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Review article

CAR-T for Lung Cancers: Challenges and Innovations

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ABSTRACT

Lung cancer (LC) is the leading cause of cancer mortality worldwide. Despite current therapies, including surgery, radiotherapy, targeted therapies, and immunotherapy, most patients experience relapse. Immune checkpoint inhibitors (ICIs) have revolutionized LC treatment, but only a subset of patients benefit from them. Chimeric antigen receptor (CAR) T cell therapy emerges as an innovative and promising strategy in oncology. CAR T cells are genetically modified T lymphocytes that express a chimeric receptor specific for a tumor antigen. Very promising in hematology, CAR T has so far struggled to be transferred into the clinic for solid tumors, including LC. CAR T strategy against LC presents challenges in the selection of the optimal antigen to avoid off-target effects, for the known antigen heterogeneity and immunosuppressive environment of LC and the relatively short persistence of CAR T that may encounter disseminated diseases. Despite these limitations, here we describe growing preclinical and clinical studies that are exploring various LC antigens for CAR T within a variety of novel approaches and combinatorial strategies to overcome the barriers. Considering this emerging critical mass and despite the limits, we expect this endeavour to translate a fraction CAR T into clinical practice with efficacy against the still deadly LCs.

1. Introduction

Lung cancer (LC) remains the leading cause of cancer mortality worldwide, accounting for 2.2 million new cases and 1.8 million deaths in 2020, approximately 11.4 % of global cancer diagnoses and 18 % of cancer-related deaths [1]. According to the 2021 WHO classification, over 95 % of lung carcinomas fall into four histotypes: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell carcinoma (SCLC) [2]. The first three comprise non-small cell lung cancer (NSCLC), which represents ~85 % of cases, while SCLC accounts for ~15 %[1].

Despite curative potential in early-stage disease, over 70 % of patients relapse, posing significant therapeutic challenges [3]. Available treatments include surgery, radiotherapy, targeted therapies, and immunotherapy. Immune checkpoint inhibitors (ICIs), such as pembrolizumab, nivolumab, cemiplimab, atezolizumab, and durvalumab (targeting PD-1/PD-L1), and ipilimumab (targeting CTLA-4), have reshaped the therapeutic landscape of both NSCLC and SCLC. They are now standard in first-line settings, combined with chemotherapy or as monotherapy. Except for NSCLC with targetable oncogenic drivers,

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nearly all patients with metastatic LC now receive PD-1/PD-L1 inhibitors as frontline therapy [4,5].

However, due to tumor heterogeneity and host factors, only a subset of patients benefits from ICIs. Thus, ongoing research focuses on two main goals: identifying reliable predictive biomarkers and developing alternative therapies for ICI-resistant patients. Among emerging strategies, chimeric antigen receptor (CAR) T cell therapy is gaining attention as a promising and innovative approach.

1.1. Chimeric antigen receptor T-cells

CAR T cells are genetically engineered T lymphocytes that express a chimeric receptor targeting a specific tumor antigen, combining antibody-like specificity with T cell cytotoxicity. Patient- or donor-derived T cells are modified to express CARs, expanded ex vivo, and reinfused. Once in the host, CAR T cells rapidly proliferate, recognize target antigens, and initiate effector functions such as cytokine release and cytolysis. Beyond direct tumor killing, CAR T cells may enhance long-term immune surveillance through antigen spreading, support of endogenous tumor-infiltrating lymphocytes, or prolonged persistence, reported in some cases for up to a decade [6].

1.2. CAR structure and generations

CARs comprise an extracellular antigen-binding domain, a transmembrane and hinge region anchoring the receptor to the cell membrane, and an intracellular signalling domain activated upon antigen engagement. The antigen-binding domain is typically a single-chain variable fragment (scFv) derived from the variable regions of an antibody's heavy and light chains, providing specificity independent of HLA-peptide presentation. Unlike physiological TCRs, CAR scFvs can recognize unprocessed antigens across different HLA backgrounds, including tumors with HLA downregulation or impaired antigen processing, a common immune escape mechanism. CARs can bind proteins, carbohydrates, and glycolipids, broadening targetable antigens [7].

The Hinge region extends the scFv from the transmembrane domain, which anchors the CAR to the membrane and is often derived from CD3ζ, CD4, CD8α, or CD28 [8].

The Intracellular signalling domain typically includes CD3ζ, containing three immunoreceptor tyrosine-based activation motifs (ITAMs) essential for signal transduction [9].

First-generation CARs included only the CD3ζ domain and showed limited persistence and efficacy in both vitro and clinical setting. To improve performance, second-generation CARs incorporated a co-stimulatory domain alongside CD3ζ. The two most common, FDA-approved co-stimulatory domains are CD28 and 4-1BB (CD137). Co-stimulatory domains shape T cell behaviour: CD28 promotes rapid effector responses, high IL-2 secretion, and increased glycolysis, while 4-1BB enhances persistence, memory formation, oxidative metabolism, and reduces exhaustion. Other co-stimulatory domains are under investigation. Third-generation CARs include two co-stimulatory domains in tandem with CD3ζ, aiming for more complete activation. While some studies reported enhanced cytokine release and tumor reduction, others showed no added benefit in preclinical model. Fourth-generation "Armored CARs" are engineered to secrete cytokines such as IL-2 or IL-12 to enhance the persistence of engineered T cells in the tumor microenvironment. Fifth-generation CARs add a truncated IL-2 receptor β-chain domain with a STAT3-binding site to second-generation backbones, enabling JAK-STAT signalling and potentially boosting T cell proliferation and survival [9,10].

Although these innovations are promising, their therapeutic relevance remains under investigation.

2. CAR T between Hematology and Oncology

Most clinical trials on CAR T therapy have focused on $CD19^{+}$ hematologic malignancies. CD19 is an ideal target due to its B-lineage specificity and absence in non-hematopoietic tissues, with the main toxicity B cell aplasia, being manageable. A second-generation CD19 CAR (CD28/CD3ζ) showed high remission rates in relapsed/refractory B-ALL. CD19 CAR T cells have also been effective in CLL, NHL, FL, and DLBCL [11]. Additionally, CD22-directed CARs have shown responses, including in CD19-negative relapses [12]. The standard workflow, apheresis, transduction, expansion, lymphodepletion, and reinfusion, varies by protocol. Key toxicities include cytokine-release syndrome (CRS), triggered by massive cytokine release, and neurotoxicity. CRS, occurring in 37–93 % of lymphoma and up to 93 % of leukemia cases, presents with fever, hypotension, and hypoxia, and can escalate to life-threatening capillary leak syndrome. Its severity correlates with tumor burden and is managed with IL-6 blockade [13,14]. Neurotoxicity (~40 % of cases) typically manifests as aphasia, seizures, or delirium; it is usually reversible but can rarely lead to fatal cerebral edema [7].

