CAR T-Cell Therapy and the Emerging Threat of Secondary Cancers: A Targeted Look

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Rajeshwari Bhat, Padma Ramasamy, Vatsal Chhaya*, Kapil Khambholja
Catalyst Clinical Research, Wilmington, NC, USA

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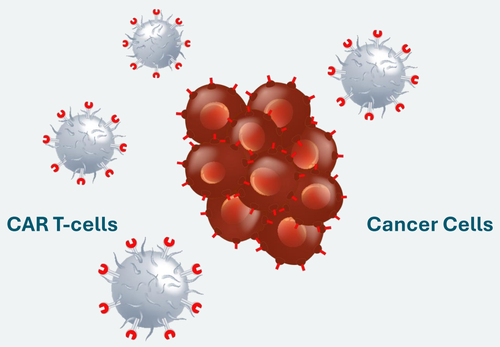
INTRODUCTION

- **Chimeric antigen receptor (CAR) T-cell therapy** is a novel treatment for blood cancers that uses engineered T-cells to target tumor markers, such as CD19 and BCMA.
- This therapy represents a significant advancement in the treatment of various cancers, demonstrating improved patient outcomes and survival rates.
- The **FDA has approved six CAR T-cell products**, reflecting the therapy's growing acceptance in clinical practice.
- Despite its benefits, **emerging evidence indicates a risk of secondary malignancies or second primary malignancy (SPM)** associated with CAR T-cell therapy, necessitating ongoing vigilance and patient monitoring.
- In November 2023, the **FDA began investigating over 20 cases of such cancers** in treated patients.



- In response to these concerns, the FDA added a **"black box" warning** to CAR T-cell therapy labels in January 2024, highlighting the risk of secondary cancers.[1]

Research gap: There is a need for comprehensive data on SPM linked to CAR T-cell therapy and clear monitoring guidelines to address emerging safety concerns.

OBJECTIVES

- To understand the clinical landscape of CAR T-cell products.
- To assess the risk of secondary malignancies associated with CAR T-cell therapy based on available evidence.

METHOD

Guidelines: Our method complies with JBI guidelines and adheres to the PRISMA-ScR checklist.

Literature Search: A literature search was conducted based on PCC framework. Database and registry used: PubMed & ClinicalTrial.gov

Data Charting: Data charting was done in Microsoft Excel-based data charting file using e (JBI) ScR data extraction template.

Table 1.
Eligibility Criteria

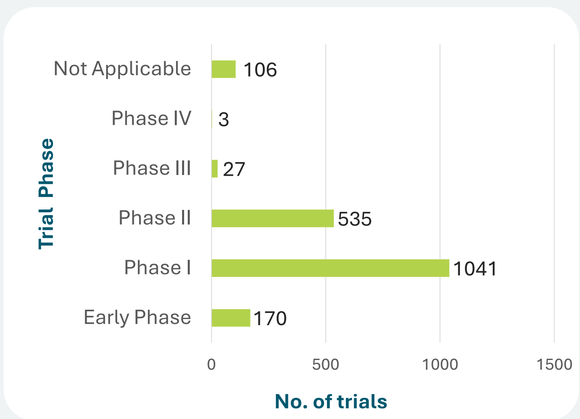
Criteria	Inclusion	Exclusion
Population	Patients with various cancers receiving CAR T-cell therapy	Patients with cancers not treated with CAR T-cell therapy
Concept	Risk of secondary malignancies post CAR T-cell therapy	Other Adverse Events (AEs) after CAR T-cell therapy
Context	Articles published from October 2022 to October 2024	Articles published before October 2022
Study Design	Observational studies, editorials, clinical trials, systematic reviews and reviews	Books and documents
Publication Type	PubMed indexed articles and ClinicalTrial.gov	Articles not indexed in PubMed
Language	English	Non-English

RESULTS

Registry-based Findings (ClinicalTrail.gov)

- A total of 1,882 trials have been conducted across various phases, with a significant number of trials in Phase I and Phase II.

