

Supplementary Table 1. Pre-clinical studies of CAR-NK therapy

Targeted specific antigen	Source of NK cells	Engineered CAR	Treated cancer types	Mechanisms of action and effects	Report year	REF
EGFR and EGFRvIII	NK-92 and NKL	CD28+CD3 ζ CAR-NK cells	Glioblastoma	enhanced cytolytic capability and IFN- γ production, suppression of tumor growth	2015	(1)
PSCA	NK cell line YTS and primary NK cells	DAPI2 CAR-NK cells	PSCA-expressing solid tumor	enhanced cytotoxicity, tumor eradication	2015	(2)
ErbB2 (HER2)	NK-92	CD28+CD3 ζ /4-1BB CAR-NK cells	breast cancer, pulmonary metastasis of renal cell carcinoma	Efficient tumor cell lysis, reduction of metastasis	2015	(3)
ErbB2 (HER2)	NK-92	CD28+CD3 ζ CAR-NK cells	Glioblastoma	Potent antitumor activity, extension of survival, induction of antitumor immunity and protection against tumor rechallenge	2016	(4)
EGFR	NK-92 and primary NK cells	CD28+CD3 ζ CAR-NK cells	Breast cancer brain metastases	enhanced cytotoxicity and IFN- γ production, suppression efficient tumor killing	2016	(5)
EGFR and EGFRvIII	NK-92	CD28+CD3 ζ CAR-NK cells	Glioblastoma	enhanced specific cytotoxicity and tumor cell lysis	2016	(6)
CD133	NK-92	CD28+CD3 ζ +4-1BB CAR-NK cells	Ovarian cancer	enhanced cytotoxicity and IFN- γ production	2017	(7)
GD2	primary NK cells	CD28+CD3 ζ CAR-NK cells +4-1BB CAR-NK cells	Ewing sarcomas	enhanced anti-tumor responses, overcome resistance to NK cell lysis	2017	(8)
NKG2D ErbB2 (HER2)	NK-92	DAP10+ CD3 ζ CAR-NK cells	Solid tumors	enhanced anti-tumor cytotoxicity	2018	(9)
carcinoembryonic antigen-expressing (CEA)	NK-92	CD3 ζ CAR-NK cells	colorectal cancer	Enhanced recognition and lysis of tumor cells	2018	(10)

Targeted specific antigen	Source of NK cells	Engineered CAR	Treated cancer types	Mechanisms of action and effects	Report year	REF
Mesothelin	iPSC	NKG2D+2B4+CD3 ζ CAR-NK cells, NKG2D+2B4+DAP10+CD3 ζ CAR-NK cells, NKG2D+4-1BB+2B4+CD3 ζ CAR-NK cells	Ovarian cancer	enhanced anti-tumor activity, suppression of tumor growth	2018	(11)
EGFRvIII	KHYG-1	CD28+CD3 ζ CAR-NK cells +4-1BB CAR-NK cells	Glioblastoma	Specific induction of apoptosis in EGFRvIII-expressing tumor cells	2018	(12)
EGFRvIII	NK-92	CD28+CD3 ζ CAR-NK cells	colorectal cancer	Evaluating CAR efficacy and tumor specificity	2019	(13)
c-MET	primary NK cells	DAP12+4-1BB CAR-NK cells	liver cancer	enhanced specific cytotoxicity	2019	(14)
NKG2D	primary NK cells	DAP12+ CD3 ζ CAR-NK cells chemokine receptor CXCR1 CAR-NK cells	Ovarian cancer	increased migration capacity and augmented tumor infiltration	2020	(15)
Glypican-3 (GPC3)	iPSC	CD28+CD3 ζ +4-1BB CAR-NK cells	Ovarian cancer	Effective cytotoxicity and IFN- γ production, prolonged survival	2020	(16)
Glypican-3 (GPC3)	NK-92	CD3 ζ , CD3 ζ +CD28 CAR-NK cells, CD28+CD3 ζ +4-1BB CAR-NK cells, CD3 ζ +DNAM1 CAR-NK cells, CD3 ζ +DNAM1+2B4 CAR-NK cells	Hepatocellular cancer	Improving expansion, persistence and cytotoxicity	2020	(17)
tissue factor (TF)	NK-92	CD28+CD3 ζ +4-1BB CAR-NK cells CD16 (Fc γ III) CAR-NK cells	Triple-negative breast cancer	Enhanced tumor killing	2020	(18)
GPC3	primary NK cells	CD3 ζ +4-1BB CAR-NK cells	Hepatocellular carcinoma	Increased cytotoxicity and IFN- γ production	2021	(19)
Bispecific: NKG2D ErbB2 (HER2)	primary NK cells	CD3 ζ CAR-NK cells	breast carcinoma	enhance tumor antigen-specific cytotoxicity, to target tumors with heterogeneous target antigen expression	2021	(20)
NKG2D	NK-92	CD28+CD3 ζ +4-1BB (dual-promoter pCDHdp) CAR-NK cells	gastric carcinoma	robust expression of CAR and enhanced cytotoxicity against cancer cells	2023	(21)