The success of CD19 CAR T therapies led to FDA approvals: tisagenlecleucel (KYMRIAH, Aug 2017), axicabtagene ciloleucel (YESCARTA, Oct 2017) and AUCATZYL (obecabtagene autoleucel, Nov 2024) for r/r B-ALL and DLBCL/FL; brexucabtagene autoleucel (TECARTUS, Jul 2020) for MCL; lisocabtagene maraleucel (BREYANZI, Feb 2021) for r/r large B-cell lymphoma; morover, two CAR T-cell products targeting BCMA were approvedidecabtagene vicleucel (ABECMA, Mar 2021) and ciltacabtagene autoleucel (CARVYKTI, Feb 2022) for r/r multiple myeloma.

The development of efficient CAR T against solid tumors has been more challenging. The hurdles to overcome might be ascribed both to CAR T cell efficacy, such as lack of persistence, poor trafficking, inefficient vascularization, and to tumor-related features [15]. Moreover, the application of CAR T cell therapy in solid tumors treatment is critically challenged by their heterogeneity, immunosuppressive microenvironment, antigen escape phenomena, and lack of tumor-specific antigens [16]. The absence of specific targetable antigens is considered a major cause for the low specificity and poor effectiveness of CAR T against cancer cells [17] and, for this reason, the choice of a valid tumor-associated antigen (TAA) plays a crucial role.

Several studies are dedicated to improving CAR T cell-based technology for treating solid tumors. To address these hurdles, strategies include enhancing T cell infiltration with cytokines or chemokines, optimizing CAR design and culture conditions, dual-targeting approaches, affinity tuning, and combination therapies [16].

Although many trials remain inconclusive, encouraging signs exist. Notably, the FDA recently granted accelerated approval to afamitresgene autoleucel (Tecelra), a TCR therapy targeting MAGE-A4 in synovial sarcoma. The SPEARHEAD-1 trial showed a 43.2 % ORR and a median response duration of 6 months, marking a milestone as the first gene-modified T-cell therapy approved for solid tumors [18,19].

3. CAR T and Lung Cancers

One of the main challenges, when considering CAR T therapy against solid tumors, is the choice of the optimal TAA, which is specifically highly expressed by tumor cells and not by healthy tissues to avoid severe off-target effects. LC expresses many antigens but, unfortunately, these are often also expressed by healthy tissues [20].

Here we have summarised the studies testing CAR T cells against lung tumors (both NSCLC and SCLC) and categorized them according to the target antigen. We also present data regarding CAR T in the context of mesothelioma, since it is close to the central topic. TAAs, currently being investigated, are: Mucin 1 (MUC1), Epidermal growth factor receptor (EGFR), Carcinoembryonic antigen (CEA), Mesothelin (MSLN), Tyrosine kinase-like orphan receptor (ROR1), Programmed death ligand 1 (PD-L1), Prostate stem cell antigen (PSCA), Human epidermal growth factor receptor 2 (HER2), Epithelial cell adhesion molecule (EpCAM), Glypican-3 (GPC3), Delta-like ligand 3 (DLL3), and Disialoganglioside GD2 (GD2). Clinical trials exploring CAR T cells against those targets are

ongoing and we have summarized the updated available data in Table 1.

3.1. Mucin 1

The transmembrane glycoprotein mucin 1 (MUC1) is a heavily glycosylated protein that primarily functions as a protective barrier on mucosal surfaces [21]. In various adenocarcinomas, including LC, MUC1 is frequently overexpressed and implicated in tumor progression by enhancing proliferation, growth, and metastasis [22]. Due to its tumor-associated expression, MUC1 has emerged as a promising target for CAR T cell therapy. Wei et al. evaluated MUC1- and PSCA-targeted CAR T cells in NSCLC patient-derived xenograft (PDX) models, demonstrating a synergistic anti-tumor effect when both were combined, leading to significantly reduced tumor weights compared to monotherapy [23]. Several clinical trials are currently investigating anti-MUC1 CAR T cells in solid tumors. Notably, the NCT03525782 phase I-II trial is assessing safety and efficacy of anti-MUC1 CAR T cells with or without PD-1 knockout in advanced NSCLC. Additionally, the phase I study NCT05239143 is testing P-MUC1C-ALLO1, an allogeneic CAR T therapy targeting MUC1-C, in patients with advanced or metastatic solid tumors, including NSCLC. However, clinical outcomes from these trials are still pending.

3.2. Epidermal growth factor receptor (EGFR)

One of the most frequent alterations in NSCLC is EGFR mutation, which activates oncogenic pathways promoting tumor growth [24,25]. These mutations, common in adenocarcinomas, predict sensitivity to EGFR tyrosine kinase inhibitors (TKIs), which have significantly improved patient outcomes [26–28]. Beyond TKIs, EGFR mutations have also been explored in immunotherapy, particularly in the context of EGFR-targeted CAR T cells. EGFR-targeted CAR T cells have shown promise: preclinical studies demonstrated in vitro efficacy and in vivo tumor regression in $EGFR^{+}$ NSCLC models [29]. A phase I trial (NCT01869166) using EGFR CAR T cells in relapsed/refractory NSCLC reported partial responses (PR) in 2/11 patients and disease stabilization in 5, with mostly mild toxicities and one grade 4 lipase increase [30]. Another phase I study, using the non-viral piggyBac transposon system, to engineer EGFR CAR T cells in nine patients reported no $\geq$grade 4 toxicities or severe CRS, with PR lasting over 13 months, six cases of stable disease (SD), and median PFS and OS of 7.1 and 15.6 months, respectively [31].

Li et al. engineered EGFR CAR T cells co-expressing CXCR5, a receptor for CXCL13, a chemokine highly expressed in NSCLC. This enhanced CAR T cell trafficking to tumor sites while reducing off-tumor toxicity [32]. A phase I trial is ongoing to evaluate this approach in advanced NSCLC (NCT05060796). Another ongoing phase I trial is exploring CAR T cells redirected against both EGFR and B7-H3 (CD276), a co-signal molecule abnormally upregulated in NSCLC, in patients with EGFR/$B7\text{-}H3^{+}$ advanced LC (NCT05341492). Guoping Li et al. engineered EGFR CAR T cells to overexpress SMAD7, a TGF-β signaling inhibitor to overcome the immunosuppressive tumor microenvironment. This modification boosted CAR T cell proliferation, cytokine production, and cytotoxicity in vitro, achieving complete tumor regression in vivo [33]. Wang et al. developed EGFR CAR T cells secreting PD-1 scFv (E27) and expressing CCR6, resulting in enhanced anti-tumor activity in xenograft models without systemic toxicity [34].

3.3. Carcinoembryonic antigen (CEA)

The glycoprotein CEA, involved in cell adhesion, is expressed during fetal development and downregulated before birth, thus remaining undetectable in healthy adults. It is a known tumor marker in colorectal cancer, while no correlation has been found with SCLC. Conversely, serum CEA levels may have prognostic value in NSCLC [35]. One study showed that elevated pre-treatment CEA levels significantly correlated with brain metastases in advanced NSCLC, suggesting a role in brain invasion [36]. CEA is highly expressed by NSCLC cells and minimally by healthy tissues, making it a promising target for CAR T cell therapy [37]. A phase I dose-escalation trial of anti-CEA CAR T cells in metastatic colorectal cancer demonstrated good tolerability and disease stabilization in 7 out of 10 patients [38]. This supports further exploration of CEA-targeted CAR T strategies in solid tumors, including NSCLC. Several clinical trials currently enrolling patients are ongoing to explore this approach (NCT05736731, NCT06006390, NCT06010862, NCT06126406, NCT06043466, NCT06821048, NCT06768151).

