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REVIEW

Chimeric antigen receptor natural killer (CAR-NK) cells: from preclinical promise to clinical reality in cancer immunotherapy

Hunter Cassidy Cochran[a], Kevin Ashkan Ghobadi[b] and Armin Ghobadi[a]

[a]Washington University School of Medicine, Center for Gene and Cellular Immunotherapy (CGCI), St Louis, MO, USA; [b]Mary Institute and Saint Louis Country Day School, St. Louis, MO, USA

ABSTRACT

Chimeric antigen receptor (CAR) natural killer (NK) cell therapy represents an emerging frontier in cancer immunotherapy. CAR-NK cells offer the potential for "off-the-shelf" treatments with a favorable safety profile, due in part to their innate capacity for HLA-unrestricted tumor targeting and an absence of graft-versus-host disease. Landmark clinical studies using cord blood – derived CAR-NK cells and another employing iPSC-derived CAR-NK cells have reported impressive response rates, durable remissions, and minimal toxicity. Furthermore, a growing landscape of ongoing clinical trials is exploring innovative strategies to enhance persistence, overcome solid tumor challenges, and prevent antigen escape. These advances collectively underscore the potential of CAR-NK therapies to revolutionize cancer treatment while addressing limitations associated with current CAR-T cell approaches.

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1. Introduction

The landscape of cancer immunotherapy has been transformed by cellular therapies, most notably by the advent of chimeric antigen receptor (CAR) T cells [1–10]. However, CAR-T cell therapies are not without limitations. Their autologous nature, complex manufacturing process, and potentially severe toxicities – including cytokine release syndrome (CRS) and neurotoxicity – have spurred the search for alternative effector cells. Natural killer (NK) cells, as innate lymphoid effectors with inherent cytotoxic capacity, offer a promising platform for cellular therapy. Unlike T cells, NK cells mediate cytotoxicity in an HLA-unrestricted manner, eliminating the risk of graft-versus-host disease (GVHD) and allowing for the development of allogeneic, "off-the-shelf" products [11,12].

Over the past decade, preclinical studies have elucidated the unique biology of NK cells, detailing their repertoire of activating and inhibitory receptors and highlighting their role in immunosurveillance [11]. These insights have facilitated the engineering of NK cells to express CARs specific for tumor antigens (e.g., CD19) while incorporating cytokine armoring (such as IL-15) to bolster persistence and antitumor activity. The integration of safety switches – such as inducible caspase-9 (iC9) – further enhances the safety profile of these engineered cells. Considering these advances, several clinical studies have begun to evaluate the efficacy and safety of CAR-NK cells in both hematologic and solid tumors [13–17].

The primary objective of this review is to provide a balanced, comprehensive overview of CAR-NK cell therapies, synthesizing both evidence supporting their therapeutic promise and studies highlighting limitations or challenges in clinical efficacy.

A comprehensive literature review was conducted to identify relevant preclinical and clinical studies evaluating CAR-NK cell therapies. PubMed, ClinicalTrials.gov, and key oncology and immunotherapy journals were searched, covering articles published up to April 2025. Articles were selected based on relevance to CAR-NK cell biology, preclinical evidence, clinical trial outcomes, and critical evaluations of therapeutic efficacy and safety. Both positive studies demonstrating clinical promise and studies presenting negative or neutral findings were included to ensure balanced representation and evaluation.

In this review, we begin by summarizing the preclinical science that underpins CAR-NK cell development. We then provide an in-depth discussion of two pivotal clinical trials: the study by Liu et al., which employed cord blood – derived CAR-NK cells, and the study by Ghobadi et al., which utilized induced pluripotent stem cell (iPSC) – derived CAR-NK cells. Subsequently, we present a table summarizing current and past CAR-NK clinical trials focusing on hematologic malignancies as listed on ClinicalTrials.gov. Finally, we discuss the strengths, challenges, and unmet needs of CAR-NK cell therapy, particularly in comparison to CAR-T approaches, and offer insights into future directions for this rapidly evolving field.

2. Preclinical science behind CAR-NK cells

2.1. NK cell biology and rationale for car engineering

NK cells are cytotoxic lymphocytes that originate from CD34+ hematopoietic progenitors in the bone marrow [18]. They possess a diverse array of activating receptors (e.g., NKG2D, NKp46, and CD16) and inhibitory receptors (e.g., KIRs and NKG2A) that govern their ability to discriminate between healthy and transformed cells.

CONTACT Armin Ghobadi arminghobadi@wustl.edu Washington University School of Medicine, Center for Gene and Cellular Immunotherapy (CGCI), Division of Medical Oncology, Section of Cellular Therapy, 660 S. Euclid Avenue, Campus Box 8007-29, St. Louis, MO 63110, USA

Article highlights

- CAR-NK therapy offers an off-the-shelf cellular immunotherapy platform with a favorable safety profile, leveraging the innate, HLA-unrestricted cytotoxicity of NK cells and minimizing the risk of cytokine release syndrome or neurotoxicity.
- Clinical trials using cord blood – and iPSC-derived CAR-NK cells have demonstrated encouraging response rates, durable remissions in select patients, and excellent tolerability, supporting feasibility for large-scale allogeneic use.
- Engineering innovations – such as IL-15 armoring, memory-like programming, and non-cleavable CD16 incorporation – have improved CAR-NK cell persistence, ADCC activity, and antitumor potency.
- Emerging strategies, including CRISPR-based gene editing, multispecific CAR designs, and cytokine priming, aim to overcome antigen escape, exhaustion, and tumor microenvironment suppression.
- Next-generation CAR-NK therapies are poised to expand into solid tumors and broader hematologic indications, with ongoing trials emphasizing scalability, durability, and combination with checkpoint inhibitors or monoclonal antibodies.

Preclinical studies have demonstrated that NK cells can target tumor cells that downregulate HLA class I molecules – a common escape mechanism from T cell recognition – thereby positioning them as ideal candidates for adoptive immunotherapy [19–22].

Engineering NK cells with CAR constructs further augments their specificity. Chimeric antigen receptors (CARs) were initially developed for T cells. A typical second-generation CAR in CAR-T cells consists of an extracellular single-chain variable fragment (scFv) binding domain, a transmembrane domain (commonly derived from CD8 or CD28), an intracellular costimulatory domain (e.g., CD28, 4-1BB, OX40, and ICOS), and an intracellular activating domain (CD3ζ). CARs engineered for NK cells incorporate costimulatory and activating domains tailored to NK cell signaling (Figure 1) [23–31].

The incorporation of a high-affinity, non-cleavable CD16 receptor (hnCD16) enhances ADCC and enables the redirection of CAR-NK cells to a second tumor antigen when used in combination with a monoclonal antibody (Figure 2). Additionally, CAR-NK cell function and persistence can be improved by incorporating an IL-15/IL-15 receptor fusion protein, which provides continuous CAR-NK cell stimulation (Figure 2) [32]. Preclinical studies in murine models and *in vitro* assays have shown that CAR-NK cells can mediate robust cytotoxicity against tumor cells while maintaining a favorable safety profile [13,33,34].

2.2. NK cell sources

Natural killer (NK) cells can be obtained from a variety of sources, each with unique characteristics that influence their utility in adoptive cell therapy. Primary NK cells isolated from peripheral blood mononuclear cells (PBMCs) are the most used source and are characterized by their mature phenotype and potent cytotoxic activity [14,35–37]. These cells express high levels of activating receptors such as CD16, which enables them to mediate antibody-dependent cellular cytotoxicity (ADCC), and they have been extensively studied in clinical settings. However, their use is sometimes limited by donor-to-donor variability and the logistical challenges associated with apheresis and ex vivo expansion [38–41]. An emerging and highly promising variant of PBMC-derived NK cells are cytokine-induced memory-like (CIML) NK cells, generated through brief pre-activation with interleukin-12 (IL-12), IL-15, and IL-18. These CIML NK cells exhibit enhanced cytokine responsiveness, proliferation, and cytotoxicity compared to conventional NK cells, and have shown standalone antileukemia activity in both preclinical and early-phase clinical studies [33,42]. Recent work has demonstrated that CIML NK cells can also be engineered with CAR constructs, resulting in CAR-ML NK cells that synergize the potent effector functions of memory-like programming with the targeted specificity of CARs. This source offers a compelling alternative for CAR-NK manufacturing, especially in hematologic

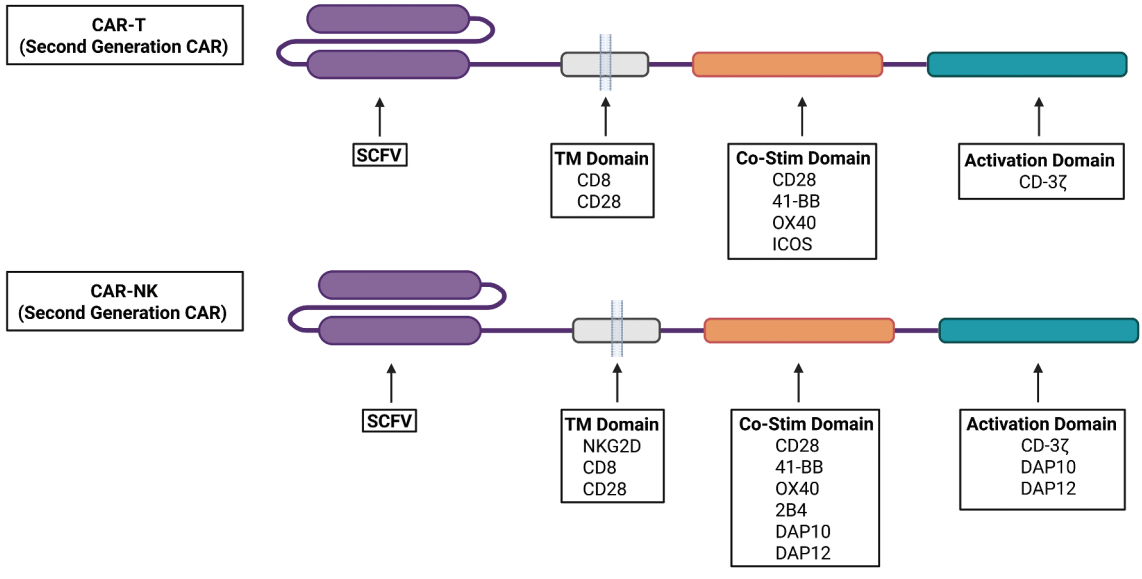

Figure 1. Chimeric antigen receptor design in CAR-T vs. CAR-NK. Both CAR-NK and CAR-T have similar CAR designs: with enhanced optimization strategies to incorporate NK-specific components in CAR-NK. DAP10 and DAP12 are NK-specific activation domains that have been studied instead of CD3ζ or in combination with CD3ζ [23–29]. TM, transmembrane; Co-stim, costimulatory; DAP10, DNAX-activation protein 10; DAP12, DNAX-activation protein 12. (Created with BioRender; Ghobadi, K., 2025; https://BioRender.com/dhp6zf2).

