation drives them to express PD-1. PD-L1 on tumor cells and throughout the microenvironment then engages PD-1, switches on its intracellular ITIM/ITSM motifs, and draws in the phosphatases SHP-1 and SHP-2. The resulting brake on CAR-driven, TCR-like signaling manifests as poorer proliferation, thinner cytokine output, and weaker cytotoxicity, and over time the cells settle into exhaustion. Blocking PD-1 displaces this interaction, keeps the phosphatases from being recruited, and restores phosphorylation of signaling intermediates including zeta-chain-associated protein kinase 70 (ZAP70) and PI3K; exhausted CAR-T cells consequently regain proliferative capacity, resume secretion of IFN-gamma and TNF-alpha, and recover killing activity.

Preclinical work consistently shows that giving PD-1 antibodies after CAR-T infusion strengthens in vivo antitumor activity and helps the engineered cells infiltrate tumors and survive there. In patients with relapsed/refractory B-cell lymphoma, PD-1 inhibition has been documented to trigger renewed expansion of circulating CAR-T cells and to bring effector function back—direct clinical support for combining the two. Genetic strategies push the same idea further: CAR-T cells engineered to secrete a PD-1-blocking scFv or to carry a disrupted PD-1 gene receive durable, local relief from inhibitory signaling, which reverses exhaustion while sparing the patient systemic exposure.

4.2. Remodeling the tumor immune microenvironment and overcoming the immunological barriers of solid tumors

For solid tumors, the steepest hurdle facing CAR-T therapy is a microenvironment that is both potently immunosuppressive and physically obstructive. It is densely populated by regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2-polarized tumor-associated macrophages, and bathed in suppressive cytokines such as transforming growth factor-beta (TGF- β) and interleukin-10 (IL-10). High PD-L1 on tumor and stromal cells compounds the problem by curtailing CAR-T infiltration, survival, and effector function. On top of this, the rigid extracellular matrix, disorganized tumor vasculature, and chemokine mismatch all conspire to keep the engineered cells from reaching and penetrating the lesion [7].

PD-1 blockade acts at several levels to remodel this microenvironment and break down the defenses of solid tumors. Most directly, it removes the PD-1/PD-L1 brake on CAR-T cells, restoring proliferation, cytokine release, and cytotoxicity and extending their survival within the tumor. It also rewrites the cellular makeup of the lesion: Treg suppression is weakened, MDSC activity declines, dendritic cells mature and present antigen more effectively, and natural killer cells become more cytotoxic, nudging the milieu from suppressive toward inflammatory. Chemokine traffic improves as well, because checkpoint inhibition raises intratumoral C-X-C motif chemokine ligand 9/10 (CXCL9/CXCL10), which draw CAR-T and other effector T cells into the tissue. In some models it even encourages vascular normalization, improving perfusion and oxygenation and thereby easing the delivery and function of the infused cells [9].

These effects find clinical support in a phase I trial of regionally delivered mesothelin-targeted CAR-T cells given with pembrolizumab for malignant pleural disease, where the combination prolonged CAR-T persistence at the tumor and yielded early signs of antitumor activity—evidence

that PD-1 blockade can help CAR-T cells contend with the suppressive solid-tumor microenvironment.

4.3. CAR-T-Mediated precise tumor killing releases antigens and amplifies PD-1-Mediated systemic immune responses

Using their scFv, CAR-T cells selectively lyse target-antigen-positive tumor cells without MHC restriction. This killing is immunogenic: it releases tumor-associated antigens, neoantigens, and damage-associated molecular patterns (DAMPs) including adenosine triphosphate (ATP) and high mobility group box 1 (HMGB1). Dendritic cells and other antigen-presenting cells in the TME take up this material and cross-present it to endogenous CD8⁺ T cells, launching responses against antigens beyond the CAR target—a phenomenon termed epitope spreading. In effect, the immune attack broadens from the single engineered specificity to a wider antigenic landscape, which counters both heterogeneity and antigen escape. PD-1 inhibition amplifies this loop, because lifting the PD-1/PD-L1 brake lets the newly recruited endogenous T cells proliferate, secrete cytokines, and kill more vigorously. CAR-T cells thus act not only as direct killers of antigen-positive cells but also as an "in situ vaccine," whose released antigens spark endogenous immunity; PD-1 blockade then magnifies that response, clearing local disease while building systemic, tumor-directed protection [10].

4.4. Dual blockade of immune evasion and reduction of the risk of tumor drug resistance and relapse

The first layer of synergy is straightforward: CAR-T killing and PD-1 blockade complement each other by lifting T-cell inhibition. CAR-T cells recognize and destroy target-antigen-positive cells independently of MHC, cutting tumor burden directly. Yet chronic antigen exposure raises PD-1 on these cells, and engagement with PD-L1 on tumor or stromal cells pushes them toward exhaustion and blunts their cytotoxicity—a major reason monotherapy relapses occur. Interrupting the PD-1/PD-L1 interaction restores proliferation, cytokine production, and killing, so exhaustion is delayed or reversed and antitumor activity is sustained longer.

