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Review

Adopting tomorrow's therapies today: a perspective review of adoptive cell therapy in lung cancer

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***Abstract*:** Lung cancer is the leading cause of all cancer-related deaths in the United States and remains a global health challenge. While targeted therapy has revolutionized the treatment landscape of nonsmall cell lung cancer, many patients lack actionable mutations. Immunotherapy, particularly immune checkpoint inhibitors (ICIs), have significantly impacted outcomes in lung cancer in the last decade. Some patients, however, never respond or become refractory to ICIs. Newer therapies aimed at augmenting the immune system and enhancing antitumor effects are currently being explored. Adoptive cell therapy (ACT) employs T cells isolated from either tumors or peripheral blood and often engineers them to effect antitumor immune response. Chimeric antigen receptor T (CAR-T) cell therapy, engineered T cell receptor therapy, and tumor-infiltrating lymphocytes are examples of adoptive cellular therapies. CAR-T cell therapy has been successful in the treatment of hematological malignancies with several CAR products gaining approval in the treatment of refractory blood cancers. The success of ACTs in hematological cancers has fueled research into the role of these therapies in solid cancers including lung cancer. Many trials have had early promising results, with many clinical trials currently enrolling. There are many limitations to the efficacy of ACTs, as well as risks and benefits with the individual subtypes of ACT. With growing knowledge about tumor antigens and more advanced cell engineering, there is potential for ACT to result in durable responses in immunologically "cold" tumors. Here, we review the major subtypes of ACTs, evidence supporting their use in lung cancer, challenges, and future perspectives in ACTs. Additionally, we include T cell engagers and mRNA vaccine studies and potential combinatorial strategies in lung cancer.

Plain language summary

Adopting tomorrow's therapies today: a perspective review of immune cell therapies and mRNA vaccines targeting lung cancer cells

Lung cancer is a prominent cause of cancer-related deaths in the United States and worldwide. Several approaches to treat lung cancer has been used over the years. We know that the immune system is not only designed to fight infections but also to recognize and kill cancer cells. A group of immune cells called killer T cells can bind to markers on the surface of cancerous cells. The understanding of the role the immune system plays in attacking cancer cells led to the development of immunotherapy. Immune checkpoint inhibitors are drugs that target proteins that act as "off-switches" in the immune system. Outcomes in lung cancer have improved with the introduction of immune checkpoint inhibitors, but still only a minority of patients have long term benefit. A new type of immunotherapy called adoptive cell therapy (ACT) is the focus of this perspective review. ACT is also referred to as cellular immunotherapy. This is an umbrella term including treatment that uses the cells of the immune system to get rid of cancer. There are different ways of utilizing ACT

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in the treatment of lung cancer. One way is to remove patient's immune cells and culture them in the laboratory. Additionally, there might be changes made to the genes of the patient's immune cells in the laboratory to boost their cancer-fighting abilities. Several clinical trials have demonstrated early promise, but these trials are still enrolling, and we have yet to fully understand how safe and effective these treatments are in lung cancer.

Keywords: adoptive cell therapy, cancer vaccines, CAR-T cell therapy, immunotherapy, lung cancer, tumor-infiltrating lymphocytes

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Introduction

Lung cancer is the second most prevalent malignancy in the United States and globally. Roughly 234,580 new lung cancer cases are expected in 2024. It is the leading cause of all cancer-related deaths in the United States with approximately 340 deaths reported daily.[1]

The poor outcomes in lung cancer are largely attributed to the fact that more than 50% of lung cancer patients present with locally advanced or metastatic disease at diagnosis.[1,2] Targeted therapies have greatly added to the treatment arsenal for lung cancer patients. However, unfortunately most patients still experience disease progression and death.

Immunotherapy has revolutionized the treatment landscape of lung cancer. One class of immunotherapies consists of immune checkpoint inhibitors (ICIs), which impede important immunosuppressive molecules including PD-1, programmed death ligand 1 (PD-L1), and CTLA4, resulting in tumor elimination via cytotoxic T-cells. In the last decade, ICIs have advanced care for patients with nonsmall cell lung cancer (NSCLC) in first-line and second-line settings, as well as across tumor stages.[3] Despite the impact of ICIs in NSCLC management, response rates may be limited by tumor immune escape strategies.[4] In addition, the use of ICIs in small cell lung cancer (SCLC) has improved outcomes, though only for a minority of patients. Those with inflamed tumors appear to have increased benefit from the addition of ICI to the chemotherapy backbone.[5] The 3-year relative survival for NSCLC improved from 26% to 40% between 2004 and 2017, as opposed to the 4% increase (9%–13%) for SCLC.[1] The limitations of ICIs have encouraged further research to explore other mechanisms of improving T-cell-dependent tumor cytotoxicity.

Adoptive cell therapy (ACT) is a broad term referring to T-cell-based cellular immunotherapies that are developed, expanded, and sometimes genetically engineered in vitro and administered to patients.[6] ACTs employ immunostimulatory pathways to improve cancer-directed T-cell killing. Over the past several decades, different classes of ACTs have been developed and have been transformative in the management of hematological malignancies as well as a few solid tumors such as melanoma. Chimeric antigen receptor-T (CAR-T) cell therapy, tumor-infiltrating lymphocytes (TILs), engineered T-cell receptor (TCR) therapy, and natural killer cell (NK cell) therapy are novel treatments within the umbrella of ACT.[6] In ACT, T cells are isolated via extraction from either the tumor or from the peripheral blood, expanded ex vivo, and sometimes genetically modified.[7] The host immune milieu is typically altered by administering nonmyeloablative lymphodepleting chemotherapy to reduce endogenous lymphocytes, which compete for the same stimulatory cytokines such as IL-17 and IL-15.[6] An alternative approach is to stimulate T cells in vivo using mRNA vaccines and bispecific T cell engagers (BiTEs). These treatments are now experimental in solid tumors, with the first BiTE, tarlatamab, recently receiving FDA approval in the treatment of SCLC. The hope with this arsenal is to improve the durability of response as well as increase the number of patients who can be successfully treated with immunotherapy. In this article, we review recent literature on emerging ACTs for lung cancer.