3.4. Mesothelin (MSLN)

Mesothelin (MSLN) is a glycosylphosphatidylinositol-anchored protein normally expressed by mesothelial cells of the pleura, peritoneum, pericardium, and tunica vaginalis [39], but aberrantly overexpressed in several solid tumors, including LC. It promotes proliferation, apoptosis resistance [40], and enhances cell migration and invasion [41]. In LC, MSLN overexpression correlates with poor prognosis, including reduced recurrence-free survival in early stages and lower overall survival in advanced disease [42–44]. Due to its limited expression in normal tissues and high tumor selectivity, MSLN is a promising CAR T target. Ye et al. developed second-generation MSLN CAR T cells for NSCLC and mesothelioma, showing potent cytotoxicity even at low effector-to-target ratios (0.5:1), with enhanced efficacy at higher ratios. In patient-derived xenografts, intravenous MSLN CAR T cells significantly reduced tumor burden [45]. In mesothelioma models, intrapleural delivery improved CAR T cell activation, expansion, and persistence [46]. The first clinical experiences with MSLN-targeting CAR T cells (NCT01355965, NCT01897415) confirmed safety and feasibility, with both treated patients achieving SD [47]. A phase I trial (NCT01583686) in advanced solid tumors, including LC, was terminated due to low accrual; among 15 patients, only one achieved SD, while others experienced progressive disease (PD), and 40 % had serious adverse events, including hypoxia. Among the targets discussed in this review, mesothelin is the most frequently investigated in ongoing clinical trials, with some studies specifically focusing on mesothelioma (NCT04577326, NCT05568680), and others including mesothelin-expressing solid tumors more broadly, such as LC (NCT05166070, NCT02414269, NCT02414269, NCT05848999, NCT05783089, NCT06196294, NCT06256055, NCT06051695, NCT06717022, NCT06885697). Among the most recent anti-mesothelin trials, which also include LC patients, two are of particular interest as they involve CAR T cells engineered to secrete anti-immune checkpoint nanobodies, a strategy designed to overcome the immunosuppressive barriers imposed by the tumor and its microenvironment (NCT06249256, NCT06248697).

3.5. Tyrosine kinase-like orphan receptor (ROR1)

ROR1 is widely expressed during embryogenesis and in several tumors, including ovarian cancer, TNBC, and lung adenocarcinoma, but also found in normal tissues like the parathyroid, pancreatic islets, and GI tract [48]. Although ROR1 is a promising target in epithelial cancers, its expression in healthy tissues raises concerns about on-target, off-tumor toxicity. Preclinical studies have shown potent antitumor activity of anti-ROR1 CAR T cells in 3D models of NSCLC and TNBC [49]. In the NCT02706392 trial, anti-ROR1 CAR T cells were tested in hematologic and solid cancers. Among 18 patients with $ROR1^{+}$ solid tumors (TNBC or NSCLC), 13 (72 %) had severe adverse events, including CRS in 3 and encephalopathy in 1, though no dose-limiting toxicity occurred. One year post-treatment, all patients were alive, and 7 (39 %) had not progressed [50]. Ongoing trials are further evaluating anti-ROR1 CAR T cells in TNBC, NSCLC, and other $ROR1^{+}$ solid tumors (NCT05274451, NCT05748938).

Table 1
Clinical trials investigating CAR T cells against lung cancer.

Target	Enhancement/ Combination	Tumor	Status	Phase	First posted	Country	Number ID
MUC1	Only CAR	NSCLC	Unknown	I/II	May 2018	PRC	NCT03525782
MUC1	Only CAR	NSCLC, Ovarian Cancer, Fallopian Tube Cancer, Triple Negative Breast Cancer (TNBC), Multiple Myeloma, Pancreatic Ductal Adenocarcinoma	Terminated	I	Jul 2019	US	NCT04025216
MUC1	Allogeneic CAR-T	Breast Cancer, Ovarian Cancer, Non Small Cell Lung Cancer, Colorectal Cancer, Pancreatic Cancer, Renal Cell Carcinoma, Nasopharyngeal Cancer, Head and Neck Squamous Cell Carcinoma, Gastric Cancer	Active, not Recruiting	I	Feb 2022	US	NCT05239143
MUC1	CTLA-4/PD-1 Ab-expressing	Solid Tumor	Unknown	I/II	June 2017	PRC	NCT03179007
PSCA, MUC1, TGFβ, HER2, Mesothelin, Lewis-Y, GPC3, AXL, EGFR, Claudin18.2, or B7-H3	TGFβ expressing CAR and secreting IL7/CCL19 and/ or SCFVs against PD1/ CTLA4/Tigit	Lung Neoplasm, Respiratory tract neoplasm, thoracic neoplasm	Recruiting	I	Jun 2017	PRC	NCT03198052
MUC1	Only CAR	NSCLC, Hepatocellular Carcinoma, Pancreatic Carcinoma, TNBC	Unknown	I/II	Oct 2015	PRC	NCT02587689
EGFR	PD-1 Ab-expressing	EGFR-positive Solid Tumor	Unknown	I/II	Aug 2016	PRC	NCT02862028
EGFR	Only CAR	EGFR-positive Solid Tumor	Unknown	I/II	Jun 2013	PRC	NCT01869166
EGFR	CXCR5 co-expression	NSCLC	Unknown	I	Jun 2019	PRC	NCT04153799
EGFR/B7H3	Bispecific CAR	NSCLC, TNBC	Recruiting	Early Phase I	Apr 2022	PRC	NCT05341492
EGFR	CXCR5 co-expression	NSCLC	Recruiting	Early Phase I	Sep 2021	PRC	NCT05060796
EGFR	TGF-β KO	EGFR-positive Solid Tumor	Unknown	I	Jul 2021	PRC	NCT04976218
EGFR	Only CAR	EGFR-positive Solid Tumor and have lost HLA-A*02 expression	Recruiting	I/II	Nov 2024	US	NCT06682793
EGFR	CTLA-4/PD-1 Ab-expressing	EGFR-positive Solid Tumor	Unknown	I/II	Jun 2017	PRC	NCT03182816
CEA	Only CAR	CEA-positive Solid Tumors and have lost HLA-A*02 expression	Recruiting	I/II	Feb 2023	US	NCT05736731
CEA	Only CAR	CEA-positive Solid Tumor	Unknown	I	Jan 2015	PRC	NCT02349724
CEA	Only CAR	CEA-positive Solid Tumors	Unknown	I/II	Apr 2020	PRC	NCT04348643
CEA	Only CAR	CEA-positive Solid Tumors	Recruiting	I/II	Aug 2023	PRC	NCT06006390
CEA	Only CAR	CEA-positive Solid Tumor	Recruiting	I	Aug 2023	PRC	NCT06010862
CEA	Only CAR	CEA-positive Solid Tumor	Recruiting	I	Nov 2023	PRC	NCT06126406
CEA	Only CAR	CEA-positive Solid Tumors	Recruiting	I	Sep 2023	PRC	NCT06043466
CEA	Only CAR	CEA-positive Solid Tumors	Recruiting	I	Jul 2024	PRC	NCT06821048
CEA	Only CAR	NSCLC, SCLC	Recruiting	I	Dec 2024	PRC	NCT06768151
MSLN	Only CAR	MSLN-positive Solid Tumor	Terminated	I	Apr 2012	PRC	NCT01583686
MSLN	Only CAR	MSLN-positive Solid Tumor	Unknown	I	Oct 2016	PRC	NCT02930993
MSLN	CTLA-4/PD-1 Ab-expressing	MSLN-positive Solid Tumor	Unknown	I	Jun 2017	PRC	NCT03182803
MSLN	PD-1 Ab-expressing	MSLN-positive Solid Tumor	Unknown	I/II	Jan 2017	PRC	NCT03030001
MSLN	PD-1 KO	MSLN-positive Solid Tumor	Unknown	I	Nov 2018	PRC	NCT03747965
MSLN	PD-1 Ab-expressing	MSLN-positive Solid Tumor	Unknown	I/II	Aug 2018	PRC	NCT03615313
MSLN	PD-1/TCR KO	MSLN-positive Solid Tumor	Unknown	I	Jun 2018	PRC	NCT03545815
MSLN	Only CAR	MSLN-positive Solid Tumor	Recruiting	I	Dec 2021	PCR	NCT05166070