Figure 1.
Landscape of CAR T Clinical Trials by Phase



Database-based Findings

- We retrieved 1,009 records, of which 11 studies were included for analysis.
- The overall incidence of SPMs ranged from **3.4% to 4.2%**.
- Among all the SPMs reported hematological malignancies were the most common followed by other solid carcinomas and skin neoplasms.

Figure 2.
PRISMA Diagram

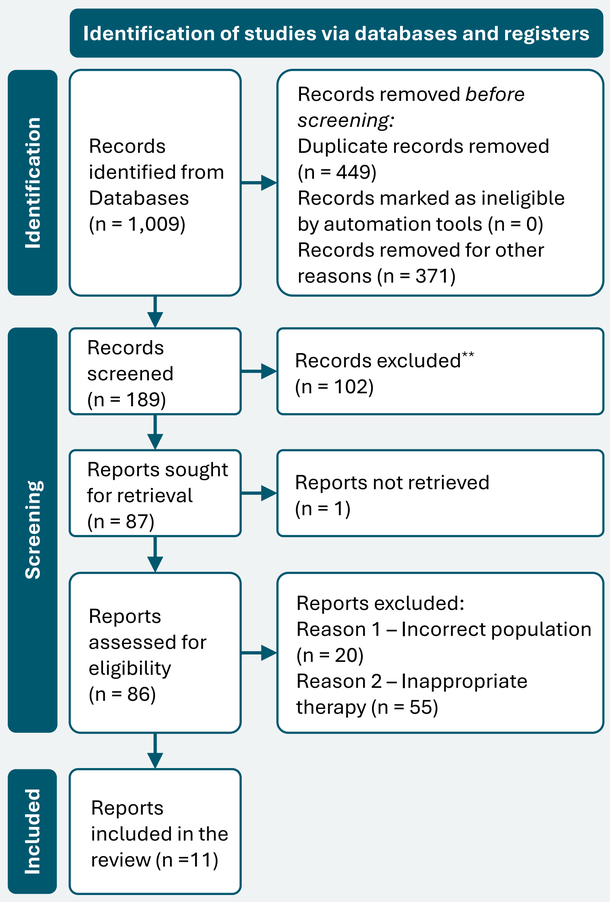


Figure 3.
Study Characteristics

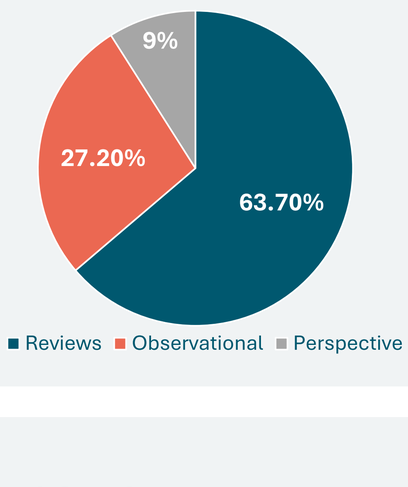


Table 2:
Second Primary Malignancies Reported in Key Studies

Author, Year	Title of study	Second Primary Malignancies (SPMs), Numbers (%)
Elsallab et al., 2024	Second malignancies post CAR T: FAERS analysis	**Overall Incidence of SPM 536 of 12,394 (4.3%)** **Leukemia: 333 of 536 (62.1%) ;** AML: 106 of 536 (19.8%); MDS: 208 of 536 (38.8%); T-cell LCLL: 2 of 536 (0.37%) ; **Skin Neoplasms: 54 of 536 (10.1%);** Nonmelanoma Skin Neoplasms: 42 of 536 (7.8%); Skin Melanomas: 12 of 536 (2.2%); **T-cell Non-Hodgkin Lymphomas: 17 of 536 (3.2%);** Anaplastic Large T-cell Lymphomas: 12 of 536 (2.2%); Enteropathy-associated T-cell Lymphoma: 1 of 536 (0.2%);
Shen et al., 2024	Second malignancies post CAR T therapy	**Overall Incidence of SPM FAERARS: 310 of 6370 (4.8%) VigiBase: 297 of 6942 (4.2%)** MDS – FEARS: 112; VigiBase: 115; Basal cell carcinoma – FAERS: 14; T-cell lymphoma – FAERS: 13; VigiBase: 8; AML – FAERS: 55; VigiBase: 52; Large granular lymphocytosis – FAERS: 2; **Nervous System Tumors: 21 of 536 (3.9%); Respiratory Neoplasms: 20 of 536 (3.7%);**
Zhou et al., 2024	Mechanisms of CAR T-triggered T-cell cancers	**22 T-cell SPM**
Verdun et al., 2023	Secondary cancers after CAR T	**22 T-cell SPM** including T-cell lymphoma, T-cell large granular lymphocytosis, peripheral T-cell lymphoma, and cutaneous T-cell lymphoma
Hamilton et al., 2024	Risk of Second Tumors after CAR T	**Overall incidence of SPM 25 of 724 (3.4%)** **Hematologic second tumors: 14 of 25 (56%)** Melanomas: 4 of 25; Prostate carcinomas: 2 of 25 AML: 13 of 25; T-cell lymphoma: 1 of 25. Breast ductal carcinomas: 2 of 25; Endometrial adenocarcinoma: 1 of 25 **Solid second tumors: 11 of 25 (44%);** Lung adenocarcinoma: 1 of 25; Metastatic mesothelioma: 1 of 25 **Cumulative incidence of hematologic SPM at 3 years: 6.5%**