Methods

This perspective review was based on an extensive literature search performed on August 1, 2024, in PubMed as well as ClinicalTrial.gov. We retrieved information using the following queries:

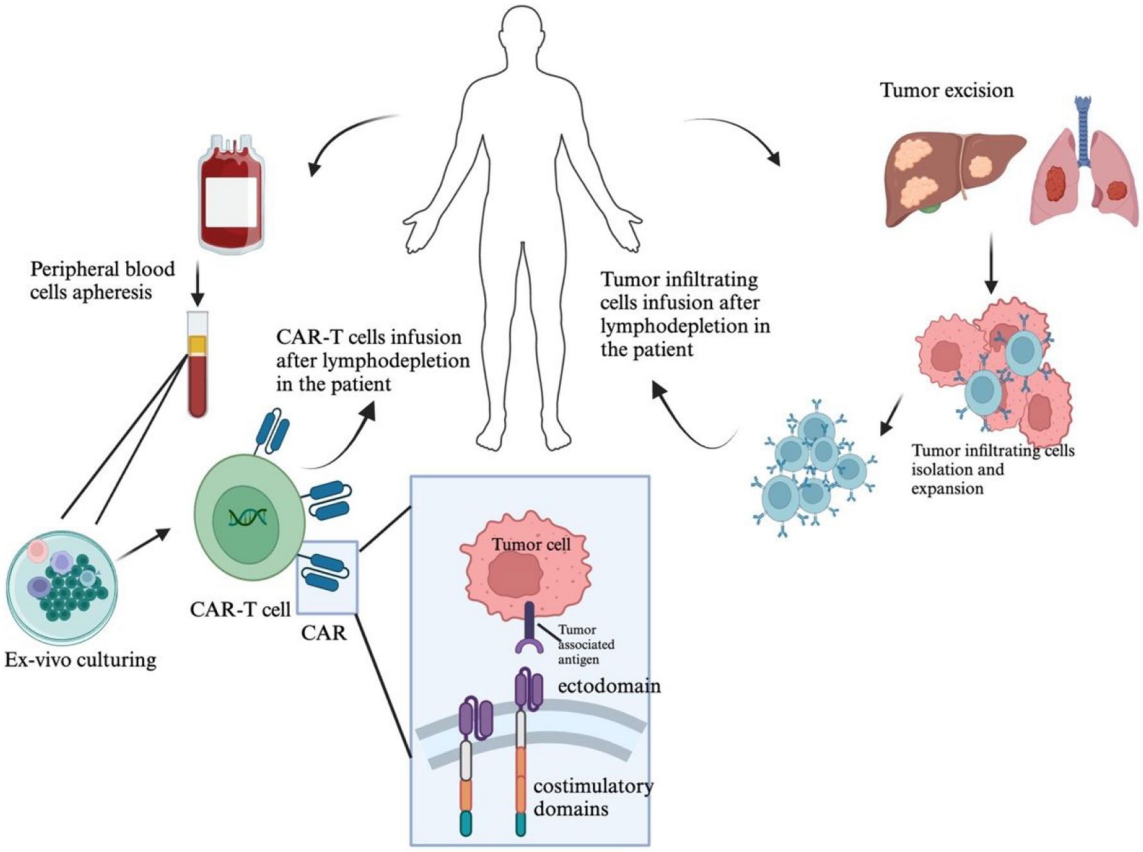

Figure 1. The development of CAR-T cells begins with peripheral blood apheresis which is followed by transduction of the CAR gene into autologous T cells. The CAR has an ectodomain which acts as the antigen-binding domain, the endo domain contains costimulatory domains in newer generations of CARs. The construct of the CAR allows for MHC independent tumor binding and killing. For the development of TILs, tumor tissue is obtained from the patient and then expanded ex vivo and returned to the patient.
Source: This figure created using Biorender.[13]
CAR-T, chimeric antigen receptor T-cell; TILs, tumor-infiltrating lymphocytes.

"lung cancer AND BiTEs," "lung cancer AND CAR-T therapy," "lung cancer AND TCR therapy," "lung cancer AND TILs," "lung cancer AND NK cells," and "lung cancer AND mRNA vaccines." We also queried the meeting abstracts of American Society of Oncology, World Conference on Lung Cancer, Society for Immunotherapy of Cancer, and the American Association for Cancer Research to identify ongoing and completed trials in lung cancer. Abstracts and clinical trials were reviewed for relevance to the topic.

TILs therapy in lung cancer

TILs are a heterogeneous group of cells consisting of CD4+ and CD8+ αβ T cells located in the tumor microenvironment (TME).[8] ACT with TILs has shown significant efficacy with durable responses in certain solid tumors including melanoma and cervical cancer.[9] Lung cancer is associated with several somatic mutations which lead to the formation of tumor neoantigens that can be targeted by TILs.[10]

The first step in this personalized autologous treatment is harvesting TILs from resected tumors. The cells are expanded and cultured ex vivo using cytokines like IL-2 before returning the product to the patient (see Figure 1). In preparation for the cells, patients receive nonmyeloablative lymphodepleting chemotherapy, usually fludarabine and cyclophosphamide.[8] The lymphodepleting therapy is thought to cause better antitumor efficacy and persistence of TILs by reducing cells such as CD4+cd25+ Tregs, and myeloid-derived suppressor cells that affect the activity of tumor-reactive cytotoxic T cells.[11]

Table 1. TILs adoptive therapy trials.