(*continued on next page*)

Table 1 (*continued*)

Target	Enhancement/ Combination	Tumor	Status	Phase	First posted	Country	Number ID
MSLN	Only CAR	MSLN-positive Solid Tumor	Unknown	I	Jul 2021	PCR	NCT04981691
MSLN	Plus Pembrolizumab	Lung Cancer, Breast Cancer, mesothelioma, malignant pleural disease	Active, not recruiting	I/II	Apr 2022	US	NCT02414269
MSLN	Only CAR	Mesothelioma	Active, not recruiting	I	Oct 2020	US	NCT04577326
MSLN	Only CAR	MSLN-positive Solid Tumors	Unknown	I	Oct 2015	PRC	NCT02580747
MSLN	Only CAR	NSCLC, Ovarian Cancer, Peritoneal Carcinoma, Fallopian Tube Cancer, Mesotheliomas Pleural, Mesothelioma Peritoneum	Completed	I	Feb 2017	US	NCT03054298
MSLN	Secreting PD-1 nanobodies	NSCLC, Mesothelioma	Unknown	Early Phase I	Jul 2020	PRC	NCT04489862
MSLN	Secreting PD-1 nanobodies	MSLN-positive Solid Tumors	Unknown	I	May 2022	PRC	NCT05373147
MSLN	Only CAR	Mesothelioma, Ovarian Cancer, Cholangiocarcinoma Recurrent	Recruiting	I	Oct 2022	US	NCT05568680
MSLN	Only CAR	MSLN-positive Solid Tumors	Recruiting	I	May 2023	PRC	NCT05848999
MSLN	Only CAR	MSLN-positive Solid Tumors	Not yet recruiting	I	Mar 2023	PRC	NCT05783089
MSLN	Only CAR	MSLN-positive Solid Tumors	Unknown	I	Mar 2023	PR	NCT05775666
MSLN/GPC3	CAR-γδT Plus PD1/PDL1/ CTLA4 antibodies	Pancreas Cancer, NSCLC, Liver Cancer, Mesothelioma	Recruiting	I	Jan 2024	PRC	NCT06196294
MSLN	Only CAR	MSLN-positive Solid Tumors	Recruiting	I	Feb 2024	PRC	NCT06256055
MSLN	Secreting PD-1 nanobodies	MSLN-positive Solid Tumors	Recruiting	I	Feb 2024	PRC	NCT06249256
MSLN	Only CAR	MSLN-positive Solid Tumors and have lost HLA-A*02 expression	Recruiting	I/II	Sep 2023	USA	NCT06051695
MSLN	Secreting PD1/CTLA-4 nanobodies	MSLN-positive Solid Tumors	Recruiting	I	Feb 2024	PRC	NCT06248697
MSLN/GPC3/GUCY2C	Secreting fusion protein of IL21 and scFv against PD1	MSLN-positive Solid Tumors	Recruiting	I	June 2024	PRC	NCT05779917
MSLN	Only CAR	MSLN-positive Solid Tumors	Recruiting	I	Dec, 2024	PRC	NCT06717022
MSLN	Only CAR	MSLN-positive Solid Tumors	Not yet recruiting	I	Mar 2025	USA	NCT06885697
ROR1	Only CAR	NSCLC, TNBC, Hematopoietic and Lymphoid Cell Neoplasm	Terminated	I	Mar 2016	US	NCT02706392
ROR1	Only CAR	NSCLC, TNBC	Active, no Recruiting	I	Mar 2022	US	NCT05274451
ROR1	Only CAR	ROR1-positive Solid Tumors	Unknown	I/II	Mar 2023	PRC	NCT05748938
PDL-1	Only CAR	NSCLC	Terminated (serious adverse event)	I	Jun 2017	PRC	NCT03330834
HER2	Plus Binary Oncolytic Adenovirus	Advanced HER2 positive solid Tumor	Recruiting	I	Nov 2018	US	NCT03740256
EpCAM/TM4SF1	Only CAR	EpCAM-positive Solid Tumors	Unknown	I	Nov 2019	PRC	NCT04151186
EpCAM	Only CAR	EpCAM-positive Solid Tumors	Unknown	I/II	Jan 2017	PRC	NCT03013712
EpCAM	Only CAR	EpCAM-positive Solid Tumors	Active, not recruiting	I	Jul 2016	PRC	NCT02915445
GPC3	Dual targeting: GPC3 + soluble TGFβ	Lung squamous cell carcinom, HCC	Recruiting	I	Jun 2017	PRC	NCT03198546
GPC3	GOT2 expressing	Lung squamous cell carcinoma, Hepatocellular Carcinoma, Merkel Cell Carcinoma, Myxoid/Round Cell Liposarcoma	Recruiting	I/II	Nov 2021	US	NCT05120271
GPC3	Only CAR	Lung squamous cell carcinoma	Unknown status	I	Aug 2016	PRC	NCT02876978
GPC3	IL-15 co-expression	GPC3-positive Solid Tumors	Recruiting	I	Jun 2021	US	NCT05103631
GPC3	Novel universal CAR-T cell platform	HCC, NSCLC	Recruiting	I	Oct 2024	PRC	NCT06653023
GD2	IL-15 co-expression	NSCLC, SCLC	Recruiting	Early Phase I	Nov 2022	US	NCT05620342
GD2, MSLN, MAGE-A1, MAGE-A4, MUC1	Only CAR	NSCLC, SCLC	Unknown	I/II	Nov 2017	PRC	NCT03356808

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Table 1 (*continued*)