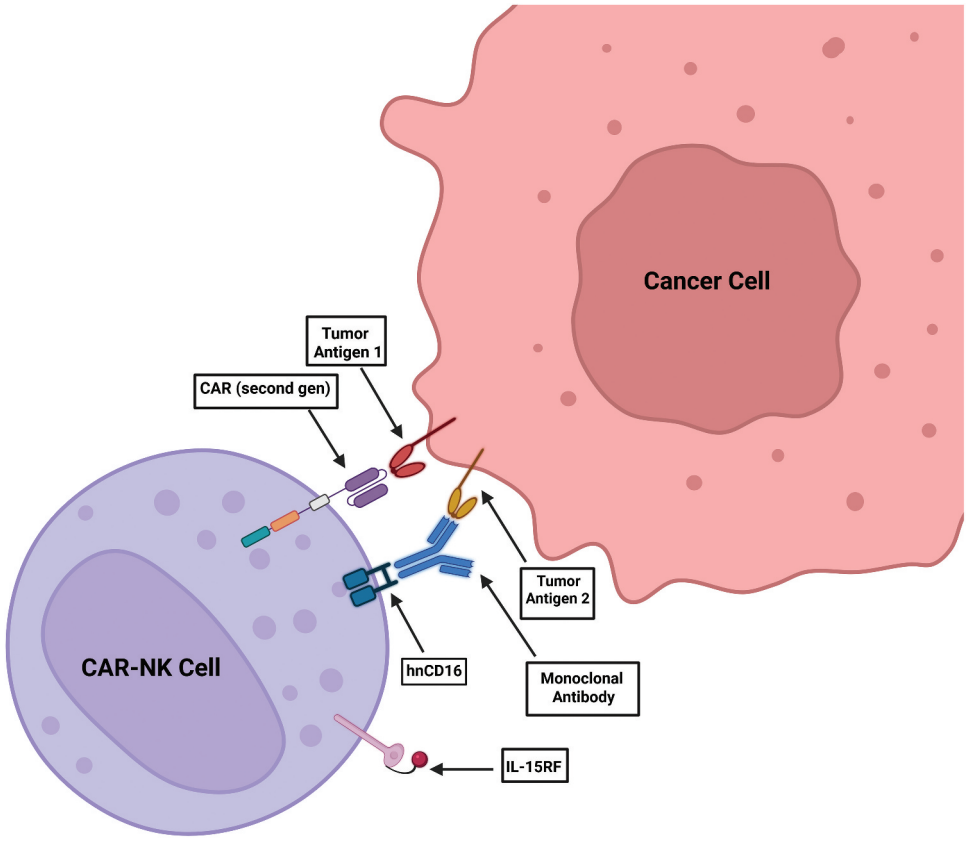

Figure 2. Design of CAR-NK cells. The incorporation of CAR in NK cells redirects NK cells to tumor cells. Additionally, CAR-NK redirection to a second tumor antigen is enabled through the incorporation of hnCD16 in CAR-NK cells when used in addition to a monoclonal antibody. The addition of IL-15RF can enhance the function and persistence of NK cells. hnCD16, high-affinity, non-cleavable CD16 receptor; IL-15RF, IL-15 receptor fusion. (Created in BioRender; Ghobadi, K., 2025; https://BioRender.com/rjtd4f5).

malignancies such as acute myeloid leukemia and B-cell lymphomas.

Umbilical cord blood (CB) represents an attractive alternative source. Cord blood-derived NK cells are relatively naïve compared with their peripheral counterparts, which can confer a lower risk of alloreactivity and make them well-suited for off-the-shelf applications. In addition, cord blood units are readily available through established banking systems, ensuring a consistent and standardized starting material. Nevertheless, cord blood NK cells may require additional activation and cytokine support to achieve optimal cytotoxic function, as their maturation state can be less pronounced than that of peripheral blood NK cells [14,33,35,36,43–48].

Another promising source is NK cells derived from hematopoietic stem and progenitor cells (HSPCs). These cells are generated by differentiating $CD34^+$ progenitor cells in vitro, offering a renewable source that can be tailored to produce large cell numbers [14,35]. While HSPC-derived NK cells have demonstrated promising antitumor activity in preclinical models, the differentiation process is typically lengthy and may yield cells with a relatively immature phenotype. This immaturity can necessitate further ex vivo expansion or additional genetic modifications to enhance their cytolytic potential before clinical application [49–51].

Induced pluripotent stem cells (iPSCs) have emerged as a particularly attractive source due to their capacity for clonal expansion and differentiation into homogeneous NK cell populations. iPSC-derived NK cells can be produced in large quantities under controlled conditions, offering the potential for highly standardized, off-the-shelf products [16,17,52,53]. However, these cells often require further engineering – for example, to upregulate CD16 for improved ADCC – and there are concerns regarding epigenetic memory that could influence their functional differentiation. Despite these challenges, iPSC-derived NK cells are increasingly viewed as a scalable platform for next-generation NK cell therapies [54–56].

Finally, the NK-92 cell line represents a well-characterized, immortalized NK cell source that has been widely utilized in both preclinical research and early-phase clinical trials. A major advantage of the NK-92 cell line is that these cells lack expression of most killer cell immunoglobulin-like receptors (KIRs), which makes them less likely to be inhibited by self-antigens, thus enhancing their cytotoxic potential. Additionally, NK-92 cells can be expanded ex vivo to achieve large cell numbers, a feature that significantly facilitates manufacturing and scalability. However, their malignant origin necessitates irradiation prior to clinical use to prevent potential tumorigenicity, and this irradiation adversely affects their long-term in vivo persistence. Moreover, NK-92 cells lack expression of CD16, rendering them unable to mediate ADCC – an important mechanism of antitumor activity observed with other NK cell sources [37,57–61].

Collectively, the diversity of NK cell sources – from peripheral blood and cord blood to HSPCs, iPSCs, and established cell lines like NK-92—provides a versatile toolbox for the development of CAR-NK cell therapies. Each source has its own set of advantages and limitations that must be carefully considered when designing a therapeutic product, with ongoing research aimed at optimizing manufacturing protocols and enhancing the functional attributes of the final cell product.

2.3. Preclinical evidence supporting efficacy

Multiple preclinical investigations have firmly established the antitumor activity and translational promise of CAR-NK cells, highlighting their potential across a range of tumor types and antigen targets. In early studies using cord blood – derived NK cells, researchers demonstrated that these cells, when genetically modified to express an anti-CD19 CAR, could rapidly lyse CD19-positive leukemic cells in vitro while exhibiting robust in vivo expansion and persistence in murine xenograft models. These results underscored the feasibility of sourcing functional NK cells from cryopreserved cord blood units, a strategy that enables standardized manufacturing and off-the-shelf availability.

Subsequent work focused on refining CAR constructs and incorporating additional transgenes, such as interleukin-15 (IL-15), to further enhance NK cell survival and proliferative capacity [62]. For instance, preclinical testing showed that CAR-NK cells armed with IL-15 and an inducible caspase-9 safety switch retained potent cytotoxic activity and improved engraftment in immunodeficient mouse models, without causing graft-versus-host disease [36]. Beyond cytokine support, a novel strategy combined cytokine-induced memory-like (ML) NK cell differentiation with CAR engineering. In a seminal study, Gang et al. demonstrated that 19-CAR-ML NK cells exhibited superior cytotoxicity, cytokine production, and in vivo persistence compared to either conventional CAR-NK cells or ML NK cells alone. These dual-enhanced cells effectively targeted NK-resistant B-cell lymphomas, including autologous tumor samples from lymphoma patients, and controlled tumor burden in xenograft models with improved survival outcomes [42]. Other groups have explored the use of dual- or multi-targeting CAR designs to address tumor antigen escape, a common mechanism of relapse following single-antigen therapy [63]. These multi-antigen CAR-NK cells proved capable of recognizing and eradicating both antigen-positive and antigen-negative tumor subclones, thereby minimizing the risk of disease recurrence.

Parallel to cord blood – derived NK platforms, induced pluripotent stem cell (iPSC) technology has emerged as an attractive approach for generating uniform and renewable NK cell populations. In particular, iPSC-derived NK cells have demonstrated notable efficacy against a broad spectrum of hematologic malignancies and solid tumors, both in vitro and in vivo [37,64]. By engineering iPSC-NK cells to co-express optimized CARs, high-affinity non-cleavable CD16 (hnCD16), and membrane-bound IL-15 or IL-15/IL-15 R fusion proteins, researchers achieved enhanced antibody-dependent cellular cytotoxicity, improved in vivo persistence, and robust antitumor activity [65–67]. These preclinical findings highlight the versatility of iPSC-derived NK cells, which can be produced in large batches with consistent phenotypes, offering a scalable and potentially cost-effective manufacturing platform.