TIL product name	Clinical trial ID	Phase/status	IL-2, nonmyeloablative lymphodepleting chemotherapy	Genetically modified	Primary outcome
LN-145	NCT04614103	II/recruiting	Yes, yes	No	ORR
GC203	NCT06375187	I/recruiting	No, yes	Yes, mbIL7	MTD
CD40L TIL	NCT05681780	I/II, recruiting	Yes, yes	Yes, CD40L	AE
GT201	NCT06519669	I, recruiting	Yes, yes	Yes, mbIL15	ORR
TBio-4101	NCT05576077	I, recruiting	Yes, yes	No	AE
ATL001	NCT04032847	I/IIa, recruiting	Yes, yes	No	TEAE
CheckCell-2	NCT05566223	I/II, not recruiting	Yes, yes	Yes, CISH	Safety, ORR
IOV-4001	NCT05361174	I/II, recruiting	Yes, yes	Yes (PD-1 knockout)	Safety, ORR
LYL 845	NCT05573035	I, recruiting	Yes, yes	Yes, epigenetic-R	DLT, TEAE
ITIL-306	NCT05397093	Ia/Ib, not recruiting	No, yes	Yes, folate receptor	AEs
NEO TIL	NCT04643574	I, not recruiting	Yes, yes	No	AE, ORR
OBX-115	NCT06060613	I/II, recruiting	No, yes	Yes, mbIL15	AE, ORR

AEs, adverse events; CD40L, CD40 ligand; CISH, cytokine-induced SH2 protein inactivated; DLT, dose-limiting toxicity; mbIL7, membrane bound il7; mbIL15, membrane bound il15; MTD, maximum tolerated dose; ORR, objective response rate; TEAE, treatment emergent adverse events; TILs, tumor-infiltrating lymphocytes.

Following the infusion of autologous T lymphocytes, cytokines such as IL-2, alone or in combination with IL-7, IL-15, and/or IL-21, are often given to stimulate T cell proliferation.[12]

Researchers at the National Cancer Institute first developed TIL therapy in the late 1980s.[14] More than two decades later, Lifileucel, became the first TIL product approved in the treatment of cancer following results from a study that showed an improved median PFS of 7.2 months in patients with unresectable/advanced melanoma compared to 3.1 months with ipilimumab.[15]

The clinical experience of TILs in lung cancer has been somewhat limited relative to melanoma. TILs were given in combination with nivolumab to patients with metastatic NSCLC following progression on single-agent nivolumab in a single-arm, open-label phase I study (NCT03215810). The primary endpoint of safety based on prespecified criteria was met. Out of 20 participants enrolled in the study, 13 patients were evaluable with three confirmed responses. Additionally, at the time of reporting two patients had durable, ongoing complete responses at the 1.5-year mark.[16] A recent phase II trial (NCT04614103) assessed the safety and efficacy of lifileucel (LN-145) in patients with heavily pretreated metastatic NSCLC.[17] The study population included patients who had progressed on their recent therapy and had received prior ICIs. Of 28 patients, 6 patients (21.4%) achieved an objective response. At the time of data cutoff, two responses were ongoing at 30 months. The treatment was also well tolerated with an expected adverse profile consistent with advanced disease, IL-2 treatment, and lymphodepleting chemotherapy. Two patients died from cardiac failure and multiorgan failure. Other ongoing TILs trials in lung cancer are included in Table 1.

Limitations of TILs therapy in lung cancer and future perspectives

Despite the promise of TILs therapy, there are still several challenges and drawbacks associated with its use. Conditioning chemotherapy used prior to receiving TILs results in depletion of immune cells such as lymphocytes and neutrophils and can increase the risk for infections. IL-2 which is also used in the process, is associated

with fever, hypotension, and in some cases, cytokine release syndrome (CRS).[18] The toxicity of conditioning chemotherapy and IL-2 limits eligibility for TIL therapy, particularly for heavily pretreated lung cancer patients. New TIL products such as OBX-115 seek to replace the need for IL-2. OBX-115 is a recombinant TIL engineered to express a stabilized membrane-bound IL-15 and is currently being investigated in an ongoing trial (NCT06060613). In the limited data published thus far, no dose-limiting toxicities have yet been reported. There is a certain proportion of nonresponders who are naturally resistant or acquire resistance to immunotherapy.[19] More is to be understood about the underlying mechanisms of resistance to TILs; however, antigenic heterogeneity and impaired trafficking have been implicated.[16] The paucity of tumor-reactive T cells in the TME portends a major challenge in immunologically cold tumors. Selection of neoantigen-reactive T cells can be an alternative approach to obviate this problem and has been successful in gastrointestinal and breast cancers.[7,20,21]

CAR-T therapy in lung cancer

CAR-modified T cell therapy is an innovative form of ACT that utilizes genetically modified autologous or allogeneic T cells engineered ex vivo and returned to the patient to recognize and bind to cancer cells (see Figure 1).[22] A CAR consists of a single-chain variable fragment (scFv) of an antigen-specific antibody which serves as its extracellular antigen-binding domain or ectodomain,[23,24] in addition to a transmembrane domain and an endodomain, which is its intracellular signal transduction domain. Based on modifications in the intracellular domains, different generations of CARs have been developed.[25] The intracellular domain of the CAR is composed of an activation domain with one or two costimulatory domains, which were added in subsequent generations of CAR. The presence of costimulatory molecules such as CD28, OX40, and 4-1BB has improved the persistence and growth of CAR-T cells over first-generation CARs.[6] Fourth-generation CARs, also referred to as TRUCKs (T cells redirected for antigen-unrestricted cytokine-initiated killing) are designed to release cytokines upon CAR binding to the target tissue.[26] The synthetically developed CAR is retrovirally transduced into T cells and binds to tumor cells in an human leukocyte antigen (HLA)-unrestricted process.[22]

The success of CAR-T cellular therapies in blood cancers has sparked interest in studying their efficacy and safety in solid cancers like lung cancer. Several tumor-associated antigens have been identified in lung cancer, some of which are under investigation for use in CAR-T cell therapy. A suitable target antigen is ubiquitously expressed on cancer tissue with little to no expression in normal cells. Carcinoembryonic antigen (CEA), mucin 1 (MUC1), epidermal growth factor (EGFR), human epidermal growth factor receptor 2 (HER2), mesothelin, ROR1, DLL3, programmed death ligand 1 (PD-L1), and CD80/86 are examples of target antigens.[27]