A second layer of synergy lies in epitope spreading, which counters antigen escape. Escape—tumor cells downregulating or losing the target, as in CD19-negative relapse—is a leading cause of CAR-T failure. But the immunogenic cell death caused by CAR-T killing releases antigens that antigen-presenting cells cross-present to endogenous CD8⁺ T cells, generating responses against additional tumor antigens. PD-1 blockade strengthens these fresh endogenous responses and widens the antitumor net, so that even tumor cells that have shed the original antigen can be eliminated and the odds of escape-driven relapse fall.

A third layer is the remodeling of the immune microenvironment, which dilutes immunosuppression. Tregs, myeloid-derived suppressor cells, suppressive cytokines, and high PD-L1 together build a barrier that shields tumors from attack. PD-1 blockade does more than act on CAR-T cells directly: it also constrains Treg function, blunts MDSC suppression, promotes dendritic-cell maturation, and tips the microenvironment from suppressive toward inflammatory. CAR-T cells consequently infiltrate and survive better, and failures rooted in microenvironmental suppression become less likely [11].

5. Clinical research progress of CAR-T combined with PD-1 therapy

5.1. Clinical progress of combination therapy in hematologic malignancies

In hematologic malignancies, the clinical pairing of CAR-T with PD-1 inhibitors has been examined mainly in relapsed/refractory B-cell lymphomas, where safety has looked acceptable and early efficacy signals have appeared. Three issues dominate the discussion: when to give the PD-1 inhibitor; how to manage overlapping toxicities—and particularly how to tell immune-related pneumonitis apart from ICANS; and the fact that no randomized controlled trial has yet shown the combination superior to CAR-T alone, since available data come from phase I/II or retrospective studies.

Solid tumors tell a more cautious story, because CAR-T monotherapy is held back by microenvironmental suppression, poor T-cell infiltration, and antigen heterogeneity, and its results lag far behind those in blood cancers. Preclinical models indicate that anti-PD-1 antibodies alongside CAR-T cells can slow the growth of several solid-tumor types, improve CAR-T infiltration and survival, and partly reverse exhaustion; engineering the cells to secrete a PD-1-blocking scFv or to lose PD-1 expression can strengthen local activity even further. On the clinical side, the phase I trial by Adusumilli and colleagues, which combined regionally delivered mesothelin-targeted CAR-T cells with pembrolizumab in malignant pleural disease, reported acceptable safety, durable CAR-T persistence, and preliminary activity, although objective response rates stayed low. Early work in other solid tumors has pointed in the same direction.

5.2. Safety and adverse reaction profiles of combination therapy

On balance, combining CAR-T cells with PD-1 inhibitors is tolerable, although several overlapping risks deserve careful attention—CRS and irAEs in particular, together with neurotoxicity, autoimmune phenomena, and susceptibility to infection.

CRS and irAEs can overlap. The frequency and grade of CRS under combination regimens look similar to historical CAR-T monotherapy figures. Holding the PD-1 inhibitor until roughly 2-4 weeks after infusion, once severe CRS has been excluded, may keep CRS from worsening, but fever and hypotension still demand careful differential diagnosis. Neurologic toxicity is trickier, because ICANS and PD-1-related neurotoxicity such as immune encephalitis present alike and are hard to distinguish, yet they are managed differently and call for multidisciplinary assessment. Autoimmune disease is another concern, since checkpoint blockade can trigger or aggravate it; patients should be screened for autoimmune background beforehand and monitored during treatment for thyroid, hepatic, cutaneous, and intestinal involvement. CAR-T therapy itself commonly causes B-cell aplasia and immunosuppression, so combinations call for heightened vigilance against viral (cytomegalovirus (CMV), Epstein-Barr virus (EBV)), bacterial, and opportunistic infections, with immunoglobulin replacement and prophylactic anti-infective therapy given when needed. A "delayed combination" schedule, together with a multidisciplinary monitoring system that repeatedly scores CRS, neurologic status, organ function, and infection markers, is currently the most practical way to catch severe events early.