In addition to CD19-targeting strategies, multiple research teams have explored CAR-NK cells directed against various antigens relevant to solid tumors – such as HER2, EGFR, and mesothelin – demonstrating that NK cells can infiltrate solid tumor xenografts and mediate significant tumor regression [68]. Although challenges remain, including immunosuppressive tumor microenvironments and the need for improved homing and persistence, these proof-of-concept studies lay the groundwork for ongoing clinical trials investigating CAR-NK therapies in both hematologic and solid malignancies [69–71]. Overall, the robust preclinical evidence base provides strong rationale for advancing CAR-NK cells into clinical development, where early-phase trials have already shown favorable safety and promising efficacy.

2.4. Preclinical advantages over CAR-T

CAR-NK cells offer some advantages over CAR-T cells due to their controlled immune activation. Their balance of activating and inhibitory receptors – such as killer-cell immunoglobulin-like receptors (KIRs) and NKG2A/CD94—helps prevent excessive immune responses. Unlike CAR-T cells, which rely heavily on antigen recognition and costimulatory domains that can lead to cytokine surges, CAR-NK cells primarily secrete cytokines like IFN-γ, GM-CSF, and IL-15 while avoiding excessive IL-6 production. This cytokine profile mitigates the risk of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), making CAR-NK cells inherently safer [69,72,73].

In contrast, CAR-T cells induce rapid clonal expansion and sustained immune activation, a process that increases the risk of neuroinflammation. CAR-NK cells, however, exhibit controlled expansion and reduced persistence, thereby lowering the likelihood of prolonged neurotoxicity. Their limited secretion of IL-1β also contributes to reduced blood-brain barrier disruption – a major factor implicated in the pathogenesis of ICANS. Moreover, the regulated interaction of CAR-NK cells with immune components prevents excessive endothelial activation and minimizes the expression of inflammatory markers, further reducing systemic toxicity [69,72,74].

Beyond their safety profile, NK cells possess innate tumor-targeting capabilities. Their natural cytotoxicity receptors (NCRs), including NKp30, NKp44, and NKp46, enable them to detect stress-induced ligands on tumor cells, thereby initiating effective cytotoxic responses. Through receptors such as NKG2D, NK cells recognize molecules like MICA/B and ULBPs that are upregulated in transformed cells. This intrinsic mechanism of tumor cell recognition and killing provides a robust foundation for tumor elimination that extends beyond the specificity provided by CAR constructs [71,75,76].

Building on these innate properties, researchers have developed strategies to further amplify antitumor efficacy by incorporating monoclonal antibodies into CAR-NK cell therapy [71]. For example, rituximab – a monoclonal antibody targeting the CD20 antigen on B cells – plays a crucial role by

facilitating antibody-dependent cellular cytotoxicity (ADCC). Rituximab binds to CD20 on malignant cells and engages CD16 receptors on NK cells, thereby recruiting them to kill tumor cells [77]. When combined with CAR-NK cells, this dual mechanism allows the CAR construct to redirect NK cell specificity toward antigens such as CD19, while rituximab simultaneously induces ADCC. This synergistic approach not only amplifies tumor cell killing but also helps overcome antigen escape by targeting multiple tumor-associated antigens [63]. Additionally, the presence of rituximab can further potentiate NK cell activation, particularly in engineered systems where modifications – like the expression of a high-affinity, non-cleavable CD16 receptor – restore ADCC functionality and ultimately lead to improved clinical outcomes [65].

NK cells also enhance tumor clearance by secreting cytokines such as IFN-γ and TNF-α, which activate dendritic cells and macrophages to amplify the antitumor immune response [24]. Their ability to work in concert with monoclonal antibodies not only enhances direct tumor cell killing but also boosts tumor immunogenicity, making NK cells a compelling tool for comprehensive cancer therapy [78].

Another key advantage of CAR-NK cells lies in their resilience to exhaustion. Unlike CAR-T cells, which can experience functional decline after prolonged antigen exposure, NK cells employ multiple activating receptors that reduce the risk of immune escape [79]. Their balanced expression of activating and inhibitory receptors – such as KIRs and NKG2A/CD94—helps sustain long-term cytotoxicity without overactivation [80]. Moreover, NK cells retain remarkable metabolic flexibility, maintaining both oxidative phosphorylation and glycolysis even in nutrient-deprived tumor microenvironments, in contrast to exhausted T cells that often suffer from mitochondrial dysfunction [81]. Recent studies further indicate that NK cells exhibiting a memory-like phenotype possess a stable epigenetic landscape that is resistant to exhaustion [82]. Under chronic stimulation, CAR-T cells frequently upregulate inhibitory checkpoints like PD-1 and LAG-3, whereas NK cells maintain a durable effector phenotype with lower expression of these markers [83]. Their inherent regulatory mechanisms enable them to function efficiently over prolonged periods without significant functional decline [84].

In conclusion, CAR-NK cells provide a safer and more durable alternative to CAR-T cells in cancer immunotherapy. Their reduced toxicity, robust innate tumor surveillance capabilities, effective ADCC function when combined with monoclonal antibodies, and resilience to exhaustion position them as a next-generation cellular therapy with broad clinical applications in both hematologic malignancies and solid tumors.

2.5. Key clinical trials

2.5.1. Off-the-shelf CAR-NK cell therapy for CD19+ malignancies: results from phase 1/2 clinical trials and the impact of donor selection

The following landmark studies – by Liu et al. and Ghobadi et al.—represent the largest clinical experiences to date with CAR-NK cell therapies, providing critical insights into feasibility, safety, and early efficacy in CD19-positive lymphoid malignancies.

2.5.2. Off-the-shelf CAR-NK cell therapy for CD19+ malignancies and impact of donor selection

The initial phase 1/2 clinical trial conducted by Liu et al. evaluated allogeneic cord blood-derived CAR-NK cells in patients with relapsed or refractory CD19-positive lymphoid malignancies [37]. Unlike individualized CAR-T therapies, these CAR-NK cells presented an off-the-shelf therapeutic option with improved safety profiles. Engineered with an anti-CD19 CAR, membrane-bound IL-15 for persistence, and an inducible caspase-9 safety switch, the therapy demonstrated promising initial efficacy with a 73% overall response rate and 64% complete responses among a small initial patient group. Importantly, the treatment showed an excellent safety profile without CRS, neurotoxicity, or graft-versus-host disease.

Subsequent expansion to a larger patient cohort revealed more modest efficacy, highlighting challenges in achieving durable responses with a one-year progression-free survival of only 32%. Further analysis indicated significant influence from donor cord blood characteristics, identifying optimal conditions (low nucleated red blood cell content and short collection-to-cryopreservation time) that improved CAR-NK persistence and clinical outcomes. Despite demonstrating safety, scalability, and ease of administration, durability of responses remained inferior to CAR-T cell therapy, emphasizing the need for optimized donor selection, improved CAR signaling, and potential combination strategies to enhance clinical outcomes.

2.5.3. iPSC-derived CAR-NK cells combined with rituximab for B-Cell lymphomas

Ghobadi et al. reported outcomes from a first-in-human trial of FT596, an iPSC-derived CAR-NK therapy targeting CD19-positive B-cell lymphomas [32]. FT596 is engineered with a CD19-specific CAR, high-affinity non-cleavable CD16 (hnCD16) to enable antibody-dependent cellular cytotoxicity (ADCC), and an IL-15/IL-15 Rα fusion protein to promote persistence. Evaluated alone and with rituximab, this dual-targeting strategy demonstrated clinical activity across multiple lymphoma subtypes.

Of 86 enrolled patients, 33 (38%) had received prior CD19 CAR-T therapy. Nearly half of these patients responded to FT596, with a 30% complete response rate – highlighting its potential to overcome resistance via CD20-directed ADCC. Responses were strongest in indolent and transformed lymphomas, including an 85% CR rate in follicular lymphoma. Efficacy was more limited in de novo diffuse large B-cell lymphoma (DLBCL), with an ORR of 14% and CR rate of 5%. Safety outcomes were favorable: CRS was rare and mild, and there were no cases of neurotoxicity or GVHD. FT596 persistence was modest (detectable up to 15 days), and the median PFS in combination therapy was 3.5 months. Five patients developed myelodysplastic syndrome, though most had prior HSCT or extensive cytotoxic therapy, limiting causal attribution.

In sum, FT596 shows promise as a safe, scalable option for relapsed/refractory lymphoma, especially in patients with prior CAR-T failure. Future efforts to enhance persistence, extend durability, and optimize efficacy in aggressive subtypes are needed.

2.6. Ongoing clinical trials: current landscape

Beyond the two landmark studies described above, numerous ongoing clinical trials are evaluating CAR-NK cell therapies across a spectrum of hematologic and solid malignancies, with each study exploring unique target antigens, NK cell sources, and CAR construct designs. Table 1 summarizes these trials, highlighting key parameters such as the trial identifier, phase, CAR construct, cell source, targeted malignancy, and status. For instance, multiple trials have focused on CD19-targeted CAR-NK cells, which represent one of the most extensively studied platforms [85–89]. Beyond CD19, other trials are exploring CAR-NK therapies that target additional antigens. For example, investigational products aimed at CD7 are being evaluated in relapsed or refractory leukemia and lymphoma using platforms such as the NK92 cell line. Similarly, clinical studies focusing on CD22-targeted CAR-NK cells – often utilizing iPSC-derived cells – are underway to address scenarios where antigen loss contributes to therapeutic resistance.