CEA is preferentially expressed in lung cancer, with increased expression associated with metastases and worse cancer outcomes.[22] Approximately 70% of NSCLCs have overexpression of CEA.[28] Ongoing trials evaluating CEA-targeted CAR-T therapy in lung cancer and other CEA-positive solid tumors (see Table 2). A phase I study investigating the use of CEACAM5+-specific CAR-T cells was closed prematurely due to transient acute respiratory toxicity and the absence of prolonged CAR-T cell persistence. The acute respiratory failure event was deemed an off-target toxicity and linked to the expression of CEACAM5 on normal lung epithelial cells.[29]

Additionally, EGFR has been investigated as a target in NSCLC using CAR-T therapy. EGFR is found in normal epithelial cells and overexpressed or mutated in several malignancies.[23,27] The expression of EGFR in normal cells presents the concern for off-tissue, on-target side effects. EGFR-directed CAR-T cells engineered to express the CXCR5 receptor have been developed to reduce on-target toxicity and are under investigation (NCT04153799, NCT05060796). There are significant opportunities to develop ACT strategies that can treat genomic subsets of NSCLC by targeting associated tumor antigens whose expression is promoted by a specific driver mutation such as KRAS. Additional tumor antigens under investigation in CAR-T therapy include MSLN, MUC1, HER2, GPC3, and ROR1 (see Table 2).

DLL3 CAR-T therapy

DLL3 targeting CAR-T cell therapies are being developed for patients with SCLC. AMG-119 is a DLL3-directed CAR-T therapy which is engineered by the transduction of a self-inactivating

Table 2. Ongoing trials investigating CAR-T cell therapy in lung cancer.

Target antigen	Trial identifier	Phase	Autologous/ allogeneic?	Cancers tested	Primary outcome	Status
CEA	NCT06010862	I	Autologous	Gastric, colon, pancreas, esophagus, cholangiocarcinoma, lung, breast cancers	Incidence of adverse events, MTD	Recruiting
	NCT06126406	I	Autologous	Gastric, colon, rectal, breast, esophagus, cholangiocarcinoma, pancreas, and lung cancer	TEAE, recommended treatment dose	Recruiting
	NCT06006390	I	Autologous	Gastric, colon, rectal, breast, esophagus, cholangiocarcinoma, pancreas, and lung cancer	TEAE, DLT	Recruiting
	NCT06043466	I	Autologous	Colorectal, esophagus, gastric, pancreas, breast, bile duct, NSCLC	TEAE, DLT	Recruiting
MUC1C	NCT05239143	I	Allogeneic	HNSCC, nasopharyngeal, RCC, breast, ovarian, gastric, pancreatic, colorectal, NSCLC	DLT, TEAE, ORR	Recruiting
GPCR3/ Mesothelin/ Claudin 18.2/ B7-H3/GUCY2C/ PSCA/PSMA/ MUC1/TGFB/ HER2/Lewis-Y/ AXL/EGFR	NCT03198052	I	Autologous	Lung cancer	DLT	Recruiting
GPC3 and/or GPC3/TGFB	NCT03198546	I	Autologous	HCC, SCLC	DLT	Recruiting
GPC3 (BOXR1030)	NCT05120271	I/II	Autologous	HCC, SCC of the lung, Merkel cell carcinoma, Myxoid/round cell liposarcoma	DLT, MTD, RP2D	Recruiting
EGFR/B7H3	NCT05341492	I	Autologous	Lung and TNBC	TEAE	Recruiting
EGFR (CXCR5 modified)	NCT05060796	I	Autologous	NSCLC	TEAE	Recruiting
ROR1 (LYL797)	NCT05274451	I	Autologous	NSCLC/TNBC	DLTs, TEAE	Recruiting
Mesothelin	NCT02414269	I/II	Autologous	Malignant pleural disease, mesothelioma, breast and lung cancer	TEAE, clinical benefit rate	Not recruiting
DLL3 (LB21202)	NCT05680922	I	Autologous	SCLC	Safety/MTD	Recruiting

CAR-T, chimeric antigen; CEA, carcinoembryonic antigen; DLL3, delta-like ligand 3; DLT, dose-limiting toxicities; EGFR, epidermal growth factor receptor; GPC3, glypican-3; HCC, hepatocellular cancer; HNSCC, Head and neck squamous cell cancer; MTD, maximum-tolerated dose; MUC1, mucin-1; NSCLC, nonsmall cell lung cancer; ORR, objective response rate; PSCA, prostate-specific cancer antigen; RCC, renal cell cancer; RDE, recommended dose for expansion; RP2D, recommended phase II dose; SCC, squamous cell cancer; SCLC, small cell lung cancer; TEAE, treatment emergent adverse events; TGFB, transforming growth factor beta; TNBC, triple negative breast cancer.

lentiviral vector into autologous T cells. AMG-119 consists of an anti-DLL3-binding domain, two costimulatory domains—CD28 and 4-1BB—and a CD3 domain.[5] Antitumor activity was seen in SCLC patient xenograft models in response to AMG-119 in preclinical studies.[5,30,31]

Limitations of CAR-T therapy in lung cancer and future perspectives

There remain several limitations to the development and utilization of CAR-T ACT in lung cancer. The activation of CAR-T cells and associated cytokine release in vivo leads to the most concerning CAR-T-related toxicities including CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS is characterized by fever, tachycardia, dyspnea, and peaks in the first week following CAR-T cell therapy, while ICANS manifests as tremor, seizures, or encephalopathy and peaks in the second week.[32] Another significant issue with the utilization of CAR-T cell therapy in solid malignancies is T cell exhaustion and decreased infiltration of T cell in the TME.[33] Solid malignancies can produce chemokines such as CXCL5 which stimulate T regulatory cells and in turn suppresses tumor-associated effector T cells.[33,34] Tumor antigen heterogeneity is another issue as certain antigens in solid malignancies are also expressed on normal tissue and CAR-T directed at such antigens can lead to so-called "on-target/off-tumor toxicity."[33,35] On-target/off-tumor toxicity is a major issue and emphasizes the need to choose a suitable target when designing CAR-T cells. The HLA-independent antigen binding of CAR-T cells limits its antigen recognition to only surface antigens. Tumor evolution causes cancer cells to lose their antigen expression, which can cause CAR-T cells to lose their activity.[26,36]