Target	Enhancement/ Combination	Tumor	Status	Phase	First posted	Country	Number ID
GD2 and/or CD56 (NCAM)	Bispecific CAR T	SCLC	Recruiting	I/II	Jun 2022	PRC	NCT05437328
DLL3	Only CAR	SCLC	Suspended	I	Jan 2018	US	NCT03392064
DLL3	Only CAR	SCLC, Large Cell Neuroendocrine Carcinoma of the Lung	Recruiting	I	Jan 2023	US	NCT05680922
DLL3	PD-L1 scFv-expressing	SCLC	Not yet recruiting	I	Apr 2024	PRC	NCT06348797
DLL3	Only CAR	SCLC, LNEC	Recruiting	I	Apr 2024	PRC	NCT06384482
B7-H3	Only CAR	Lung Cancer, Malignant Melanoma, Colorectal Cancer	Recruiting	I	Jan 2022	PRC	NCT05190185
N/D	Only CAR	Melanoma, NSCLC, Head and Neck Squamous Cell Carcinoma	Not yet Recruiting	I	Nov 2021	PRC	NCT05117138
B7-H3	Only CAR	Lung Cancer, Gastric Cancer, neuroblastoma, osteosarcoma	Unknown	Early Phase I	Apr 2021	PRC	NCT04864821
FAP	Only CAR	Mesothelioma	Completed	Early Phase I	Nov 2012	Switzerland	NCT01722149

3.6. Programmed death-ligand 1 (PD-L1)

PD-L1, expressed by various tumors, is the ligand of the immune checkpoint receptor PD-1 (Programmed Cell Death Protein 1), found on T cells, NK cells, B cells, and dendritic cells. The PD-1/PD-L1 interaction suppresses immune responses, enabling tumor immune evasion and progression [51,52]. As previously discussed, therapies targeting this axis have revolutionized the treatment of LC over the past decade. Beyond monoclonal antibodies, CAR T cells targeting PD-L1 have emerged as a complementary strategy. Quin et al. developed two anti–PD-L1 CAR T constructs: one incorporating a dominant-negative PD-1 receptor to simultaneously target PD-L1 and PD-L2 with low affinity, and another expressing a high-affinity scFv specific for human PD-L1. Both constructs effectively lysed PD-L1$^+$ tumor cells in vitro and suppressed NSCLC growth in PDX models [53]. However, since PD-L1 is also expressed on normal tissues, PD-L1-targeting CAR T cells carry a significant risk of on-target, off-tumor toxicity. Indeed, a phase I clinical trial (NCT03330834) evaluating their safety in advanced LC was terminated early due to severe adverse events.

3.7. Prostate stem cell antigen (PSCA)

PSCA is a 123 amino-acid-glycoprotein typically expressed by androgen-dependent and independent prostate cancers [54], later shown to be highly expressed in NSCLC and significantly correlated with worse prognosis [55]. As seen in the section on MUC1, Wei et al. evaluated anti-PSCA CAR T cells alone and in combination with anti-MUC1 CAR T cells in PDX mouse models of human NSCLC. Seven of the eight patient samples analyzed resulted positive for PSCA, and two also expressed MUC1. They demonstrated the effectiveness of anti-PSCA CAR T cells against PSCA$^+$ PDX tumors and the synergistic effectiveness of a combinatorial approach with anti-MUC1 CAR T cells against PSCA$^+$/MUC1$^+$ PDX tumors [23].

3.8. Human Epidermal Growth Factor Receptor 2 (HER2)

ERBB2 (HER2) mutations occur in ~3 % of non-squamous NSCLC and drive cell proliferation, differentiation, and survival via receptor oligomerization [56]. Despite its potential as a target, HER2's expression in healthy tissues, including heart and lungs, raises concerns about on-target, off-tumor toxicity. To mitigate this, strategies such as low-affinity CAR T cells and dual-targeting CARs (e.g., HER2/CEA in colorectal cancer) are being explored [57,58].

Preclinical studies in LC models have shown promising antitumor activity of HER2 CAR T cells, alongside proposed combination strategies (detailed in a later section). While no clinical data are available yet for LC, a recent phase I trial in sarcoma reported clinical benefit in 50 % of patients, with an acceptable safety profile [59].

3.9. Epithelial cell adhesion molecule (EpCAM)

EpCAM is a transmembrane glycoprotein expressed on the basolateral surface of most normal epithelial tissues and it is involved in intracellular adhesion. EpCAM is overexpressed in various epithelial malignancies, such as LC, where its expression exceeds 50 % and remains conserved in the metastatic stage [60]. In a recent and intriguing study, Xu et al. investigated the potential role of anti-EpCAM CAR T cells in reducing brain metastases from LC. The CAR T treatment was injected intravenously or into the adjacent brain parenchyma in mice models: while the intravenous approach proved unsuccessful, local infusion led to reduced tumor growth and prolonged survival, without any observed systemic toxicity. Nonetheless, the intratumoral amount of anti-EpCAM CAR T cells declined throughout the observation period, indicating inadequate persistence [61].

3.10. Glypican-3 (GPC3)

Glypican-3 (GPC3) is a membrane-bound glycoprotein implicated in cell growth and proliferation. It is overexpressed in several solid tumors, particularly hepatocellular carcinoma (HCC) and lung squamous cell carcinoma, but minimally present in healthy tissues [62], making it a promising immunotherapy target [63]. Anti-GPC3 CAR T cells have demonstrated in vitro and in vivo efficacy against HCC, both alone and combined with sorafenib [63,64]. A phase I trial in 13 advanced HCC patients showed a favorable safety profile, with 6-month, 1-year, and 3-year overall survival rates of 50.3 %, 42.0 %, and 10.5 %, respectively [65]. More recent early-phase trials, including patients with solid tumors such as LC (NCT05103631), tested IL-15–engineered anti-GPC3 CAR T cells, reporting enhanced expansion, persistence, and antitumor activity, with a 66 % disease control rate and 33 % response rate [66].

Currently, three phase I trials (NCT02876978, NCT03198546, NCT05120271) are enrolling patients with GPC3$^+$ solid tumors, including lung squamous cell carcinoma. Notably, two recent studies are testing innovative platforms: NCT06653023 evaluates an off-the-shelf universal CAR T system, while NCT06196294 investigates γδ CAR T cells, potentially offering superior infiltration and MHC-independent targeting.

3.11. Disialoganglioside GD2 (GD2)

GD2 is a disialoganglioside highly expressed in neuroectodermal tumors, with limited presence in healthy tissues [67]. Its tumor-

restricted profile makes it a valuable target for immunotherapies, including monoclonal antibodies and CAR T cells [68]. Several anti-GD2 CAR T constructs, especially for CNS tumors like neuroblastoma and glioblastoma, have shown strong preclinical efficacy [69,70]. A phase I trial in DIPG patients (NCT04196413) confirmed feasibility, with on-tumor neurotoxicity but no off-tumor effects, supporting further investigation in $GD2^{+}$ malignancies [71]. GD2 is variably expressed in both SCLC and NSCLC [72,73], though only one CAR T strategy targets both. Reppel et al. developed IL-15–secreting anti-GD2 CAR T cells, confirming GD2 expression in SCLC and lung adenocarcinoma/squamous carcinoma. In orthotopic and metastatic mouse models, these CAR T cells controlled tumor growth even after rechallenge, emphasizing IL-15′s role in persistence [74]. Based on these findings, a phase I trial (NCT05620342) is underway in extensive-stage LC refractory to platinum and anti-PD-1/PD-L1 therapies. Additionally, Kinoshita et al. introduced GD2-CAR into iPSC-derived rejuvenated cytotoxic T lymphocytes (GD2-CARrejT), which exhibited superior antitumor activity in vitro and in vivo compared to conventional GD2 CAR T cells. Single-cell RNA sequencing revealed reduced TIGIT expression in GD2-CARrejT cells, suggesting low TIGIT levels may be critical for sustained cytotoxic function [75].