CAR-NK cell approaches are also being extended to myeloid malignancies. In another trial targeting acute myeloid leukemia (AML), CAR-NK cells are directed against CD33—a surface antigen commonly expressed on myeloid blasts. Registered under NCT02944162 and utilizing the NK92 cell line, this study employs a CAR design that integrates CD33 specificity with costimulatory signaling domains [61]. By focusing on CD33, researchers hope to overcome the limitations seen in therapies for myeloid malignancies, where antigen loss and heterogeneity have traditionally limited treatment success. Although NK92 cells offer advantages in terms of rapid expansion and standardized production, their required irradiation and lack of CD16 expression – which precludes antibody-dependent cellular cytotoxicity (ADCC) – remain key areas that the trial seeks to address through refined engineering approaches.

In the realm of multiple myeloma, CAR-NK cells directed against BCMA are being investigated using both NK92 and iPSC-derived platforms [90–92]. These studies aim to overcome challenges such as antigen heterogeneity and poor durability of responses in heavily pretreated patients. Additional targets in myeloma, including CD70, CD38, and SLAMF7, are under active investigation, further broadening the applicability of CAR-NK cell therapies in hematologic malignancies.

Beyond hematologic cancers, early-phase clinical trials are beginning to assess CAR-NK cell efficacy in solid tumors. Investigational studies targeting antigens such as HER2, PSMA, mesothelin, and CD276 are exploring innovative engineering strategies to improve NK cell trafficking, persistence, and function within the immunosuppressive tumor microenvironment (see Table 2). These trials typically integrate advanced modifications – ranging from chemokine receptor overexpression to metabolic reprogramming – to enhance NK cell homing and overcome the physical and biological barriers unique to solid tumors.

Overall, the diversity of ongoing clinical trials reflects a robust, dynamic effort to optimize CAR-NK cell therapy. By evaluating different target antigens, utilizing a range of NK cell sources (including peripheral blood, cord blood, HSPCs, iPSCs, and the NK92 cell line), and implementing various engineering strategies, these studies aim to identify the most effective and safe approaches for harnessing the innate antitumor properties of NK cells. The outcomes of these trials are expected to be instrumental in shaping the future of adoptive cell therapy, potentially paving the way for more accessible, off-the-shelf immunotherapeutic options for patients with both hematologic malignancies and solid tumors.

2.7. Unmet needs and future directions

2.7.1. Limitations of CAR-NK cell therapy

2.7.1.1. Evidence quality and study design. The majority of clinical data on CAR-NK cell therapy stems from early-phase, single-arm studies with small patient cohorts and variable follow-up durations. These trials often lack comparator arms, precluding direct assessments of relative efficacy or safety compared to standard-of-care therapies or other cellular immunotherapies. Most studies are conducted in heavily pretreated or refractory populations, which introduces heterogeneity and confounds interpretation of response durability and generalizability. In addition, inconsistent definitions of response, endpoints, and follow-up duration further impair interpretability and make comparisons across trials difficult. Randomized controlled trials are urgently needed to establish the clinical value of CAR-NK therapy and guide appropriate patient selection [68–70,74,93–96].

2.7.1.2. Publication and selection bias. Like many emerging therapies, CAR-NK research is vulnerable to publication bias, with a disproportionate number of studies reporting positive or favorable results. Trials with neutral or negative findings are less frequently published, and preclinical models may be optimized for efficacy, failing to capture translational hurdles. This can lead to an inflated perception of clinical potential. Moreover, CAR-NK trials that fail to meet endpoints or demonstrate limited persistence or tumor control often remain unpublished or underreported. Selection bias can also arise in early trials that enroll patients with less aggressive disease biology or favorable performance status, skewing outcomes [70,93,97]. A balanced representation of both positive and negative studies is essential to fully understand the therapeutic window of CAR-NK products.

2.7.1.3. Efficacy limitations and failures. Although CAR-NK cells have shown activity in hematologic malignancies, their efficacy is variable and largely unproven in solid tumors. Response rates in hematologic diseases, such as B-cell lymphoma or AML, remain modest in most studies, with frequent relapses due to antigen escape, poor cell persistence,

Table 1. Overview of CAR-NK clinical trials for hematologic malignancies recruiting or completed from ClinicalTrials.Gov.

Disease	CAR Construct/ Target	NK Cell Source	Clinical Trial Identifier	Sponsor	First Posted	Study Status
Acute Lymphoblastic Leukemia	CD19	Cord blood	NCT05563545	Shanghai Simnova Biotechnology Co.,Ltd.	10/3/22	COMPLETED; No interim results.
AML (Acute Myeloid Leukemia)	CD123	Not disclosed	NCT06690827	Chongqing Precision Biotech Co., Ltd	11/15/24	RECRUITING
Multiple Myeloma	BCMA	Not disclosed	NCT06045091	Hrain Biotechnology Co., Ltd.	9/21/23	RECRUITING
AML	CD123	Not disclosed	NCT06006403	Chongqing Precision Biotech Co., Ltd	8/23/23	RECRUITING
Relapsed Adult AML	CLL-1	Not disclosed	NCT06307054	Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine	3/12/24	RECRUITING
Acute Myeloid Leukemia Refractory	CD123	Not disclosed	NCT05574608	Affiliated Hospital to Academy of Military Medical Sciences	10/10/22	RECRUITING
B-cell Non Hodgkin Lymphoma	CD19	Cord blood	NCT05472558	Second Affiliated Hospital, School of Medicine, Zhejiang University	7/25/22	ENROLLING BY INVITATION
Acute Lymphoblastic Leukemia	CD19	Not disclosed	NCT05739227	Xuzhou Medical University	2/22/23	RECRUITING
B-cell Non Hodgkin Lymphoma	CD10, CD19, IL-10	Cord blood	NCT06707259	Second Affiliated Hospital, School of Medicine, Zhejiang University	11/27/24	RECRUITING
Primary Mediastinal B-cell Lymphoma	CD19	Cord Blood	NCT06464861	Second Affiliated Hospital, School of Medicine, Zhejiang University	6/18/24	RECRUITING
Refractory/Recurrent CNS Lymphoma	CD19	Cord blood	NCT06827782	Second Affiliated Hospital, School of Medicine, Zhejiang University	2/14/25	ENROLLING BY INVITATION
AML in Relapse	CD123	Not disclosed	NCT06201247	Peking University People's Hospital	1/11/24	RECRUITING
AML, Adult	CLL1	iPSC	NCT06027853	Zhejiang University	9/7/23	RECRUITING
B-Lymphoid Malignancies	CD19	Cord blood	NCT03056339	M.D. Anderson Cancer Center	2/17/17	Day 30 and 100 ORR = 48.6% 1-year OS = 68% 1-year PFS = 32% Higher CAR-NK persistence and function associated with optimal CBUs (≤8 × 10^7 nRBCs, ≤24 h collection-to-cryopreservation) Improved antitumor activity confirmed in vivo
AML, Adult	CLL1, CD33	iPSC	NCT06367673	Zhejiang University	4/16/24	RECRUITING
B-cell Non-Hodgkin Lymphoma	CD19, CD70	Cord blood	NCT05667155	Second Affiliated Hospital, School of Medicine, Zhejiang University	12/28/22	RECRUITING
Hematological Malignancy	CD5	Cord blood	NCT05110742	M.D. Anderson Cancer Center	11/8/21	RECRUITING
B-Cell Lymphoma	CD70/IL-15 transduced	Cord blood	NCT05092451	M.D. Anderson Cancer Center	10/25/21	RECRUITING
Refractory/Relapsed B-cell NHL	CD19, 70	Cord blood	NCT05842707	Aibin Liang, MD, PhD	5/6/23	RECRUITING
AML/MDS	CD33	Healthy Adult donors	NCT06325748	Senti Biosciences	3/22/24	RECRUITING
Healthy Donors	N/A	PBMCs vs Healthy Adult donors	NCT06727383	European Institute of Oncology	12/10/24	RECRUITING
AML, Adult	CD33	iPSC	NCT05665075	Zhejiang University	12/27/22	RECRUITING

Table 2. Overview of CAR-NK clinical trials for solid oncologic malignancies recruiting or completed from ClinicalTrials.Gov.

Disease	CAR Target	NK Cell Source	Clinical Trial Identifier	Sponsor	First Posted	Study Status
Pancreatic Cancer, Non-resectable	NKG2DL-ACE2	Not disclosed	NCT06478459	Zhejiang University	6/27/24	RECRUITING
Stage IV Ovarian Cancer	Claudin6, GPC3, Mesothelin, or AXL	PBMCs	NCT05410717	Second Affiliated Hospital of Guangzhou Medical University	6/8/22	RECRUITING
Ovarian Cancer	NKG2DL	Not disclosed	NCT05776355	Hangzhou Cheetah Cell Therapeutics Co., Ltd	3/20/23	RECRUITING
Refractory Metastatic Colorectal Cancer	NKG2DL	Not disclosed	NCT05213195	Zhejiang University	1/28/22	RECRUITING
Pancreatic Cancer, Non-resectable	NKG2DL	Not disclosed	NCT06503497	Zhejiang University	7/16/24	RECRUITING
Advanced Triple Negative Breast Cancer	SZ011	Not disclosed	NCT05686720	First Affiliated Hospital of Shantou University Medical College	1/17/23	UNKNOWN
Gastric and Pancreatic Adenocarcinoma	Claudin18.2	Cord Blood	NCT06464965	Zhejiang Provincial People's Hospital	6/18/24	RECRUITING
Ovarian Epithelial Carcinoma	SZ011	Not disclosed	NCT05856643	Shantou University Medical College	5/12/23	RECRUITING
Solid Tumors	TROP2	Cord Blood	NCT06066424	M.D. Anderson Cancer Center	10/4/23	RECRUITING
Pancreatic/Ovarian Cancer	TROP2	Cord Blood	NCT05922930	M.D. Anderson Cancer Center	6/28/23	RECRUITING
Gastroesophageal Junction & HNSCC	PDL1/FcγRIIIa	Not disclosed	NCT04847466	National Cancer Institute (NCI)	4/19/21	RECRUITING
Colorectal Cancer (MRD)	TROP2	Cord Blood	NCT06358430	M.D. Anderson Cancer Center	4/10/24	RECRUITING
Renal Cell Carcinoma, Mesothelioma, Osteosarcoma	CD70	Cord Blood	NCT05703854	M.D. Anderson Cancer Center	1/30/23	RECRUITING

or suboptimal tumor engagement [98]. In solid tumors, clinical efficacy has been minimal, owing in part to the hostile tumor microenvironment (TME), lack of robust infiltration, and limited recognition of non-hematologic antigens [93]. Durable responses remain the exception rather than the rule and identifying biomarkers that predict which patients are likely to benefit remains a significant unmet need.