These limitations remain areas of active research, and different strategies to mitigate them are in development. The issue of antigen escape and loss might be addressed by utilizing CARs that are multispecific, targeting several tumor antigens.[36,37] For example, a CAR product that binds to multiple targets including but not limited to GPCR3, Mesothelin, Claudin 18.2, B7-H3, TGFβ, HER2, and EGFR is the subject of an ongoing trial (NCT03198052). Additionally, fourth-generation CARs, also called TRUCKs, modulate the TME by releasing cytokines and augmenting the immunosuppressive environment.[26]

TCR therapy

TCR therapy is another novel ACT with a similar manufacturing process as CAR-T cell therapy. TCR therapy first entails isolating patient T cells from peripheral blood. The cells are then genetically modified in vitro via TCR engineering to express a tumor antigen-targeting TCR.[22,38] TCRs have enhanced antigen binding and recognize oncogenic peptides presented on the tumor cell or antigen-presenting cell using HLA class I.[22] Following the binding of the TCR to an MHC molecule, a cascade of intracellular protein activation occurs. Compared to their CAR-T cell counterpart, TCRs have a wide spectrum of activity as they can also identify intracellular tumor antigens. In solid cancers, TCR therapy appears to be more suitable than CAR-T.[22]

Different antigens have been investigated in the development of TCRs for solid tumors (see Table 3). Cancer testis antigens (CTA), which are typically upregulated in embryogenesis and remain present in adult testes, are examples of explored antigens. These antigens are abnormally expressed in several solid tumors.[7] New York esophageal squamous carcinoma 1 (NY-ESO-1) is a CTA expressed in different cancers including lung cancer and was explored as a target for TCR therapy in lung cancer patients.[7] Letetresgene autoleucel, NY-ESO-1 TCR-transduced T-cell therapy, has been investigated in lung cancer and was found to be safe in lung cancer patients (NCT02588612). There are other clinical trials evaluating NY-ESO-1 TCR-adoptive cellular therapy alone or in combination with ICIs (NCT03709706, NCT03029273). Kita-Kyushu lung cancer antigen 1 (KK-LC-1) is an antigen that has been found and expressed in high levels of adenocarcinoma of the lung compared to squamous cell NSCLC.[39] Clinical trials using KK-LC-1 targeting TCR-therapy are ongoing (NCT05483491, NCT05035407).

IMA203 is a TCR-engineered T-cell therapy that targets an HLA-A*02:01-antigen derivative of preferentially expressed antigen in melanoma (PRAME). PRAME is a ubiquitously expressed tumor antigen found in several types of tumors including melanoma, breast, endometrial, ovarian, and lung cancer.[40] IMA203 is currently being investigated in a phase I clinical study (NCT03686124) in patients with solid tumors including NSCLC. A confirmed ORR of 67% (six out of nine) across multiple tumor types was reported at the 3-month mark in preliminary data

Table 3. Representative active trials in TCR-T therapies in lung cancer.

Clinical trial identifier	Trial title	Phase/ status	Target antigen	Combination therapies?	Primary outcome
NCT03412877	A phase II study using the administration of autologous T-cells genetically engineered to express TCRs reactive against neoantigens in patients with metastatic cancer	II/recruiting	Yes	Pembrolizumab	Response rate
NCT05483491	TCR gene therapy targeting KK-LC-1 for gastric, breast, cervical, lung, and other KK-LC-1 positive cancers	I	KK-LC-1	Aldesleukin	DLT, MTD
NCT05035407	A phase I trial of TCR gene therapy targeting KK-LC-1 for gastric, breast, cervical, lung, and other KK-LC-1 positive epithelial cancers	I	KK-LC-1	Aldesleukin Fludarabine Cyclosphophamide	DLT, MTD
NCT05296564	A phase I/II dose escalation, safety, and efficacy study of anti-NY-ESO-1 TCR-gene engineered lymphocytes given by infusion to patients with NY-ESO-1-expressing metastatic cancers	I/II	NY-ESO-1	Fludarabine Cyclophosphamide Aldesleukin	AE, objective tumor regression
NCT02869217	Phase Ib study of TBI-1301 (NY-ESO-1 specific TCR gene transduced autologous T lymphocytes) in patients with solid tumors	I	NY-ESO-1	Fludarabine Cyclophosphamide	AE, R2PD
NCT01967823	Phase II study of metastatic cancer that expresses NY-ESO-1 using lymphodepleting conditioning followed by infusion of anti-NY ESO-1 murine TCR-gene engineered lymphocytes	II	NY-ESO-1	Fludarabine Cyclophosphamide Aldesleukin	Percentage of participants with a response
NCT06043713	Phase I study of autologous CD8+ and CD4+ transgenic T cells expressing high affinity KRASG12V mutation-specific TCRs in participants with metastatic pancreatic, colorectal, and NSCLCs with KRASG12V mutations	I	KRASG12V	Bendamustine Fludarabine Cyclophosphamide	AE
NCT04262466	Phase I/II study of IMC-F106C in advance PRAME-positive cancers	I/II	PRAME/ HLA-A2	Pembrolizumab Monoclonal antibodies Tebentafusp Bevacizumab	DLT, best overall response

AE, adverse event; DLT, dose-limiting toxicity; HLA-A2, human leukocyte antigen-A2; KK-LC-1, Kita-Kyushu lung cancer antigen-1; MTD, maximum-tolerated dose; NY-ESO-1, New York esophageal squamous cell carcinoma 1; PRAME, preferentially expressed antigen in melanoma; RP2D, recommended phase II dose; TCR-T, T cell receptor therapy.