Supplementary Table 2. Clinical studies of CAR-NK therapy

Targeted specific antigen	CAR-NK Product or name	Source of NK cells	Treated cancer types	Stage of trials or phase	Study objectives	Outcome	Year	ClinicalTrials.gov ID /REF	Status
MUC1	Anti-MUC1 CAR-pNK cells	NK92 cell line	Hepatocellular carcinoma Non-small cell lung cancer Pancreatic carcinoma Triple-negative invasive breast carcinoma Malignant glioma of the brain Colorectal carcinoma Gastric carcinoma	Phase 1/2	Evaluation of safety and effectiveness of CAR-pNK cell immunotherapy in patients with MUC1 positive relapsed or refractory solid tumor	Not reported	2016	NCT02839954	Unknown status
HER2	(NK-92/5.28.z) anti-HER2 CAR NK cells + Ezabenlimab	NK92 cell line	Glioblastoma	Phase 1	Evaluation of safety and tolerability of NK-92/5.28.z in patients with recurrent HER2-positive Glioblastoma	induced robust anti-tumor response, long-term survival, increased CD4 ⁺ T cell infiltration	2017	NCT03383978 (22)	Recruiting
NKG2D	CAR-NK cells targeting NKG2D ligands	Autologous or allogeneic NK cells	solid tumors	Phase 1	Evaluation of safety and feasibility of CAR-NK cell therapy in subjects with metastatic solid tumors	significantly augmented the cytolytic activity of NK cells against solid tumor cell, decrease in number of tumor cells	2018	NCT03415100 (23)	Unknown status
PSMA	Anti-PSMA CAR NK Cells	Human primary NK cells	Metastatic castration-resistant prostate cancer	Early Phase 1	Evaluation of safety and efficacy of Anti-PSMA CAR NK Cells in Metastatic Castration-resistant Prostate Cancer	exhibited specific lysis for PSMA-positive C4-2 cells, significantly higher concentrations of IFN- γ , TNF- α and granzyme B, significantly inhibited tumor growth and exerted a more consistent killing effect than NK92MI cells.	2018	NCT03692663 (24)	Unknown status

Targeted specific antigen	CAR-NK Product or name	Source of NK cells	Treated cancer types	Stage of trials or phase	Study objectives	Outcome	Year	ClinicalTrials.gov ID /REF	Status
ROBO1	BiCAR-NK/T cells (ROBO1 CAR-NK/T cells)	N/A	Malignant Tumor	Phase 1/2	Evaluation of safety and efficacy of ROBO1 CAR-NK/T cell immunotherapy for malignant tumors	Not reported	2019	NCT03931720	Unknown status
ROBO1	ROBO1 CAR-NK cells	Human primary NK cells	Solid Tumor	Phase 1/2	Evaluation of safety and efficacy of cell therapy using ROBO1 CAR-NK cells to treat solid tumors	Not reported	2019	NCT03940820	Unknown status
ROBO1	BiCAR-NK cells (ROBO1 CAR-NK cells)	N/A	Pancreatic Cancer	Phase 1/2	Evaluation of safety and efficacy of ROBO1 CAR-NK cell immunotherapy for pancreatic cancer	Not reported	2019	NCT03941457	Unknown status
Mesothelin	Anti-Mesothelin Car NK Cells (Mesothelin Car NK-HNRM-01)	Human primary NK cells	Epithelial ovarian cancer	Early Phase 1	Evaluation of safety, tolerability and efficacy of anti-Mesothelin Car NK Cells with Epithelial ovarian cancer	Not reported	2019	NCT03692637	Unknown status
NKG2D	NKG2D CAR-NK Cell	N/A	Refractory Metastatic Colorectal Cancer	Phase 1	Investigation of NKG2D CAR-NK Cell Therapy in Patients With Refractory Metastatic Colorectal Cancer	preliminary efficacy and tolerable toxicity	2021	NCT05213195 (24)	Recruiting
PD-L1	PD-L1-targeted CAR NK cells (PD-L1 t-haNK), with IL-15 fusion protein(N803) + pembrolizumab	human, allogeneic, NK cell line	Gastroesophageal junction cancers, advanced head and neck squamous cell carcinoma	Phase 2	To test the effectiveness of irradiated PD-L1 CAR-NK cells, combined with pembrolizumab and N-803, in people with advanced forms of gastric or head and neck cancer	Not reported	2021	NCT04847466	Active, not recruiting