2.7.1.4. Safety and toxicity. One theoretical advantage of CAR-NK therapy is an improved safety profile compared to CAR-T cells, particularly with a lower incidence of cytokine release syndrome (CRS) and immune effector cell – associated neurotoxicity syndrome (ICANS). However, this hypothesis is not yet supported by high-quality comparative data. Most published studies report only short-term safety outcomes, with limited information on late adverse events or cumulative toxicities. Additionally, cytokine engineering (e.g., IL-15 expression) could lead to unanticipated toxicities such as prolonged cytopenias, off-target effects, or sustained immune activation [68–70,93–95]. Systematic long-term safety monitoring and pharmacovigilance efforts are needed as these therapies advance to later-phase trials.

3. Biological and technical challenges

Several intrinsic and extrinsic biological factors limit the therapeutic potential of CAR-NK cells:

3.1. Limited in vivo persistence

NK cells lack the ability to expand and persist long-term in vivo without exogenous cytokine support. This is particularly true for cord blood-derived NK cells, which exhibit replicative senescence and are often cleared by the recovering immune system post-lymphodepletion. The absence of homeostatic cytokine signaling (e.g., IL-15) and inadequate co-stimulation further impair persistence [70].

3.2. Restricted tumor infiltration

In solid tumors, CAR-NK cells face challenges trafficking across the abnormal vasculature and dense stroma. Hypoxia and metabolic suppression in the TME limit NK cell survival and function, reducing effective tumor engagement [93,94].

3.3. Functional exhaustion and variability

NK cells demonstrate variable cytotoxic potential, influenced by donor source, cytokine priming, and CAR construct design. This heterogeneity contributes to inconsistent potency across trials and patient populations [97].

3.4. Antigen escape and tumor heterogeneity

Tumors may downregulate or shed the targeted antigen, enabling immune evasion. This is compounded by intratumoral heterogeneity, which makes single-antigen targeting less effective and prone to relapse [98].

4. Solutions attempted and ongoing

To address these limitations, several approaches are under investigation:

4.1. Cytokine engineering

Transgenic expression of IL-15 within CAR constructs has improved proliferation and survival in preclinical models. Trials incorporating membrane-bound or secreted IL-15 are

ongoing and may enhance durability without systemic cytokine administration [36,41,62].

4.2. Combination therapies

Checkpoint inhibitors (e.g., anti-PD-1/PD-L1), monoclonal antibodies (e.g., anti-CD38), and chemotherapy or radiotherapy have been combined with CAR-NK therapy to augment efficacy, particularly in solid tumors. These combinations aim to enhance infiltration, reduce immunosuppression, and promote epitope spreading [99,100].

4.3. Advanced genetic modifications

CRISPR/Cas9 and TALEN editing tools are being used to enhance homing, resistance to TME-derived suppression, and multi-antigen recognition. Bispecific and tandem CAR designs are being developed to reduce antigen escape and target tumor heterogeneity [44,45].

4.4. Enhanced manufacturing protocols

Optimized ex vivo expansion techniques using feeder cells, cytokines (IL-2, IL-15, IL-21), and serum-free media have improved NK cell yields [33]. For iPSC-derived NK cells, protocols now emphasize genetic stability and maturation uniformity to reduce functional variability.

4.5. Integrative high-dimensional and transcriptomic profiling

Recent analytical platforms now integrate high-dimensional phenotyping and single-cell transcriptomics to map signaling dynamics and cell-to-cell variability in engineered immune cells. Using spectral flow cytometry and longitudinal profiling, Cadinanos-Garai et al. demonstrated how phenotypic and metabolic remodeling during CAR-T manufacturing influences effector function and checkpoint expression, providing a framework for optimizing culture and expansion parameters [101]. Complementary single-cell RNA-seq studies have revealed functional heterogeneity and exhaustion signatures within CAR-expressing subpopulations, emphasizing the need for transcriptomic quality control to guide next-generation CAR engineering. Together, these tools are transforming CAR and CAR-NK development from empirical design toward data-driven cellular engineering [102].

5. Future perspectives

5.1. Fc-receptor optimization and antibody-dependent cellular cytotoxicity (ADCC) enhancement

One innovative approach to augment NK-mediated ADCC is the engineering of high-affinity Fc receptors, particularly CD16 (FcγRIIIa), to improve binding to therapeutic antibodies. Native CD16 is susceptible to cleavage by ADAM17, limiting its durability and cytotoxic capacity. To address this, Fc-engineered NK cell platforms have incorporated non-cleavable CD16 variants (e.g., CD16-158 V and ADAM17-resistant mutants), resulting in sustained receptor expression and enhanced cytotoxicity [103].

A prominent example is the iPSC-derived CAR-NK product FT596, which integrates three synergistic components: a CD19-directed CAR, IL-15 receptor fusion for persistence, and a high-affinity, non-cleavable CD16 receptor. This enables dual targeting – direct cytotoxicity via CAR engagement and ADCC via CD16 when combined with anti-CD20 antibodies like rituximab.

This strategy was clinically validated in the Ghobadi et al. 2025 trial, which enrolled a heavily pretreated population, including patients previously exposed to CD19 CAR-T therapy (~38%) [32]. Among this post-CAR-T cohort, nearly 30% achieved complete responses, underscoring the potential of Fc-enhanced NK platforms to overcome antigen loss and restore sensitivity to mAb therapy.

More broadly, Fc-optimized NK cells may address several key limitations in traditional ADCC:

- Resistance due to low CD16 expression or shedding
- Poor affinity of native CD16 for therapeutic IgG1
- Monoclonal antibody monotherapy limitations in antigen-heterogeneous or immune-suppressed tumors

Ongoing strategies include combining these Fc-enhanced NK cells with Fc-engineered monoclonal antibodies (e.g., glycoengineered obinutuzumab) or with multispecific engagers to further amplify ADCC.

5.2. Cytokine-driven persistence and memory programming

Cytokine priming has emerged as a critical strategy to enhance CAR-NK cell persistence, cytotoxicity, and metabolic fitness. Among the most promising approaches is the generation of cytokine-induced memory-like (CIML) NK cells through preactivation with IL-12, IL-15, and IL-18. As demonstrated by Romee et al. CIML NK cells exhibit heightened IFN-γ production, increased oxidative metabolism, and prolonged in vivo persistence after adoptive transfer [33]. These features translated into superior tumor control in murine lymphoma models, establishing a rationale for their use in CAR-based strategies.

IL-15 remains a cornerstone cytokine due to its ability to promote NK cell survival and expansion without expanding regulatory T cells, unlike IL-2. In clinical applications, such as in Liu et al.'s cord blood – derived CAR-NK trial, membrane-bound IL-15 was incorporated into the CAR construct, leading to enhanced in vivo persistence and favorable safety. This highlights IL-15's relevance not only for ex vivo priming but also as a component of the engineered therapeutic product [37,39,41,62].

Additional strategies under investigation include the exogenous administration of IL-2 or IL-15 following infusion to support CAR-NK cell expansion in vivo, as well as incorporation of IL-21 to enhance proliferation and reduce NK cell exhaustion. However, these cytokines must be balanced carefully to avoid systemic toxicity or off-target effects. The optimal combination, timing, and delivery mechanism of cytokines – whether administered exogenously or engineered

into CAR constructs – remain active areas of research to improve NK cell-based therapies.

5.3. Multispecific engagers and modular car platforms

Bispecific (BiKE) and trispecific (TriKE) NK cell engagers are an emerging class of immunotherapeutics designed to redirect and enhance NK cytotoxicity against tumor cells. These molecules typically consist of 2–3 single-chain variable fragments (scFv) that simultaneously bind to CD16 on NK cells and tumor-associated antigens. TriKEs may also incorporate an IL-15 moiety to support NK cell proliferation and survival. Unlike conventional monoclonal antibodies, BiKEs and TriKEs directly engage CD16 without relying on Fc-mediated binding, thereby overcoming competition with circulating IgG and enhancing ADCC potency [104]. Their compact size improves biodistribution and tissue penetration, and they can be rapidly engineered for diverse tumor targets.

Recent studies have shown that CD16xCD19 and CD16xCD19xCD22 engagers elicit superior cytotoxicity and cytokine secretion compared to rituximab in B-cell malignancies. In AML and MDS, CD16xCD33 BiKEs overcome HLA-mediated inhibition and restore NK function. These data highlight the potential for off-the-shelf, adaptive strategies that can be rapidly tailored to tumor antigen profiles. Some next-generation CAR-NK designs are now incorporating BiKE/TriKE logic directly into the CAR framework, enabling autonomous recognition, activation, and persistence within the tumor microenvironment [99,100,105]. Together, these advances represent a mechanistic shift in CAR-NK cell engineering – from single-target recognition to multifunctional, modular constructs capable of overcoming antigen escape and improving therapeutic durability.

