Exploring the landscape of genetically modified natural killer cell therapies: a review of clinical trials indexed on ClinicalTrials.gov

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Background

- The field of adoptive cancer immunotherapies is undergoing rapid evolution, fueled by an enhanced understanding of immune system cell biology and breakthroughs in genetic engineering techniques.[1]
- Natural killer (NK) cells, key components of the innate immune system, possess the ability to identify and eliminate both virally infected cells and tumor cells through various cytotoxic mechanisms. These mechanisms rely on interactions between an array of activating and inhibitory protein receptors on NK cells and their corresponding ligands on the surface of target cells.[1]
- Advances in genetic engineering have enabled the modification of NK cells at a genetic level to enhance their specificity, longevity, and targeting. This improvement enhances their ability to fight cancer and paves the way for genetically modified NK cell therapies.[2]
- Chimeric antigen receptors (CARs) are synthetic proteins with antigen-recognition and intracellular signaling properties that were originally designed to trigger T-cell activation for cancer immunotherapy.
- However, recent studies in adoptive cancer immunotherapy have seen a shift from T-cells to NK cells. Unlike T-cell therapies, NK cells can induce cytotoxicity without the need for prior antigen sensitization and do not pose risks of graft-versus-host rejection or other safety concerns.[1]
- Furthermore, NK cells used in CAR-engineered immunotherapies can be obtained from various sources including a patient's own or donor's peripheral blood mononuclear cells, umbilical cord blood, immortalized cell lines, hematopoietic stem and progenitor cells, as well as induced pluripotent stem cells (iPSCs).[3]
- Preclinical studies indicate that CAR-NK and gene-edited NK cell therapies hold significant potential for treating hematologic cancers such as leukemia, lymphoma, multiple myeloma as well as solid tumors.[3-4] Consequently, it is crucial to understand the clinical trial landscape for these innovative NK cell therapies.
- ClinicalTrials.gov offers comprehensive information about ongoing clinical trials investigating emerging therapies within the NK cell treatment pipeline. This freely accessible resource can be utilized to assess current research trends in this promising area of cancer treatment.

Objective

- This study examined the landscape of genetically modified NK cell therapies, including CAR and gene-editing technologies, using a comprehensive search conducted on ClinicalTrials.gov.

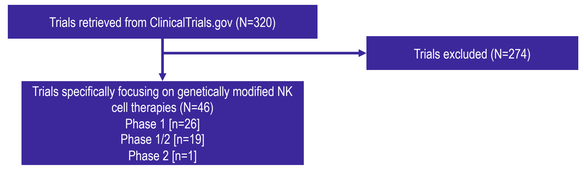
Methods

- In December 2023, ClinicalTrials.gov was searched for trials evaluating genetically modified NK cell therapies.
- Keywords and filters were used to target interventional studies and exclude early phase 1, withdrawn, or terminated studies.
- The results were exported to Microsoft Excel and screened to identify genetically modified NK cell therapy trials in phase 1 or beyond.
- One researcher conducted the screening process and a second researcher completed quality checks.

Results (cont.)

- A total of 320 trials were identified, with 46 specifically focusing on genetically modified NK cell therapies. These were included in this review (**Figure 1**).
- A comprehensive overview of the included trials is provided in **Table 1**.
- The majority (72%) of these studies were started in or after the year 2020, primarily being conducted in China (67%) and the United States (28%).
- Most trials were of therapies in early development. No phase 3 trials were identified (**Figure 2**).
- Single-group assignment was used in 80% of the trials; parallel assignment was utilized in 11%, and sequential assignment was implemented in the remaining 9%.
- Quadruple-blinding (participant, care provider, investigator, outcomes assessor) was employed in one trial, while all other trials were open-label.
- Full or partial industry funding supported 43% of these trials. Sample sizes varied across studies ranging from as few as 2 to as many as 168 patients.
- Participants of both genders were included in all the trials; however, children were only enrolled by a small percentage (13%) along with adults.
- Hematological malignancies such as multiple myeloma and non-Hodgkin lymphoma among others constituted the primary focus area (approximately 63% of studies). This was followed by solid tumors including breast cancer and glioblastoma among others (35% of studies).
- Allogeneic cells were predominantly used as their cell source in most studies (65%). However, the source remained unspecified in about 28% of the studies.
- CD19 emerged as the most targeted receptor (30% of trials), followed by CD33 and NKG2D ligands (each at 9%) (**Figure 3**).
- Most (83%) of the 35 trials reporting their activity status are in the recruitment stages, reflecting the novelty of these therapies. Only 4 trials have been completed as of the search date, with 3 focusing on hematological malignancies and 1 on a solid tumor (non-small cell lung carcinoma).
- Of the 4 completed studies, 1 (NCT03056339) has both published results[5] and results posted them on ClinicalTrials.gov. Another study (NCT03656705) has published results,6 but no results on the site. No publicly available results were found for the remaining 2 completed studies (**Table 1).**
- Nearly a quarter (24%) of the studies have an unknown status and have not been updated in over 5 years. Of these, only 2—NCT029441627 and NCT034151008—have disseminated their results in the medical literature.
- Published findings suggest that CAR-NK cells can be safely administered with no significant adverse effects. Promising clinical responses were observed, with some patients achieving complete remission.[5-8] Authors agree that improving CAR NK cell clinical trials may involve identifying the optimal patient population for this type of therapy.