3.12. Delta Like Ligand 3 (DLL3)

DLL3 is an attractive CAR T target in SCLC due to its high tumor expression and minimal presence in normal tissues. As a Notch pathway inhibitory ligand regulated by ASCL1, DLL3 is aberrantly expressed in neuroendocrine tumors [76]. Zhang et al. developed allogeneic anti-DLL3 CAR T cells, identifying three scFv clones (R2S-7, R2S-9, R2S-4) with durable in vivo tumor control at low antigen density. The lowest-affinity clone, R2S-4, suppressed tumor growth in 3/8 mice in a metastatic model [77]. Despite DLL3 mRNA presence in brain and pituitary, no off-tumor toxicity was seen, with preserved pituitary function and no cytotoxicity in co-culture assays [77]. Further enhancement was demonstrated using IL-18-secreting DLL3 CAR T cells, which improved T cell activation, infiltration, and reduced exhaustion in metastatic SCLC models [78]. An alternative non-viral strategy using circRNA to generate DLL3 CAR T cells achieved complete tumor eradication in both subcutaneous and orthotopic xenograft models, improving stability and efficacy [79]. Clinical data from a phase I trial (AMG 119) in relapsed/refractory SCLC ($n = 5$) showed good safety, with no CRS. One patient achieved PR, three had SD, and one PD. Clinical benefit correlated with greater CAR T expansion (Cmax, AUC), and longer Tmax in the PR case. Younger and female patients showed enhanced expansion, suggesting possible immunologic influences [80]. Currently, three phase I trials are ongoing (NCT05680922, NCT06348797, NCT06384482).

3.13. NCAM (CD56)

CD56 is expressed in approximately 90 % of SCLC cases, although its expression is not restricted to malignant cells [81,82]. A Sleeping Beauty transposon-based CD56R-CAR T cell platform was developed to treat SCLC and neuroblastoma. CD56R-CAR T cells were extensively characterized in terms of phenotype, cytokine secretion profile, and potential fratricide, as CD56 can also be expressed on T lymphocytes. In an in vivo subcutaneous murine model of SCLC, three different CAR T cell doses (1×10^6, 5×10^6, 1×10^7) were tested, all leading to a significant reduction in tumor volume ($p < 0.001$, 16 days post tumor injection) [83]. To date, a Phase I/II trial investigating a bispecific anti-GD2/CD56 CAR T therapy (NCT05437328) is the only clinical study involving an anti-CD56 CAR.

4. Combinatorial Approaches for Lung Cancers: When CAR T may not be Enough

Combinatorial CAR T-based strategies are actively explored to overcome the barriers of LC. We reviewed both preclinical and clinical studies combining CAR T therapies with other treatments (Table 2 and Fig. 1).

There is general consensus that solid tumors pose a broader range of challenges to CAR T cell efficacy than hematological malignancies. Unlike hematologic cancers, solid tumors reside in non-lymphoid tissues, where T cells require appropriate inflammatory cues to effectively traffic. Moreover, by expressing ligands for inhibitory receptors such as PD-1, solid tumors can directly suppress T cell function and promote immune evasion by recruiting immunosuppressive cells and releasing soluble suppressive factors [90]. A key focus is overcoming this immunosuppression through combination approaches.

Srivastava et al. demonstrated in murine models that immunogenic chemotherapy activates tumor-associated macrophages to produce chemokines that facilitate the recruitment of anti-ROR1 CAR T cells to lung tumors. Specifically, the addition of oxaliplatin to the lymphodepletion regimen led to macrophage activation and expression of chemokines that improved CAR T cell infiltration, remodeled the tumor microenvironment, and increased tumor susceptibility to anti-PD-L1 therapy. This study highlighted a promising synergistic effect when combining oxaliplatin/cyclophosphamide with anti-PD-L1 to enhance CAR T cell antitumor activity [50].

Zheng and colleagues explored an alternative strategy by integrating CAR T cell therapy with chemotherapy via targeted drug delivery. They engineered exosomes derived from CAR T cells (CAR-Exos) to express anti-MSLN scFv on their surface, enabling targeted delivery of paclitaxel (PTX) encapsulated within these vesicles. In an orthotopic LC model, inhalation of CAR-Exos led to effective delivery of PTX to tumor cells, which also expressed cytotoxic proteins such as granzyme B and perforins. This approach not only enhanced tumor cell killing but also increased $CD8^{+}$ T cell infiltration and cytokine levels (TNF-α, IFN-γ) in the tumor microenvironment, thereby overcoming some of the key immunosuppressive hurdles [88].

Gao et al. further demonstrated that chemotherapy alone can augment CAR T cell therapy. In vitro, they showed that docetaxel upregulates the expression of the chemokine CXCL11 and HMGB1 in tumor cells. In vivo, docetaxel pretreatment increased CXCL11 and HMGB1 levels, enhanced HER2-targeted CAR T cell infiltration, and significantly improved survival in murine models [84].

McKenna et al. tested a novel strategy involving a binary oncolytic adenovirus encoding IL-12 and a PD-L1 blocker, delivered via mesenchymal stromal cells (MSCs), to potentiate HER2-targeted CAR T cells. The engineered MSCs secreted active oncolytic virus, which both lysed tumor cells and promoted CAR T cell function through IL-12 and PD-L1 inhibition [85]. This approach has shown efficacy in preclinical models and is currently being evaluated in a clinical trial (NCT03740256).

In malignant pleural mesothelioma (NCT02414269), intrapleural MSLN CAR T cells combined with pembrolizumab resulted in a median OS of 23.9 months, with prolonged disease control and metabolic responses in some patients [91], suggesting potential applicability in NSCLC or SCLC [89].

To address low/heterogeneous antigen expression, Zhou et al. combined Tn-MUC1 CAR T cells with dabrafenib, which enhanced MUC1 expression via MAPK inhibition. This improved CAR T efficacy in vitro/in vivo in LC models. Moreover, in a phase I trial (ChiCTR1900025088), one breast cancer patient had a 40 % tumor reduction; serum CA15-3 correlated with MUC1 induction [86].

Lastly, physical techniques such as nanozyme ablation and microwave therapy have also been tested in combination with CAR T cells in preclinical models. In one study, B7-H3-targeted CAR T cells were administered after tumor ablation via nanozymes, which disrupted the compact tumor microenvironment and improved CAR T cell access [91]. In another model, CAR T cells targeting AXL were infused after local microwave ablation of the tumor, resulting in superior antitumor efficacy compared to CAR T cells alone [87].