5.4. Economic and health System uncertainties

The economic viability and cost-effectiveness of CAR-NK cell therapy remain unclear. While NK cells may offer a more scalable, off-the-shelf platform compared to autologous CAR-T products, manufacturing complexities and lack of regulatory harmonization across centers pose cost challenges. Additionally, reimbursement frameworks are ill-equipped to evaluate novel allogeneic cell therapies with limited long-term data. These uncertainties may slow adoption despite clinical interest.

5.5. Need for standardization and reporting

Significant heterogeneity exists across CAR-NK trials in terms of patient selection, cell source, transduction method, expansion protocols, outcome definitions, and correlative endpoints. This impairs data synthesis, cross-trial comparisons, and meta-analytic efforts. There is an urgent need for consensus on key reporting standards, manufacturing benchmarks, and validated biomarkers of response to guide the next phase of CAR-NK clinical development.

6. Conclusions

CAR-NK cell therapy represents a dynamic and rapidly evolving frontier in cancer immunotherapy. By leveraging the inherent cytotoxicity, safety, and allogeneic potential of NK cells, researchers have developed innovative strategies to overcome many of the limitations associated with CAR-T cell therapy. Preclinical studies have provided compelling evidence that CAR-NK cells, particularly when enhanced through cytokine armoring, memory-like induction, and optimized receptor signaling, can mediate potent and durable antitumor responses. The encouraging safety profile and rapid antitumor responses observed in early clinical trials – such as those by Liu et al. and Ghobadi et al. – underscore the potential of CAR-NK cells as off-the-shelf immunotherapeutics.

Despite these promising advances, significant challenges remain. In vivo persistence, effective trafficking to tumor sites, and overcoming the immunosuppressive tumor microenvironment are key hurdles that must be addressed to realize the full therapeutic potential of CAR-NK cells. Furthermore, the heterogeneity of NK cell sources and the complexities of donor selection underscore the need for robust manufacturing and quality-control processes.

Looking ahead, the future of CAR-NK cell therapy is bright. Advances in genetic engineering, synthetic biology, and multiomic profiling promise to drive the development of next-generation CAR constructs that are more potent, safer, and better tailored to individual patient needs. The integration of combination therapies and personalized medicine approaches will likely further enhance the efficacy of these treatments, paving the way for their application in both hematologic malignancies and solid tumors.

In summary, CAR-NK cells offer a unique and versatile platform for cancer immunotherapy. Their potential to provide off-the-shelf, safe, and effective treatments could revolutionize the management of cancer, ultimately improving outcomes for patients who currently have limited therapeutic options. Continued preclinical research, coupled with well-designed clinical trials, will be essential to address the current challenges and fully unlock the therapeutic promise of CAR-NK cell therapy.

Together, advances in molecular analytics, high-resolution immune profiling, and next-generation cell engineering are converging to transform CAR-NK therapy from an experimental concept into a rationally designed, precision-guided platform. These innovations are expected to yield products with improved persistence, antigen coverage, and manufacturing scalability – defining the next generation of CAR-NK therapies poised for durable, off-the-shelf cancer immunotherapy.

Author contributions

HCC and AG conceived the manuscript, conducted the research, and drafted the text. KAG created the figures, wrote the figure legends and the section of the manuscript on CAR structure in CAR-T and CAR-NK cells, and performed the literature review comparing CAR structures in CAR-T versus CAR-NK. All authors contributed to the article and approved the final version.

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References

1. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507–1517. doi: 10.1056/NEJMoa1407222
2. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med. 2017;377(26):2545–2554. doi: 10.1056/NEJMoa1708566
3. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531–2544. doi: 10.1056/NEJMoa1707447
4. Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. 2018;378(5):449–459. doi: 10.1056/NEJMoa1709919
5. June CH, O'Connor RS, Kawalekar OU, et al. CAR T cell immunotherapy for human cancer. Science. 2018;359(6382):1361–1365. doi: 10.1126/science.aar6711
6. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2020;382(14):1331–1342. doi: 10.1056/NEJMoa1914347
7. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med. 2019;380(18):1726–1737. doi: 10.1056/NEJMoa1817226
8. Munshi NC, Anderson LD, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705–716. doi: 10.1056/NEJMoa2024850
9. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. Lancet Oncol. 2019;20(1):31–42. doi: 10.1016/S1470-2045(18)30864-7
10. Grigor EJM, Fergusson D, Kekre N, et al. Risks and benefits of chimeric antigen receptor T-cell (CAR-T) therapy in cancer: a systematic review and meta-analysis. Transfus Med Rev. 2019;33(2):98–110. doi: 10.1016/j.tmrv.2019.01.005
11. Malmberg K-J, Carlsten M, Björklund A, et al. Natural killer cell-mediated immunosurveillance of human cancer. Semin Immunol. 2017;31:20–29. doi: 10.1016/j.smim.2017.08.002
12. Lanier LL. Nkg2d receptor and its ligands in host defense. Cancer Immunol Res. 2015;3(6):575–582. doi: 10.1158/2326-6066.CIR-15-0098
13. Romee R, Schneider SE, Leong JW, et al. Cytokine activation induces human memory-like NK cells. Blood. 2012;120(24):4751–4760. doi: 10.1182/blood-2012-04-419283
14. Spanholtz J, Tordoir M, Eissens D, et al. High log-scale expansion of functional human natural killer cells from umbilical cord blood CD34-positive cells for adoptive cancer immunotherapy. PLOS ONE. 2010;5(2):e9221. doi: 10.1371/journal.pone.0009221
15. Miller JS. Therapeutic applications: natural killer cells in the clinic. Hematology. 2013;2013(1):247–253. doi: 10.1182/asheducation-2013.1.247
16. Bachanova V, Ghobadi A, Patel K, et al. Safety and efficacy of FT596, a first-in-class, multi-antigen targeted, off-the-shelf, iPSC-derived CD19 CAR NK cell therapy in relapsed/refractory B-cell lymphoma. Blood. 2021;138(Supplement 1):823. doi: 10.1182/blood-2021-151185
17. Goodridge JP, Mahmood S, Zhu H, et al. Ft596: translation of first-of-kind multi-antigen targeted off-the-shelf CAR-NK cell with engineered persistence for the treatment of B cell malignancies. Blood. 2019;134(Supplement_1):301. doi: 10.1182/blood-2019-129319
18. Abel AM, Yang C, Thakar MS, et al. Natural killer cells: development, maturation, and clinical utilization. Front Immunol. 2018;9:1869. doi: 10.3389/fimmu.2018.01869
19. Joncker NT, Fernandez NC, Treiner E, et al. Nk cell responsiveness is tuned commensurate with the number of inhibitory receptors for self MHC class I: the rheostat model. J Immunol Baltim Md 1950. 2009;182(8):4572–4580.
20. Joncker NT, Shifrin N, Delebecque F, et al. Mature natural killer cells reset their responsiveness when exposed to an altered MHC environment. J Exp Med. 2010;207(10):2065–2072. doi: 10.1084/jem.20100570
21. Burshtyn DN, Scharenberg AM, Wagtmann N, et al. Recruitment of tyrosine phosphatase HCP by the killer cell inhibitor receptor. Immunity. 1996;4(1):77–85. doi: 10.1016/S1074-7613(00)80300-3
22. Yokoyama WM, Kim S. How do natural killer cells find self to achieve tolerance? Immunity. 2006;24(3):249–257. doi: 10.1016/j.immuni.2006.03.006
23. Peng L, Sferruzza G, Yang L, et al. Car-T and car-nk as cellular cancer immunotherapy for solid tumors. Cell Mol Immunol. 2024;21(10):1089–1108. doi: 10.1038/s41423-024-01207-0
24. Laskowski TJ, Biederstädt A, Rezvani K. Natural killer cells in anti-tumour adoptive cell immunotherapy. Nat Rev Cancer. 2022;22(10):557–575. doi: 10.1038/s41568-022-00491-0
25. Lanier LL, Corliss BC, Wu J, et al. Immunoreceptor DAP12 bearing a tyrosine-based activation motif is involved in activating NK cells. Nature. 1998;391(6668):703–707. doi: 10.1038/35642
26. Zhao R, Cheng L, Jiang Z, et al. Dnax-activating protein 10 co-stimulation enhances the anti-tumor efficacy of chimeric antigen receptor T cells. Oncoimmunology. 2019;8(1):e1509173. doi: 10.1080/2162402X.2018.1509173
27. Töpfer K, Cartellieri M, Michen S, et al. Dap12-based activating chimeric antigen receptor for NK cell tumor immunotherapy. J Immunol Baltim Md 1950. 2015;194(7):3201–3212. doi: 10.4049/jimmunol.1400330
28. Billadeau DD, Upshaw JL, Schoon RA, et al. NKG2D-DAP10 triggers human NK cell-mediated killing via a Syk-independent regulatory pathway. Nat Immunol. 2003;4(6):557–564. doi: 10.1038/ni929
29. Daher M, Rezvani K. Outlook for new CAR-based therapies with a focus on CAR-NK cells: what lies beyond CAR-engineered T cells in the race against cancer. Cancer Discov. 2021;11(1):45–58.
30. Xu Y, Liu Q, Zhong M, et al. 2b4 costimulatory domain enhancing cytotoxic ability of anti-CD5 chimeric antigen receptor engineered natural killer cells against T cell malignancies. J Hematol Oncol. 2019;12(1):49. doi: 10.1186/s13045-019-0732-7
31. Imai C, Iwamoto S, Campana D. Genetic modification of primary natural killer cells overcomes inhibitory signals and induces specific killing of leukemic cells. Blood. 2005;106(1):376–383. doi: 10.1182/blood-2004-12-4797
32. Ghobadi A, Bachanova V, Patel K, et al. Induced pluripotent stem-cell-derived CD19-directed chimeric antigen receptor natural killer cells in B-cell lymphoma: a phase 1, first-in-human trial. Lancet. 2025;405(10473):127–136. doi: 10.1016/S0140-6736(24)02462-0
33. Romee R, Rosario M, Berrien-Elliott MM, et al. Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. Sci Transl Med. 2016;8(357):ra357123–ra357123. doi: 10.1126/scitranslmed.aaf2341
34. Shapiro RM, Birch GC, Hu G, et al. Expansion, persistence, and efficacy of donor memory-like NK cells infused for posttransplant