Figure 1. Flowchart identification of trials from ClinicalTrials.gov



Key: GMNKC – gene-modified natural killer cell.

Figure 2. Phase of included trials

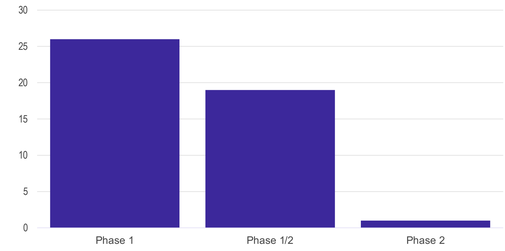
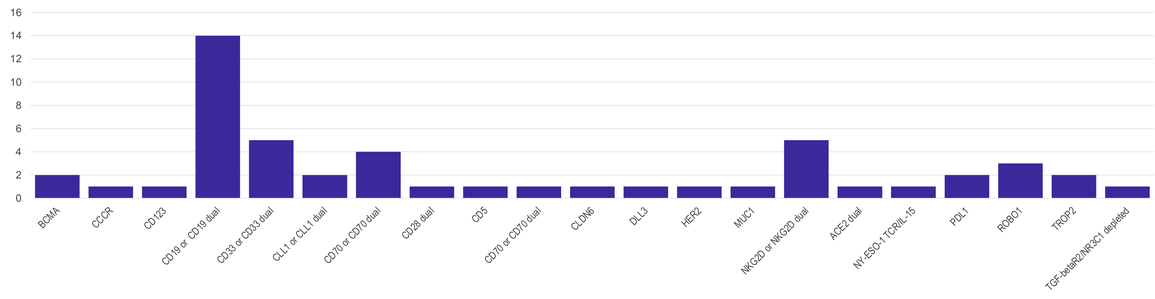


Figure 3. Target genes of genetically-modified NK cell therapies



A study with more than 1 target gene is included in counts for both genes.

Table 1. Overview of publicly available results for included trials

NCT number	Citation	Geography	Target gene	Cell source	Phase	N	Conditions	Key publicly available results
NCT03056339	Liu 2020	US	CD19/CD28	Allogeneic CB-NK cells	1, 2	49	B-lymphoid malignancies; ALL; CLL; NHL	Grade 3 toxicities: 28/49 Grade 4 toxicities: 0 PR/CR (30 days): 21/49 CR/PR (100 days): 18/49
NCT02944162	Tang 2018	China	CD33	Allogeneic NK cells (NK-92 cell line)	1, 2	10	AML	Results only reported for phase 1, n=3 No significant adverse effects were observed.
NCT03656705	Zhang 2022	China	CCCR	Allogeneic CB-NK cells (NK-92 cell line)	1, 2	2	NSCLC	Case report on occurrence of cytokine release syndrome
NCT03415100	Xiao 2019	China	NKG2D ligands	Unspecified	1	20	Solid tumors	Results reported for n=3 with mCRC Rapid tumor regression in the liver region was observed with Doppler ultrasound imaging and complete metabolic response in the treated liver lesions was confirmed by positron emission tomography-computed tomographic scanning.

Key: ALL – acute lymphocytic leukemia; AML – acute myeloid leukemia; CB – cord blood; CCCR – Chimeric Costimulatory Converting Receptor; CLL – chronic lymphocytic leukemia; CR – complete response; mCRC – metastatic colorectal cancer; N – number; NHL – non-Hodgkin lymphoma; NK – natural killer; NSCLC – non-small cell lung carcinoma; PR – partial response; US – United States.

Conclusions

- The significant number of clinical trials dedicated to investigating genetically modified NK cell therapies indicates an active pipeline poised to deliver novel oncologic treatments in forthcoming years.

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