presented in 2023 with a reasonable safety profile, demonstrating promise for patients with PRAME-positive cancers.[40] The challenges associated with TCR-therapy include on-target and off-target tumor effects which belabors the importance of choosing an ideal target antigen. Another big drawback of TCR T-cell therapy is the limitation of MHC compatibility and the potential for increasing disparities in the treatment of lung cancer. As an example, one common HLA allele HLA-A*2:01 which is present in almost half of Caucasians but found in only 34.6% of African and 36% of Asian populations.[41] The MHC-dependent nature of this adoptive therapy is also limited by the fact that certain tumors can evade the immune system by downregulating MHC and affecting antigen presentation.[6]

NK cell therapy in lung cancer

NK cells are key components of the innate immune system that play a role in antitumor immunity. NK cells lack TCRs and mediate cell killing in an HLA-independent manner. The cytotoxicity and antitumor effects of NK cells occur in different ways including antibody-dependent cellular cytotoxicity.[42] Different strategies employing NK cells are currently under exploration, including cytokines, small molecules, and autologous or allogeneic genetically engineered NK cells. NK cells are obtained through apheresis of peripheral blood and are then expanded and in some cases engineered ex vivo.[43,44] In the treatment of hematologic malignancies, NK-cell-based immunotherapy appears to be promising. In solid tumors like lung cancer, however, several barriers exist to the incorporation on NK-cell-based ACT to the treatment paradigm. The suppressive TME and reduced trafficking of NK cells into lung cancer tissue are examples of such challenges. Strategies to reinvigorate NK-cells after exhaustion in NSCLC including the combination of autologous or allogeneic NK cells to checkpoint inhibitors such as PD-(L)1 antibodies and are currently being explored (NCT05334329, NCT03987867, NCT02843204).[45–47] In a study involving 109 previously treated advanced NSCLC patients, the combination of pembrolizumab and allogeneic NK cells resulted in improved survival compared to patients who received only pembrolizumab. The study showed a median OS of 15.5 versus 13.3 months ($p < 0.05$) and median PFS of 6.5 versus 4.3 months ($p < 0.05$).[47] Another strategy utilizing NK cells in lung cancer therapy is through in vitro expansion of human NK cells and increasing the expression of CXCR3. Enhancing CXCR3 expression in NK cells leads to improved NK-cell infiltration into lung cancer TME.[45] Additionally, NK cells can be transduced with CARs and/or engineered with IL-15 to improve their persistence in the TME. For example, the DLL-3 CAR NK-92 cells have shown efficacy and safety in early studies.[48] Regarding safety, studies show that patients can receive high doses of NK-cell infusion with no major adverse events.[46,49,50] At this time, it remains unclear which strategy will be most successful for the incorporation of NK cells into the treatment of lung cancer.

mRNA vaccines

Conventional protein and peptide-based cancer vaccines have several limitations, including their poor immunogenicity and the lack of personalization associated with their construct.[51] There is also the challenge of adaptability and the absence of rapid effect to match the speedy growth of cancer cells. As a result, therapeutic cancer vaccines have not been integrated into clinical practice and have not advanced at a similar pace as other immunotherapies.[51]

However, the widespread popularity of mRNA vaccines in the recent COVID-19 pandemic has raised interest in the development of mRNA cancer vaccines. When administered, mRNA vaccines are encoded into neoantigen proteins in antigen-presenting cells like dendritic cells.[51–53] Following the expression of the neoantigens, dendritic cells are activated and travel to the lymph nodes leading to antitumor immunity.[54] When mRNA vaccines get into antigen-presenting cells, they are encoded into a wide range of full-length antigens which are then presented on both class I and II HLA. This makes the activity of these mRNA vaccines less limited to specific HLA types. Thus, mRNA vaccines create the possibility of developing HLA-independent personalized vaccines on a large scale in a timely manner.[51] Compared to other nucleotide-based vaccines such as DNA vaccines, mRNA vaccines carry no risk for insertional mutagenesis.[55] Certain mRNA vaccines also have the advantage of being able to deliver multiple tumor-associated antigens.[56] The instability of mRNA vaccines due to the rapid degradation of naked mRNAs mediated by RNAses was an early recognized limitation to their application.[57] Current research efforts are

Table 4. Completed or ongoing mRNA vaccines in lung cancer.

Trial name/NCT	mRNA vaccine name	Target antigens	Combination therapy	Phase/ sample size	Setting	Primary endpoints
KEYNOTE-603/ NCT03313778	mRNA-4157/ V940	Individualized neoantigens up to 34	Pembrolizumab SOC chemotherapy	I/242	Adjuvant	AEs
INTerpath-202/ NCT06077760	mRNA-4157/ V940	Individualized neoantigens up to 34	Pembrolizumab	III/848	Adjuvant	DFS
NCT03948763	mRNA-5671/ V941	Tetravalent vaccine against KRASG12D, G12V, G13D, or G12C	Pembrolizumab	I/100	Metastatic	DLT/AEs
LuCa-MERIT-1/ NCT05142189	BNT116	Six tumor associated antigens	Cemiplimab Docetaxel Carboplatin Paclitaxel	I/130	3L metastatic	DLT/AEs
EMPOWERVAX/ NCT05557591	BNT116	Six tumor associated-antigens	Cemiplimab	II/100	1L metastatic	ORR
NCT03164772	BI361849/ CV9202	Six tumor associated-antigens	Durvalumab Tremelimumab	I/II, 61	Metastatic	AEs
NCT05533697	mRNA-4359-P101	PD-L1/IDO1	Pembrolizumab	I/II, 194	Metastatic	DLT/AE

AE, adverse event; DFS, disease-free survival; DLT, dose-limiting toxicity; ORR, objective response rate; PD-L1, programmed death ligand 1.

geared at optimizing the delivery systems of these vaccines through nanoparticles or antigen-presenting cells.