relapse. J Clin Invest. 2022;132(11):e154334. doi: 10.1172/JCI154334
35. Dolstra H, Roeven MWH, Spanholtz J, et al. Successful transfer of umbilical cord blood CD34+ hematopoietic stem and progenitor-derived NK cells in older acute myeloid leukemia patients. Clin Cancer Res Off J Am Assoc Cancer Res. 2017;23(15):4107–4118. doi: 10.1158/1078-0432.CCR-16-2981
36. Liu E, Tong Y, Dotti G, et al. Cord blood NK cells engineered to express IL-15 and a CD19-targeted CAR show long-term persistence and potent antitumor activity. Leukemia. 2018;32(2):520–531. doi: 10.1038/leu.2017.226
37. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. N Engl J Med. 2020;382(6):545–553. doi: 10.1056/NEJMoa1910607
38. Denman CJ, Senyukov VV, Somanchi SS, et al. Membrane-bound IL-21 promotes sustained ex vivo proliferation of human natural killer cells. PLOS ONE. 2012;7(1):e30264. doi: 10.1371/journal.pone.0030264
39. Liu M, Meng Y, Zhang L, et al. High-efficient generation of natural killer cells from peripheral blood with preferable cell vitality and enhanced cytotoxicity by combination of IL-2, IL-15 and IL-18. Biochem Biophys Res Commun. 2021;534:149–156. doi: 10.1016/j.bbrc.2020.12.012
40. Nakazawa T, Morimoto T, Maeoka R, et al. Establishment of an efficient ex vivo expansion strategy for human natural killer cells stimulated by defined cytokine cocktail and antibodies against natural killer cell activating receptors. Regen Ther. 2022;21:185–191. doi: 10.1016/j.reth.2022.07.001
41. Berrien-Elliott MM, Becker-Hapak M, Cashen AF, et al. Systemic IL-15 promotes allogeneic cell rejection in patients treated with natural killer cell adoptive therapy. Blood. 2022;139(8):1177–1183. doi: 10.1182/blood.2021011532
42. Gang M, Marin ND, Wong P, et al. CAR-modified memory-like NK cells exhibit potent responses to NK-resistant lymphomas. Blood. 2020;136(20):2308–2318. doi: 10.1182/blood.2020006619
43. Shokouhifar A, Anani Sarab G, Yazdanifar M, et al. Overcoming the UCB HSCs –derived NK cells dysfunction through harnessing RAS/MAPK, IGF-1R and TGF-β signaling pathways. Cancer Cell Int. 2021;21(1):298. doi: 10.1186/s12935-021-01983-z
44. Elmas E, Saljoughian N, de Souza Fernandes Pereira M, et al. Crispr gene editing of human primary NK and T cells for cancer immunotherapy. Front Oncol. 2022;12. doi: 10.3389/fonc.2022.834002
45. Gurney M, O'Reilly E, Corcoran S, et al. Concurrent transposon engineering and CRISPR/Cas9 genome editing of primary CLL-1 chimeric antigen receptor–natural killer cells. Cytotherapy. 2022;24(11):1087–1094. doi: 10.1016/j.jcyt.2022.07.008
46. Wu X, Matosevic S. Gene-edited and CAR-NK cells: opportunities and challenges with engineering of NK cells for immunotherapy. Mol Ther Oncolytics. 2022;27:224–238. doi: 10.1016/j.omto.2022.10.011
47. Gustafson MP, Ligon JA, Bersenev A, et al. Emerging frontiers in immuno- and gene therapy for cancer. Cytotherapy. 2023;25(1):20–32. doi: 10.1016/j.jcyt.2022.10.002
48. Zhang B, Yang M, Zhang W, et al. Chimeric antigen receptor-based natural killer cell immunotherapy in cancer: from bench to bedside. Cell Death Dis. 2024;15(1):1–18.
49. Xie G, Dong H, Liang Y, et al. Car-NK cells: a promising cellular immunotherapy for cancer. EBioMedicine. 2020;59. doi: 10.1016/j.ebiom.2020.102975
50. Zhang L, Meng Y, Feng X, et al. Car-NK cells for cancer immunotherapy: from bench to bedside. Biomark Res. 2022;10(1):12. doi: 10.1186/s40364-022-00364-6
51. Fang F, Xie S, Chen M, et al. Advances in NK cell production. Cell Mol Immunol. 2022;19(4):460–481. doi: 10.1038/s41423-021-00808-3
52. Ueda T, Kumagai A, Iriguchi S, et al. Non–clinical efficacy, safety and stable clinical cell processing of induced pluripotent stem cell-derived anti–glypican-3 chimeric antigen receptor-expressing natural killer/innate lymphoid cells. Cancer Sci. 2020;111(5):1478–1490. doi: 10.1111/cas.14374
53. Chang Y, Jin G, Luo W, et al. Engineered human pluripotent stem cell-derived natural killer cells with PD-L1 responsive immunological memory for enhanced immunotherapeutic efficacy. Bioact Mater. 2023;27:168–180. doi: 10.1016/j.bioactmat.2023.03.018
54. Klaihmon P, Luanpitpong S, Kang X, et al. Anti-TIM3 chimeric antigen receptor-natural killer cells from engineered induced pluripotent stem cells effectively target acute myeloid leukemia cells. Cancer Cell Int. 2023;23(1):297. doi: 10.1186/s12935-023-03153-9
55. Chung L, Cogburn LA, Sui L, et al. Development of an induced pluripotent stem cell–specific microRNA assay for detection of residual undifferentiated cells in natural killer cell therapy products. Cytotherapy. 2022;24(7):733–741. doi: 10.1016/j.jcyt.2022.02.005
56. Fu X, Wu S, Li B, et al. Functions of p53 in pluripotent stem cells. Protein Cell. 2020;11(1):71–78. doi: 10.1007/s13238-019-00665-x
57. Gong JH, Maki G, Klingemann HG. Characterization of a human cell line (NK-92) with phenotypical and functional characteristics of activated natural killer cells. Leukemia. 1994;8(4):652–658.
58. Fabian KP, Padget MR, Donahue RN, et al. Pd-l1 targeting high-affinity NK (t-haNK) cells induce direct antitumor effects and target suppressive MDSC populations. J Immunother Cancer. 2020;8(1):e000450. doi: 10.1136/jitc-2019-000450
59. Nowakowska P, Romanski A, Miller N, et al. Clinical grade manufacturing of genetically modified, CAR-expressing NK-92 cells for the treatment of ErbB2-positive malignancies. Cancer Immunol Immunother. 2018;67(1):25–38. doi: 10.1007/s00262-017-2055-2
60. Zhang Y, Zhou W, Yang J, et al. Chimeric antigen receptor engineered natural killer cells for cancer therapy. Exp Hematol Oncol. 2023;12(1):70. doi: 10.1186/s40164-023-00431-0
61. Tang X, Yang L, Li Z, et al. First-in-man clinical trial of CAR NK-92 cells: safety test of CD33-CAR NK-92 cells in patients with relapsed and refractory acute myeloid leukemia. Am J Cancer Res. 2018;8(6):1083–1089.
62. Silvestre RN, Eitler J, de Azevedo JTC, et al. Engineering NK-CAR.19 cells with the IL-15/IL-15Rα complex improved proliferation and anti-tumor effect in vivo. Front Immunol. 2023;14. doi: 10.3389/fimmu.2023.1226518
63. Cichocki F, Goodridge JP, Bjordahl R, et al. Dual antigen-targeted off-the-shelf NK cells show durable response and prevent antigen escape in lymphoma and leukemia. Blood. 2022;140(23):2451–2462. doi: 10.1182/blood.2021015184
64. Cichocki F, Bjordahl R, Gaidarova S, et al. iPSC-derived NK cells maintain high cytotoxicity and enhance in vivo tumor control in concert with T cells and anti-PD-1 therapy. Sci Transl Med. 2020;12(568):eaaz5618.
65. Zhu H, Blum RH, Bjordahl R, et al. Pluripotent stem cell-derived NK cells with high-affinity noncleavable CD16a mediate improved antitumor activity. Blood. 2020;135(6):399–410. doi: 10.1182/blood.2019000621
66. Li Y, Hermanson DL, Moriarity BS, et al. Human iPSC-derived natural killer cells engineered with chimeric antigen receptors enhance anti-tumor activity. Cell STEM Cell. 2018;23(2):181–192.e5. doi: 10.1016/j.stem.2018.06.002
67. Meng F, Zhang S, Xie J, et al. Leveraging CD16 fusion receptors to remodel the immune response for enhancing anti-tumor immunotherapy in iPSC-derived NK cells. J Hematol Oncol. 2023;16(1):62. doi: 10.1186/s13045-023-01455-z
68. Marofi F, Abdul-Rasheed OF, Rahman HS, et al. Car-NK cell in cancer immunotherapy; a promising frontier. Cancer Sci. 2021;112(9):3427–3436. doi: 10.1111/cas.14993
69. Rafei H, Daher M, Rezvani K. Chimeric antigen receptor (CAR) natural killer (NK)-cell therapy: leveraging the power of innate immunity. Br J Haematol. 2021;193(2):216–230. doi: 10.1111/bjh.17186
70. Kong JC, Sa'ad MA, Vijayan HM, et al. Chimeric antigen receptor-natural killer cell therapy: current advancements and strategies to overcome challenges. Front Immunol. 2024;15. doi: 10.3389/fimmu.2024.1384039
71. Li T, Niu M, Zhang W, et al. Car-NK cells for cancer immunotherapy: recent advances and future directions. Front Immunol. 2024;15. doi: 10.3389/fimmu.2024.1361194
72. Ebrahimiyan H, Tamimi A, Shokoohian B, et al. Novel insights in CAR-NK cells beyond CAR-T cell technology; promising advantages.