Table 2
Combinatorial strategies for CAR T-based therapy against lung cancers.

Target	Tumor	Combination	Aim	Trial	Reference
ROR	NSCLC	Oxalilplatin	Chemotherapy induces macrophages to produce chemokines to facilitate the recruitment of CAR T	No	Srivastava S. et al., 2018 [50]
HER-2	NSCLC	Docetaxel	Docetaxel increases the expression of CXCL11 and HMGB1 which results in enhanced CAR T infiltration	No	Gao Q., et al, 2019 [84]
HER-2	NSCLC	MSC-produced oncolytic virus secerning IL-12 and PD-L1 blocker	Oncolytic viruses produces the tumor lysis liberating IL-12 and PD-L1 in TME to enhance CAR T cell response	NCT03740256	McKenna M., 2021 [85]
B7-H3	NSCLC	Nanozymes	Cu-nanozymes destroy tumor extracellular matrix to enhance CAR T cell toxicity	No	Zhu L., 2021 [86]
AXL	NSCLC	Microwaves	Local mass ablation before CAR T cell administration	No	Cao B., 2022 [87]
MSLN	NSCLC	Exosome, paclitaxel	Inhalation of CAR-T cell-derived exosomes targeting MSLNs	No	Zheng W., 2023 [88]
MSLN	Mesothelioma	Anti −PD1 (pembrolizumab) administration	Pembrolizumab administration rescues functionality in exhausted CAR T cells and increases anti-tumor efficacy	NCT02414269	Adusumilli PS., 2021 [89]
MUC1	NSCLC	Dabrafenib	Combination with Dabrafenib enhanced MUC1 expression via MAPK inhibition	ChiCTR1900025088	Zhou Z., 2024 [86]

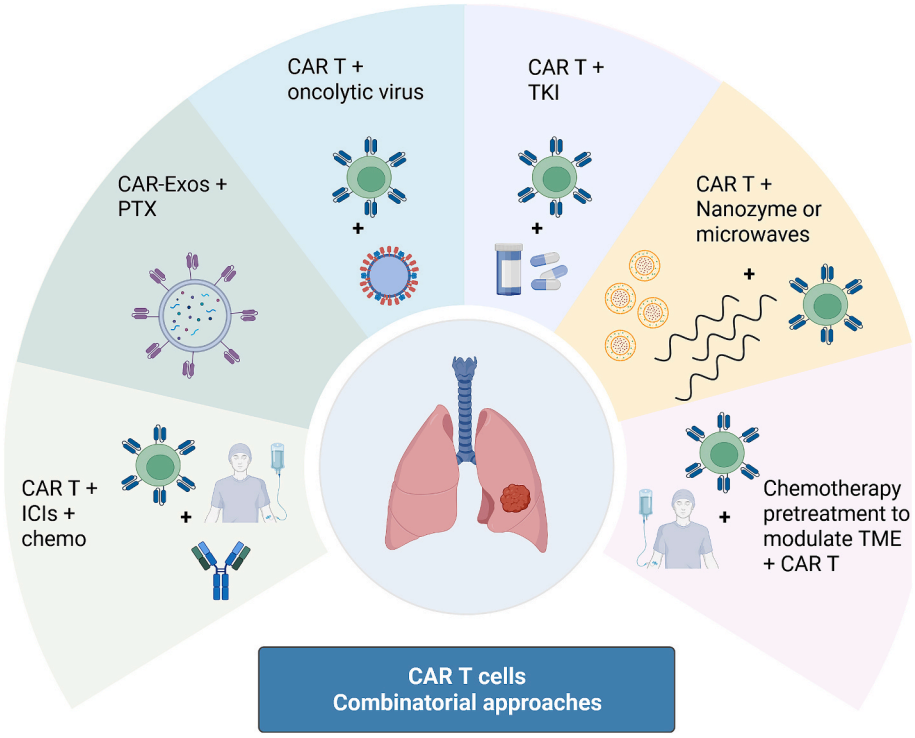

Fig. 1. Preclinical and clinical studies combining CAR T therapies with other treatments. From left to right: CAR T with chemotherapy and immunocheckpoint inibitors (ICI), CAR-exos with paclitaxel (PTX), CAR-T and oncolytic virus, CAR T and Tyrosine Kinase Inhibitor (TKI), CAR-T and nanozyme or microwaves, CAR T and chemotherapy pretreatment to modulate Tumor microenvironment (TME). Created with BioRender.com.

5. Conclusions

Despite the remarkable success of CAR T cell therapies in hematologic malignancies, their translation into solid tumors, particularly LC, one of the leading causes of cancer-related mortality worldwide, remains a major challenge. In this review, we summarized the current preclinical and clinical advancements in CAR T cell therapy for LC, with a focus on the principal strategies designed to overcome both tumor-intrinsic and microenvironmental barriers. LC shares several barriers with other solid tumors, including immune evasion and inefficient T cell infiltration, while also presenting unique pathological features. To date, efforts to address these obstacles can be broadly classified into two complementary approaches: intrinsic CAR T cell enhancement by genetic engineering, as summarized in Fig. 2, and combinatorial strategies, extensively discussed in the previous section.

Among the most actively investigated areas is the reversal of tumor- and microenvironment-induced immunosuppression, particularly through targeting the PD-1/PD-L1 axis. Strategies such as engineering CAR T cells to secrete anti-PD-1 antibodies locally or to lack PD-1 expression, as well as combining CAR T therapy with systemic immune checkpoint inhibitors (ICIs), have shown encouraging preclinical results [34,50]. While both strategies are promising, each offers distinct advantages: localized checkpoint blockade may enhance CAR T efficacy in poorly infiltrated “cold” tumors, such as LC in non-smokers,while limiting systemic toxicity; conversely, systemic ICI administration could concurrently activate endogenous T cells, including naïve populations, thereby broadening the overall immune response beyond the CAR T compartment. Importantly, the existing clinical experience with ICIs in LC offers a solid foundation for their integration into CAR T cell strategies, potentially easing the path toward clinical application.