6. Challenges and critical bottlenecks in combination therapy

6.1. Absence of standardized treatment protocols for combination regimens

Even now, combining CAR-T therapy with PD-1 inhibitors remains exploratory, and no single standardized protocol has won broad acceptance. Timing is a case in point: although most studies lean toward starting the PD-1 inhibitor 2-4 weeks after CAR-T infusion, once severe CRS is ruled out, that window rests largely on small cohorts and empirical consensus rather than prospective randomized evidence. Giving it too early could interfere with the initial CAR-T expansion, while waiting too long may forfeit the best chance to reverse exhaustion. Dosage and duration are equally unsettled, since it is unknown whether combination therapy requires dose adjustments, how long treatment should run, or what should prompt discontinuation. Patient selection adds a further gap: no validated biomarker yet identifies who will benefit most, and although tumor PD-L1 expression, CAR-T expansion kinetics, and baseline immune status are suggestive, none has been confirmed prospectively [12].

6.2. Significant risk of overlapping adverse reactions and pronounced interindividual variability

When CAR-T cells and PD-1 inhibitors are used together, CRS and irAEs can overlap. PD-1 blockade does not cause CRS on its own, but by intensifying T-cell activation and proliferation it could, in principle, amplify the systemic inflammation that accompanies CAR-T therapy. Tolerance of the combination also varies widely from patient to patient, as do microenvironmental features and baseline immune status—which is precisely why individualized risk assessment matters. Age, performance status, tumor burden, number of prior therapies, history of autoimmunity, and baseline lymphocyte subsets and cytokine levels can each shape both the safety and the effectiveness of treatment.

6.3. Limited efficacy and complex resistance mechanisms of combination therapy in solid tumors

Even though pairing PD-1 blockade with CAR-T therapy has produced early hints of synergy in some solid tumors, the overall benefit is still plainly limited and nowhere near what is achieved in hematologic cancers; the inherent defenses of solid tumors remain the chief bottleneck. Antigen heterogeneity is the first: subpopulations of tumor cells lack or barely express the CAR target, and although PD-1 blockade can enlist endogenous T cells and promote epitope spreading, that process is slow and incomplete, so not every clone is covered in time. The second barrier is physical, because the dense matrix, abnormal vasculature, and chemokine mismatch of solid tumors sharply restrict CAR-T homing and infiltration, and checkpoint inhibition does little to alter these structural obstacles. The third is the breadth of the immunosuppressive network itself—Tregs, MDSCs, Type 2 macrophages, suppressive cytokines, and metabolic constraints layered on one another—of which the PD-1/PD-L1 axis is only a single thread; cutting that one thread cannot by itself unravel the whole network.

7. Conclusion

Pairing CAR-T therapy with PD-1 inhibitors boosts antitumor activity along several complementary routes. Blocking PD-1 rescues exhausted CAR-T cells, bringing back proliferation, cytokine

secretion, and cytotoxicity; it also repairs the tumor microenvironment by restraining regulatory T cells and myeloid-derived suppressor cells, so that CAR-T cells infiltrate and persist more readily; and the antigens released by CAR-T killing drive epitope spreading, which recruits endogenous T cells and lowers relapse due to antigen escape. In the clinic, the combination has proved feasible and encouraging in hematologic cancers—relapsed/refractory B-cell lymphomas in particular—where it has rescued some patients who relapsed after CAR-T alone. Solid tumors have shown improved T-cell infiltration and early activity, yet antigen heterogeneity, physical barriers, and layered immunosuppressive networks still cap the benefit. The central challenges are the absence of standardized protocols (timing, dose, duration, and patient selection), overlapping CRS and irAE risks, and interpatient variability that demands personalized safety management.

Advancing this combination will depend on progress on several fronts. Timing and dosing must be refined first: the now-common delayed schedule, with PD-1 inhibition starting 2-4 weeks after CAR-T infusion, will need prospective studies to pin down the window and dose that best reconcile CAR-T expansion with timely reversal of exhaustion. Controllable switches and gene-edited CAR-T cells offer a second avenue, since suicide genes, inducible expression systems, and logic-gated designs can impose precise spatiotemporal control over both CAR activity and checkpoint blockade, curbing toxicity; PD-1 knockout via clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9), CAR-T cells secreting PD-1-blocking scFv, and armored constructs carrying immunomodulatory payloads promise stronger local effects with fewer systemic reactions. A third priority is predictive biomarkers, where integrating tumor PD-L1 expression, tumor mutational burden, CAR-T expansion kinetics, baseline lymphocyte subsets, and microenvironmental features into a multidimensional model could identify likely responders. Multicenter randomized trials are a fourth necessity, because present evidence is largely phase I/II or retrospective; well-designed trials using overall and progression-free survival as hard endpoints are urgently needed to establish the incremental benefit of the combination. Finally, therapy should become genuinely personalized, with timing, dose, and duration adjusted dynamically to each patient's immune status, tumor characteristics, and toxicity risk—a move away from fixed regimens toward tailored ones. In short, CAR-T plus PD-1 blockade is heading toward precision, engineering, and personalization, and may unlock synergistic antitumor benefit across a wider spectrum of tumors.

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