Int Immunopharmacol. 2022;106:108587. doi: 10.1016/j.intimp.2022.108587
73. Włodarczyk M, Pyrzynska B. CAR-NK as a rapidly developed and efficient immunotherapeutic strategy against cancer. Cancers (Basel). 2022;15(1):117. doi: 10.3390/cancers15010117
74. Dagher OK, Posey AD. Forks in the road for CAR T and CAR NK cell cancer therapies. Nat Immunol. 2023;24(12):1994–2007. doi: 10.1038/s41590-023-01659-y
75. Barrow AD, Martin CJ, Colonna M. The natural cytotoxicity receptors in health and disease. Front Immunol. 2019;10:909. doi: 10.3389/fimmu.2019.00909
76. Peipp M, Klausz K, Boje AS, et al. Immunotherapeutic targeting of activating natural killer cell receptors and their ligands in cancer. Clin Exp Immunol. 2022;209(1):22–32. doi: 10.1093/cei/uxac028
77. Arora J, Ayyappan S, Yin C, et al. T-cell help in the tumor microenvironment enhances rituximab-mediated NK-cell ADCC. Blood. 2024;143(18):1816–1824. doi: 10.1182/blood.2023023370
78. Bottino C, Picant V, Vivier E, et al. Natural killer cells and engagers: powerful weapons against cancer. Immunol Rev. 2024;328(1):412–421. doi: 10.1111/imr.13384
79. Vacca P, Pietra G, Tumino N, et al. Exploiting human NK cells in tumor therapy. Front Immunol. 2020;10. doi: 10.3389/fimmu.2019.03013
80. Shimasaki N, Jain A, Campana D. Nk cells for cancer immunotherapy. Nat Rev Drug Discov. 2020;19(3):200–218. doi: 10.1038/s41573-019-0052-1
81. Hodgins JJ, Khan ST, Park MM, et al. Killers 2.0: NK cell therapies at the forefront of cancer control. J Clin Invest. 2019;129(9):3499–3510. doi: 10.1172/JCI129338
82. Hu W, Wang G, Huang D, et al. Cancer immunotherapy based on natural killer cells: current progress and new opportunities. Front Immunol. 2019;10. doi: 10.3389/fimmu.2019.01205
83. Zhang X. Anti-CD19 CAR NK cell therapy for relapsed or refractory B cell non-Hodgkin lymphoma: a multi-center, uncontrolled trial. Report no.: NCT04639739. Available from clinicaltrials.gov; 2020 [cited 2025 Feb 16]. Available from: https://clinicaltrials.gov/study/NCT04639739
84. Sivori S, Pende D, Quatrini L, et al. NK cells and ILCs in tumor immunotherapy. Mol Aspects Med. 2021;80:100870. doi: 10.1016/j.mam.2020.100870
85. Hebei Yanda Ludaopei Hospital, Sanhe, Hebei, China. Anti-CD19 CAR-engineered NK cells in the treatment of relapsed/refractory acute lymphoblastic leukemia. Report no.: NCT05563545. ClinicalTrials.gov. 2025 [cited 2025 Feb 16]. Available from: https://clinicaltrials.gov/study/NCT05563545
86. Second Affiliated Hospital, School of Medicine, Zhejiang University. Clinical study of HLA haploidentical CAR-NK cells targeting CD19 in the treatment of refractory/relapsed B-cell NHL. Report no.: NCT04887012. Available from clinicaltrials.gov; 2021 [cited 2025 Feb 16]. Available from: https://clinicaltrials.gov/study/NCT04887012
87. The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, China. Safety and efficacy of allogenic CD19-CAR-NK cells in treatmenting r/r B-cell hematologic malignancies. Report no.: NCT05739227. ClinicalTrials.gov. 2025 [cited 2025 Feb 16]. Available form: https://clinicaltrials.gov/study/NCT05739227
88. Second Affiliated Hospital, School of Medicine, Zhejiang University. Sequential treatment with 7x19 CAR-T after umbilical cord blood derived CD19 CARNK in relapsed/refractory B cell lymphoma. Report no.: NCT06464861. Available from clinicaltrials.gov; 2025 [cited 2025 Feb 16]. Available from: https://clinicaltrials.gov/study/NCT06464861
89. 2nd Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China. Cord blood-derived CAR-NK cells targeting CD19 for refractory/relapsed central nervous system lymphoma. Report no.: NCT06827782. ClinicalTrials.gov. 2025 [cited 2025 Feb 16]. Available from: https://clinicaltrials.gov/study/NCT06827782
90. Shenzhen Pregene Biopharma Co. Ltd. Clinical study of the safety and efficacy of chimeric antigen receptor NK cell injection targeting BCMA (BCMA CAR-NK) in patients with relapsed/refractory multiple myeloma. Report no.: NCT05652530. Available from clinicaltrials.gov; 2022 [cited 2025 Feb 16]. Available from: https://clinicaltrials.gov/study/NCT05652530
91. Shanghai Changzheng Hospital, Shanghai, Shanghai Municipality, China. To evaluate the safety and efficacy of human BCMA targeted CAR-NK cells injection for subjects with R/R MM or PCL. Report no.: NCT06045091. ClinicalTrials.gov. 2025 [cited 2025 Feb 16]. Available from: https://www.clinicaltrials.gov/study/NCT06045091
92. The Children's Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, China. Anti-CD19/BCMA CAR-NK cells in patients with B cell mediated autoimmune disease. Report no.: NCT06792799. ClinicalTrials.gov; [cited 2025 Feb 16]. Available from: https://clinicaltrials.gov/study/NCT06792799
93. Baghery Saghchy Khorasani A, Yousefi A-M, Bashash D. CAR NK cell therapy in hematologic malignancies and solid tumors; obstacles and strategies to overcome the challenges. Int Immunopharmacol. 2022;110:109041. doi: 10.1016/j.intimp.2022.109041
94. Gong Y, Klein Wolterink RGJ, Wang J, et al. Chimeric antigen receptor natural killer (CAR-NK) cell design and engineering for cancer therapy. J Hematol Oncol. 2021;14(1):73. doi: 10.1186/s13045-021-01083-5
95. Elahi R, Heidary AH, Hadiloo K, et al. Chimeric antigen receptor-engineered natural killer (CAR NK) cells in cancer treatment; recent advances and future prospects. STEM Cell Rev Rep. 2021;17(6):2081–2106. doi: 10.1007/s12015-021-10246-3
96. Yilmaz A, Cui H, Caligiuri MA, et al. Chimeric antigen receptor-engineered natural killer cells for cancer immunotherapy. J Hematol Oncol. 2020;13(1):168. doi: 10.1186/s13045-020-00998-9
97. Valeri A, García-Ortiz A, Castellano E, et al. Overcoming tumor resistance mechanisms in CAR-NK cell therapy. Front Immunol. 2022;13:953849. doi: 10.3389/fimmu.2022.953849
98. Hosseinalizadeh H, Wang L-S, Mirzaei H, et al. Emerging combined CAR-NK cell therapies in cancer treatment: finding a dancing partner. Mol Ther. 2025;33(6):2406–2425. doi: 10.1016/j.ymthe.2024.12.057
99. Gleason MK, Ross JA, Warlick ED, et al. Cd16xCD33 bispecific killer cell engager (BiKE) activates NK cells against primary MDS and MDSC CD33+ targets. Blood. 2014;123(19):3016–3026. doi: 10.1182/blood-2013-10-533398
100. Schmohl JU, Gleason MK, Dougherty PR, et al. Heterodimeric bispecific single chain variable fragments (scFv) killer engagers (BiKes) enhance NK-cell activity against CD133+ colorectal cancer cells. Target Oncol. 2016;11(3):353–361. doi: 10.1007/s11523-015-0391-8
101. Cadinanos-Garai A, Flugel CL, Cheung A, et al. High-dimensional temporal mapping of CAR T cells reveals phenotypic and functional remodeling during manufacturing. Mol Ther J Am Soc Gene Ther. 2025;33(5):2291–2309. doi: 10.1016/j.ymthe.2025.04.006
102. Wang X, Peticone C, Kotsopoulou E, et al. Single-cell transcriptome analysis of CAR T-cell products reveals subpopulations, stimulation, and exhaustion signatures. Oncoimmunology. 2021;10(1):1866287. doi: 10.1080/2162402X.2020.1866287
103. Dixon KJ, Snyder KM, Khaw M, et al. Ipsc-derived nk cells expressing high-affinity IgG Fc receptor fusion CD64/16A to mediate flexible, multi-tumor antigen targeting for lymphoma. Front Immunol. 2024;15. doi: 10.3389/fimmu.2024.1407567
104. Felices M, Lenvik TR, Davis ZB, et al. Generation of BiKEs and TriKEs to improve NK cell-mediated targeting of tumor cells. Methods Mol Biol Clifton NJ. 2016;1441:333–346.
105. Vallera DA, Felices M, McElmurry R, et al. Il15 trispecific killer engagers (TriKE) make natural killer cells specific to CD33+ targets while also inducing persistence, in vivo expansion, and enhanced function. Clin Cancer Res Off J Am Assoc Cancer Res. 2016;22(14):3440–3450. doi: 10.1158/1078-0432.CCR-15-2710