Targeted specific antigen	CAR-NK Product or name	Source of NK cells	Treated cancer types	Stage of trials or phase	Study objectives	Outcome	Year	ClinicalTrials.gov ID /REF	Status
5T4	Anti-5T4 CAR-NK	N/A	Advanced solid tumors	Early Phase 1	Evaluation of safety, tolerability, initial efficacy and pharmacokinetics (PK) of anti-5T4 CAR-NK cells in patients with advanced solid tumors	Not reported	2022	NCT05194709	Unknown status
DLL3	DLL3-CAR-NK cells	N/A	Extensive Stage Small Cell Lung Cancer	Phase 1	Evaluation of safety and efficacy of DLL3-CAR-NK cells infusion in treatment of Relapsed / Refractory Extensive Stage Small Cell Lung Cancer	Not reported	2022	NCT05507593	Unknown status
Claudin6, GPC3, Mesothelin, or AXL	Claudin6, GPC3, Mesothelin, or AXL targeting CAR-NK cells	Human primary NK cells	Stage IV ovarian cancer Testis cancer Refractory endometrial cancer	Phase 1	Evaluation of safety and preliminary efficacy of Claudin6, GPC3, Mesothelin, or AXL targeting CAR-NK cells in patients with Claudin6, GPC3, Mesothelin, or AXL-positive advanced solid tumors	stronger cytotoxicity, effectively eliminate ovarian cancer cells, enhance the antitumor efficacy	2022	NCT05410717 (25)	recruiting
NKG2D	NKG2D CAR-NK cells	N/A	ovarian cancer	Not Applicable	Evaluation of safety and efficacy of NKG2D CAR-NK cells in treatment of platinum-resistant, relapsed epithelial ovarian cancer	Not reported	2023	NCT05776355	Unknown status

Targeted specific antigen	CAR-NK Product or name	Source of NK cells	Treated cancer types	Stage of trials or phase	Study objectives	Outcome	Year	ClinicalTrials.gov ID /REF	Status
mesothelin (MESO)	SZ011 CAR-NK	N/A	Advanced Triple Negative Breast Cancer	Early Phase 1	Evaluation of clinical safety and efficacy of SZ011 in treatment of advanced triple-negative breast cancer	Not reported	2023	NCT05686720	Unknown status
mesothelin	SZ011 CAR-NK	N/A	ovarian epithelial carcinoma	Early Phase 1	Evaluation of clinical safety and efficacy of SZ011 in treatment of ovarian epithelial carcinoma	Not reported	2023	NCT05856643	Recruiting
GPC3	SZ003 CAR-NK	N/A	advanced hepatocellular carcinoma	Not Applicable	Evaluation of clinical safety and efficacy of SZ003 in treatment of advanced hepatocellular carcinoma	Not reported	2023	NCT05845502	Terminated
TROP2	TROP2-CAR-NK cells	Human primary NK cells	advanced solid tumors	Phase 1	Determination of safety, tolerability, optimal cell dose, maximum tolerated dose, and recommended Phase 2 dose of TROP2-CAR-NK cells in participants with solid tumors with high TROP2 expression	Not reported	2023	NCT06066424	Recruiting
TROP2	TROP2-CAR-NK cells	N/A	Pancreatic Cancer Ovarian Cancer Adenocarcinoma	Phase 1/2	Determination of safety and optimal cell dose of TROP2-CAR/IL15-transduced CB-NK cells delivered intraperitoneally to patients with that are resistant to treatment	Not reported	2023	NCT05922930	Recruiting

Targeted specific antigen	CAR-NK Product or name	Source of NK cells	Treated cancer types	Stage of trials or phase	Study objectives	Outcome	Year	ClinicalTrials.gov ID /REF	Status
CD70	CAR.70/IL-15-transduced cord blood-derived NK cells + fludarabine + Cyclophosphamide	cord blood-derived NK cells	Advanced renal cell carcinoma, advanced mesothelioma, advanced osteosarcoma	Phase 1/2	Determination of safety, tolerability, optimal cell dose of CAR.70/IL15-transduced CB-derived NK cells in patients with lymphodepleting chemotherapy to patients with advanced renal cell carcinoma, mesothelioma, or osteosarcoma	Not reported	2023	NCT05703854	Recruiting
MICA/B	FT536	allogeneic NK cell produced iPSC	Gynecologic Cancer Ovarian Cancer Fallopian Tube Cancer Primary Peritoneal Cavity Cancer	Phase I	treatment of recurrent gynecologic cancers	Not reported	2024	NCT06342986	Recruiting

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