The first randomized trial of a personalized mRNA vaccine that showed relapse-free benefit in patients with solid cancer is the KEYNOTE-942 trial with mRNA-4157 for melanoma patients in the adjuvant setting (NCT03897881).[58] A relapse-free survival rate of 78.6% at 18 months was reported in patients who received pembrolizumab with mRNA-4157, compared to 62.2% in the pembrolizumab only group.[59] The vaccine is under investigation in the ongoing trial KEYNOTE-603 in the adjuvant setting for resected NSCLC (NCT03313778). The most reported side effects of the vaccine include pyrexia, influenza-like illness, and injection-site pain.[60] mRNA vaccines have also shown promise in poorly immunogenic cancers like pancreatic ductal adenocarcinoma (PDAC). A phase I study investigating the mRNA vaccine autogene cevumeran, derived from surgically resected PDAC tumors, with anti-PD-L1 immunotherapy followed by chemotherapy. Interim results from the study showed that at the 18-month median follow-up, vaccine responders had a longer median progression-free survival (PFS) than the vaccine nonresponders (not reached vs 13.4 months, $p = 0.003$).[60]

With the promising data of mRNA vaccines in other solid tumors, this modality holds a lot of potential in the management of lung cancer. The selection of tumor-associated antigens and neoantigens as well as the appropriate patient phenotype influence the effectiveness of mRNA vaccines in lung cancer. The best clinical setting to use mRNA vaccine is currently being explored.[61] In the adjuvant setting, the goal is for individualized vaccines to be manufactured from resected tumor tissue and given to control any residual disease foci. Refinement of the construct and optimizing the manufacturing of these vaccines is still needed. Table 4 includes some ongoing clinical trials studying mRNA vaccines in lung cancer.

Bispecific T-cell engagers

BiTEs are small molecules with different antigenic targets made of two fused scFVs without a fragment crystallizable (Fc) region.[62] They are designed to simultaneously bind to the invariant

part of the CD3 complex on T cells and a tumor-associated antigen. Following the binding of the BiTE, the T-cell is brought spatially close to tumor cells creating an immune synapse.[22] This in turn leads to the activation and proliferation of T cells, culminating in tumor cell lysis via cytotoxic granzymes. It is well described that SCLC evades host immunity by downregulating MHC I expression and subsequent antigen presentation failure.[4] Thus, the unique MHC-I-independent T-cell activation of BiTEs makes it advantageous. In addition, BiTEs induce T-cell mediated activation at low concentrations.[63] The first BiTE molecule approved in oncology was blinatumomab for the management of relapsed or refractory, Ph-negative B-cell acute lymphoblastic leukemia (B-ALL) in 2014 and Ph-positive B-ALL in 2017.[64,65] The improved outcomes seen with the use of BiTEs in hematological cancers have spurred interest in developing BiTEs for the treatment of solid tumors. Tebentafusp-tebn, a bispecific gp100 peptide-HLA-directed CD3 T cell engager, was approved for uveal melanoma in 2022.[66] Some of the tumor-associated antigens that are currently under exploration in the development of BiTEs in lung cancer include DLL3, EpCAM, and CEA.

DLL3-directed BiTEs

DLL3 is a protein that has been identified as an inhibitor of the Notch signaling pathway. The Notch pathway regulates several oncogenic processes including cancer cell growth, neuroendocrine differentiation, and chemoresistance.[5] The overexpression of DLL3 has been associated with increased cell proliferation, migration, invasiveness, and the development of resistance to platinum-based chemotherapy.[5,67,68] Studies have shown that up to 85% of SCLC tumors express DLL3 protein on the cell surface, and expression is independent of patient age, sex, tumor stage, performance status, and prior therapies.[69]

DLL3 is also found in other neuroendocrine tumors and its overexpression is generally associated with poor disease outcomes.[5,70] The low to absent expression of DLL3 on normal cells contrasted with the high cell surface expression on tumor cells makes it a suitable therapeutic target. As a result, different therapeutic approaches using the DLL3 notch pathway are currently being explored in SCLC and other neuroendocrine tumors with high DLL3 expression.[5]

Tarlatamab (AMG-757). Tarlatamab is a BiTE made of two scFvs with DLL3- and CD3-targeting domains, with an extended half-life in the serum.[5] The short half-life of many BiTEs has been an issue in the past with agents such as blinatumomab requiring a continuous infusion. To extend its half-life, Tartalamab's two scFVb are connected by a linker containing a stable Fc domain.[5] With its dual affinity and simultaneous binding to CD3 and DLL3, tumor cells form an immunological synapse with T cells resulting in T cell activation and proliferation. This is usually followed by the release of cytolytic, pore-forming enzymes which induce tumor cell death.[5,71,72] By causing T cell proliferation in the tumor environment, there is an increase in the overall T-cell mediated antitumor effect.[5]

Preclinically, tarlatamab was found to cause significant antitumor effect and regression in biological models of SCLC. In patient-derived xenograft models, tarlatamab caused CD4+ and CD8+ T cell infiltration and T cell activation, with the release of inflammatory cytokines and cytotoxic granules.[73] Clinically, tarlatamab has demonstrated promising results. In the phase I study DeLLPhi-300 (NCT03319940), 107 patients with relapsed or refractory SCLC following at least one prior line of therapy were enrolled. An objective response rate of 23.4% (95% confidence interval (CI), 15.7–32.5) was seen with a complete response in two patients. The median PFS and overall survival (OS) were 3.7 months (95% CI, 2.1–5.4) and 13.2 months (95% CI, 10.5%–not estimable), respectively, with a median duration of response of 12.3 months (95% CI, 6.6–14.9).[74] In the first in human study, grade $\geqslant$3 treatment adverse events (TRAE) occurred in 30.8% of patients. TRAEs leading to treatment discontinuation in the phase I study were pneumonitis, ICANS, and encephalopathy. The most-frequent TRAE was CRS, seen in 56 out of 107 patients (52%), with grade 3 seen only in one patient.[74] The phase II study DeLLPHi-301 (NCT 05060016) studied tarlatamab at two dose levels, 10 versus 100 mg, intravenously every 2 weeks. Results showed an ORR of 40% in 10 mg group and 32% in 100 mg group. However, the median PFS was 4.9 months (95% CI, 2.9–6.7) in the 10 mg group, compared with 3.9 months (95% CI, 2.6–4.4) in the 100 mg group. High grade CRS was only seen in 1% of the patients (1 out of 133) in the 10 mg group and 6% of those (5 out 87) in the 100 mg group. ICANS occurred in 8% (11 patients) in the

Table 5. Selected ongoing trials of T-cell engagers in lung cancer with drug targets.

