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INPLASY

Preclinical efficacy and translational determinants of CAR-T cell therapy in triple-negative breast cancer: a systematic review and multilevel meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202670091

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 July 2026 and was last updated on 23 July 2026.

INTRODUCTION

Review question / Objective PICOS: This systematic review will include in vivo animal studies of TNBC models (subcutaneous, orthotopic, PDX, metastatic, and syngeneic) evaluating CAR-T cell therapy of any target specificity. Eligible studies must include a comparator group (untreated, vehicle, PBS, unmodified T cells, Mock CAR-T, or irrelevant-target CAR-T) and report at least one of the following outcomes: tumor volume/weight/bioluminescence, survival, metastasis, complete response, recurrence, or toxicity. Only original preclinical studies with in vivo comparative data will be included.

Condition being studied Triple-negative breast cancer (TNBC) is the most aggressive subtype of breast cancer, characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. It accounts for approximately 15–20% of all invasive breast cancers. Compared with other subtypes, TNBC is associated with earlier age of onset, higher histological grade, greater invasive potential, an elevated risk of early recurrence, and an overall poor prognosis. Because it lacks the therapeutic targets for endocrine therapy or anti-HER2 agents, chemotherapy remains the mainstay of systemic treatment. However, most patients quickly develop resistance and disease progression, underscoring an urgent need for novel therapeutic strategies.

Chimeric antigen receptor T-cell (CAR-T) therapy has achieved remarkable success in hematological malignancies; yet its translation to solid tumors, including TNBC, faces considerable obstacles, such as tumor heterogeneity, a highly immunosuppressive tumor microenvironment, and a scarcity of ideal target antigens. Over the past few years, a growing number of preclinical studies have evaluated the antitumor activity and safety of various CAR-T constructs targeting different tumor-associated antigens in diverse TNBC animal models. Nonetheless, these studies exhibit substantial heterogeneity with regard to CAR

design, target selection, animal model types, and outcome measurements, and a systematic synthesis of the available evidence is currently lacking.

Therefore, the objective of this systematic review is to comprehensively collect and synthesize data from in vivo preclinical studies evaluating CAR-T cell therapy for TNBC, to assess its efficacy and safety, and to identify key factors that may influence treatment outcomes. The findings of this review are expected to provide a robust evidence base to guide future clinical translation of CAR-T therapy for TNBC.

METHODS

Participant or population This review will include in vivo animal models of triple-negative breast cancer (TNBC), regardless of species, strain, sex, or age. Eligible models include: (1) subcutaneous xenograft models; (2) orthotopic (mammary fat pad) models; (3) patient-derived xenograft (PDX) models; (4) metastatic models (spontaneous or experimental); and (5) syngeneic models. Studies using only in vitro or ex vivo models will be excluded. For xenograft models, any TNBC cell line is eligible; for syngeneic models, murine TNBC lines will be included.

Intervention CAR-T cells of any target, generation, or structure. CAR-NKT and CAR-NK studies excluded.

Comparator Untreated, vehicle (PBS/saline), unmodified T cells, Mock CAR-T, irrelevant-target CAR-T, or other interpretable controls. Studies without a valid comparator will be excluded.

Study designs to be included Original preclinical studies with in vivo comparative data evaluating CAR-T in TNBC models. Controlled experiments with ≥1 CAR-T group and ≥1 comparator group. Full-length articles only. Excludes in vitro/ex vivo studies, studies without comparator, non-extractable data, duplicate publications, clinical trials, and non-English/Chinese reports.

Eligibility criteria Original preclinical studies with in vivo comparative data evaluating CAR-T in TNBC models. Controlled experiments with ≥1 CAR-T group and ≥1 comparator group. Full-length articles only. Excludes in vitro/ex vivo studies, studies without comparator, non-extractable data, duplicate publications, clinical trials, and non-English/Chinese reports.

Information sources MEDLINE (PubMed), Embase, Web of Science, Scopus, CENTRAL; trial registries: ClinicalTrials.gov, WHO ICTRP; grey literature: ProQuest Dissertations, OpenGrey, Google Scholar; plus reference list and citation tracking of included studies. Searched from inception to present. No language restrictions.

Main outcome(s) Primary: (1) tumor volume or tumor weight (continuous, extracted at common time points across studies); (2) overall survival (median survival, HR, or Kaplan-Meier data). Effect measures: SMD (95% CI) for continuous outcomes; HR (95% CI) for survival. Timing: outcomes extracted at reported time points; primary meta-analysis at the most common time point across studies.

Quality assessment / Risk of bias analysis Two reviewers will independently assess risk of bias using the SYRCLE RoB tool (10 items covering selection, performance, detection, attrition, reporting, and other biases). Each item rated as Low/High/Unclear risk. Disagreements resolved by consensus or third reviewer. Results presented in tabular and graphical summary. Reporting quality will be supplemented using ARRIVE 2.0 guidelines.

Strategy of data synthesis Meta-analysis using random-effects model (DerSimonian-Laird) if ≥2 studies available. Effect measures: SMD (95% CI) for continuous outcomes; HR or RR for survival/binary outcomes. Heterogeneity: I^2 and Q test ($p<0.10$). Subgroup analyses by tumor model, CAR generation, target, comparator, RoB, and timing. Meta-regression if ≥10 studies. Sensitivity analyses excluding high-RoB studies, using fixed-effect model, leave-one-out. Publication bias: funnel plots, Egger's test (if ≥10 studies). Software: R (meta, metafor). Narrative synthesis if meta-analysis not feasible.

Subgroup analysis Subgroup analyses will be performed if ≥3 studies per subgroup, by: tumor model type, CAR generation, target antigen, comparator type, risk of bias, outcome timing, and animal immune status/CAR dose if data available. Interaction tests will be used to compare subgroups ($p<0.05$ significant). All subgroup analyses are exploratory.

Sensitivity analysis To assess robustness, sensitivity analyses will exclude: (1) high-RoB studies; (2) studies with imputed data; (3) outliers; (4) studies with <3 animals/group. Fixed-effect vs. random-effects comparison; leave-one-out analysis; alternative effect measures (MD instead of SMD). Results in tabular format. Findings

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considered robust if estimates remain materially unchanged.

Country(ies) involved China.

Keywords Triple-negative breast cancer; CAR-T cell therapy; Immunotherapy; Systematic review; Meta-analysis; Intelligent pharmacy; Artificial intelligence; Data-driven review.

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