Cappell et al., 2023	Long-term outcomes of CAR T	**Incidence of SPMs: 4-16%**
Martino et al., 2024	Effectiveness of CAR T and second malignancies	**Overall incidence of SPM 16 of 449 (3.6%)** 5-year incidence: Hematological malignancies: 2.3%; Solid tumors: 15.2%; T-cell lymphoma: 1 case

Abbreviations- SPM - Second Primary Malignancy, FAERS - FDA Adverse Event Reporting System, AML - Acute Myelogenous Leukemia, MDS- Myelodysplastic Syndromes, LCLL- Large Granular Lymphocytic Leukemia.

CONCLUSION & RECOMMENDATIONS

- Our analysis highlights the **occurrence of secondary malignancies** after CAR T therapy.
- A meta-analysis by Tix et al., found secondary malignancies to be a **significant long-term risk**, similar in frequency to traditional treatments.[2]
- The occurrence of **SPM** was associated with the duration of follow-up, number of prior therapy lines, and treatment in a clinical trial setting.[2] Risk factors for secondary malignancies might include immunosuppression, treatment side effects, and prior therapies, rather than gene mis-insertion.
- There is need for large-scale cohort studies to investigate risk factors.
- **Long-term follow-up protocols with regular assessments** for secondary malignancies are essential for patient safety. **Balancing CAR T benefits with effective risk management** can improve patient outcomes.

REFERENCES

1. FDA black box warning- (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor-car-t-cell).

2. Tix T, Alhomoud M, Shouval R, Cliff ERS, Perales MA, Cordas Dos Santos DM, Rejeski K. Second Primary Malignancies after CAR T-Cell Therapy: A Systematic Review and Meta-analysis of 5,517 Lymphoma and Myeloma Patients. *Clin Cancer Res*. 2024 Oct 15;30(20):4690-4700. doi: 10.1158/1078-0432.CCR-24-1798. PMID: 39256908.

CONTACT INFORMATION

Kapil Khambholja, Ph.D.
Executive Director, Head of Medical Writing and Product Strategy Lead
Catalyst Clinical Research
Phone: +91-77029 49998 | Email: kapil.khambholja@catalystcr.com
www.CatalystCR.com

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