T cell trafficking to tumor sites remains another critical bottleneck. Innovative strategies such as dual-receptor CAR T cells co-expressing

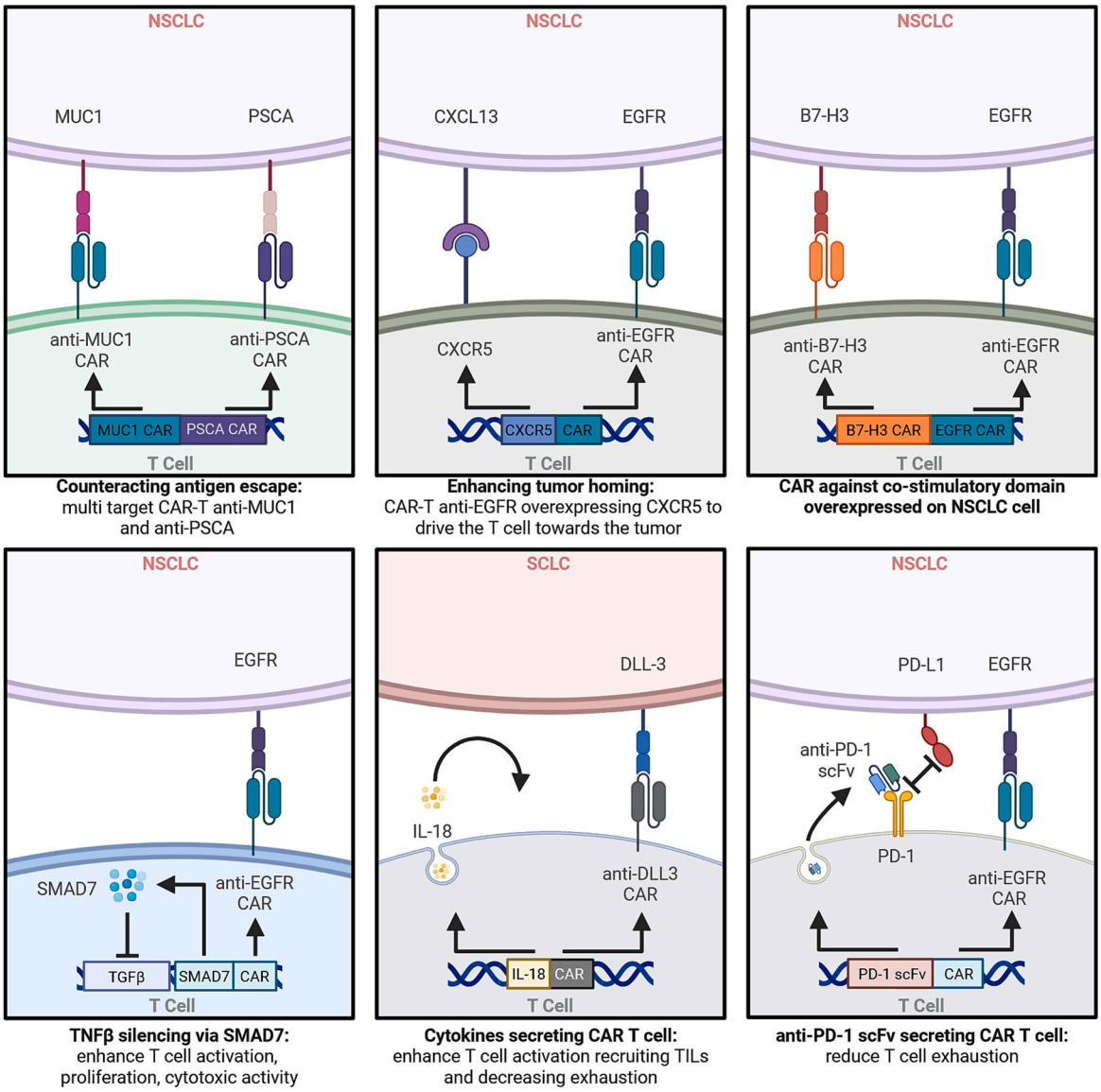

Fig. 2. CAR T cell empowerments by genetic engineering. Abbreviations: CAR, chimeric antigen receptor; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; MUC1, mucin 1; PSCA, prostate stem cell antigen; EGFR, epidermal growth factor receptor; B7-H3, B7 homolog 3; CXCL13, C-X-C motif chemokine ligand 13; CXCR5, C-X-C chemokine receptor type 5; SMAD7, SMAD family member 7; TGFβ, transforming growth factor beta; IL-18, interleukin 18; DLL3, delta-like ligand 3; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; scFv, single-chain variable fragment. Created with BioRender.com.

anti-EGFR and CXCR5 have been developed to exploit LC-derived chemokines like CXCL13, thereby improving tumor homing [32]. Notably, compared to other solid tumors, LC exhibits a particularly dense and heterogeneous population of cancer-associated fibroblasts (CAFs), some subtypes of which have been shown to actively impede immune cell infiltration. These CAF subsets represent promising candidates for future co-targeting strategies alongside CAR T cells [92].

Antigen heterogeneity and the risk of antigen escape also remain major concerns in LC. Multitarget CAR T approaches, such as those co-targeting MUC1 and PSCA [23], as well as pharmacological upregulation of target antigens (e.g., dabrafenib-mediated enhancement of MUC1 expression) [86] are being explored as potential solutions to mitigate these issues.

Importantly, any discussion on LC must extend beyond the tumor itself to encompass the patient as a whole. Patients with metastatic LC, particularly those with SCLC, often present with poor performance status (e.g., high ECOG scores) [93] significant comorbidities, and limited therapeutic windows, which may preclude timely autologous CAR T cell manufacturing and patient delivery. Additionally, prior chemotherapy, almost universal in this population, often results in T cell dysfunction, further compromising autologous product feasibility. Allogeneic ("universal") CAR T cell products derived from healthy donors offer a compelling off-the-shelf option for rapid administration. In parallel, virus-free manufacturing platforms, such as those based on transposon systems, enable faster and more streamlined CAR T cell production. Both approaches, already tested in hematologic malignancies, have shown encouraging safety and efficacy profiles [94], and may be even more crucial in the context of LC, where timely treatment delivery is often critical.

Alternatively, the administration of CAR T cells in earlier stages of disease, such as in unresectable, locally advanced LC, could improve feasibility by taking advantage of better patient fitness and allowing for potential synergistic effects with standard therapies, among which radiotherapy plays a central role. In this context, CAR T cells could potentially be integrated with radiotherapy, which has shown immunomodulatory properties and possible synergy, as supported by early data and analogous studies involving microwave ablation [91,95]. This combinatorial approach warrants further preclinical and clinical

investigation.

In conclusion, this review highlights that LC start to represent a promising target for CAR T cell therapy while also offering a fertile ground for innovation. Addressing the distinct challenges associated with LC could pave the way for effective treatment strategies for LC patients and expand the application of CAR T technologies to other solid tumors. Ongoing translational efforts will be essential to close the gap between experimental advances and clinical adoption.

CRediT authorship contribution statement

Lucia Trudu: Conceptualization, Project administration, Writing – original draft. **Giulia Rovesti:** Validation, Writing – review & editing. **Giovanni Neri:** Visualization, Writing – original draft. **Giuseppe Pugliese:** Validation. **Marco Silingardi:** Validation. **Leonardo Brini:** Validation. **Giulia Golinelli:** Validation. **Maria Cristina Baschieri:** Validation. **Eleonora Lallo:** Validation. **Giorgia Guaitoli:** Validation, Writing – review & editing. **Federica Bertolini:** Validation, Writing – review & editing. **Cinzia Del Giovane:** Validation. **Pier Luigi Filosso:** Validation. **Massimo Dominici:** Conceptualization, Supervision, Writing – review & editing. **Chiara Chiavelli:** Supervision, Writing – review & editing.

Declaration of competing interest

Giulia Golinelli and Massimo Dominici hold patents in the field of cancer and gene therapy.The other authors declare no competing interests.

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