Drug name	Target	Clinical trials	Phase	Status	Sponsor	Summary	Study primary endpoints
Tarlatamab	DLL3/CD3	DeLLphi-300 (NCT03319940)	I	Ongoing	Amgen	Safety and tolerability of tarlatamab monotherapy and in combination with anti-PD1 therapy	Number of DLTs
		DeLLphi-301 (NCT05060016)	II	Ongoing, not recruiting	Amgen	Efficacy, safety, and tolerability of tarlatamab in r/r SCLC after 2 or more prior lines of treatment	ORR by BICR
		DeLLphi-302 (NCT04885998)	IB	Ongoing, not recruiting	Amgen	Safety and efficacy of combining AMG-757 and AMG-404	Number of DLTs/AEs
		DeLLphi-303 (NCT05361395)	IB	Ongoing	Amgen	First-line Tarlatamab in combination with carboplatin, etoposide, and PD-L1 inhibitor in SCLC patients	Number of DLTs/AEs
		DeLLphi-304 (NCT05740566)	III	Ongoing, not recruiting	Amgen	Tarlatamab vs SOC in patients with relapsed SCLC after platinum-based first-line chemotherapy	OS
		DeLLphi-305 (NCT06211036)	III	Ongoing, recruiting	Amgen	Tarlatamab in combination with Durvalumab vs Durvalumab alone in patients with E-SCLC after platinum, etoposide, and durvalumab	OS
		DeLLphi-306 (NCT06117774)	III	Ongoing	Amgen	Multicenter study of Tarlatamab vs placebo in subjects with limited SCLC after concurrent chemoradiation therapy	PFS
BI764532	DLL3/CD3	NCT04429087	I	Ongoing, recruiting	Boehringer Ingelheim	Testing different doses of BI 764532 in patients with SCLC and other neuroendocrine tumors	MTD

(Continued)

Table 5. (Continued)

Drug name	Target	Clinical trials	Phase	Status	Sponsor	Summary	Study primary endpoints
		NCT05882058	II	Ongoing, recruiting	Boehringer Ingelheim	Dose selection trial for BI 764532 In relapsed refractory SCLC	OR
		NCT05879978	I	Ongoing, recruiting	Boehringer Ingelheim	Dose escalation trial for BI 764532 combined with Ezabenlimab in patients with SCLC and other neuroendocrine DLL3+ tumors	DLTs/MTD
HPN328	DLL3 Trispecific T cell engager	NCT04471727	I/II	Ongoing, recruiting	Harpoon Therapeutics	Safety/tolerability of HPN328 monotherapy vs HPN328 with atezolizumab or ifinatamab-deruxtecan in SCLC and NEC	AE/DLT
QLS31904	DLL3/CD3	NCT05461287	I	Ongoing, recruiting	Qilu Pharmaceutical	Safety, tolerability/PK of QLS31904 in SCLC	DLT/MTD
TAK-186	EGFR × CD3 COBRA	NCT04844073	I/II	Ongoing, recruiting	Takeda	Dose-escalation study of TAK186 in unresectable locally advanced or metastatic solid cancers including NSCLC	TEAEs/CRS
TAK-280	B7H3 X CD3 COBRA	NCT05220098	I/II	Ongoing, recruiting	Takeda	Dose-escalation study of TAK 280 in unresectable locally advanced or metastatic solid cancers including NSCLC	DLTs/ TEAEs
R06958688	CD3/CEA	NCT0337698	I/II	Ongoing, not recruiting	Hoffman-La Roche	Multiple immunotherapy-based treatment combinations in participants with metastatic NSCLC (Morpheus-NSCLC) (Morpheus Lung)	OR

AEs, adverse events; BICR, blind independent committee review; COBRA, conditionally bispecific redirected activation; CRS, cytokine release syndrome; DLL3, delta like ligand; DLT, dose-limiting toxicity; E-SCLC, extensive stage small cell lung cancer; MTD, maximum tolerated dose; NEC, neuroendocrine cancer; NSCLC, nonsmall cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; TEAEs, treatment-emergent adverse events.

10-mg and 28% (24 patients) in the 100 mg group.[75] Based on these data from the DeLLphi-301 study, the FDA granted accelerated approval to tarlatamab at the 10 mg dose.

Following the success of preclinical and clinical studies in previously treated SCLC, there are several ongoing trials (see Table 5) evaluating tarlatamab in the front-line setting. There are also trials assessing the efficacy of tarlatamab in combination with ICIs. The phase III DeLLphi 304 study is ongoing and aims to assess the efficacy of tarlatamab compared to standard-of-care treatment following first-line chemoimmunotherapy (Clinical trials.gov queried on August 3, NCT05740566). Another clinical trial, DeLLphi 303 is currently investigating a quadruplet regimen including tarlatamab, carboplatin-etoposide, and a PD-L1 inhibitor in the first-line setting (NCT05361395). The DeLLphi-305 study aims to compare tarlatamab and durvalumab versus durvalumab alone in extensive-stage SCLC patients who received induction chemoimmunotherapy (NCT06211036).

BI 764532, QLS31904, and HPN 328. BI 764532 is another DLL3/CD3 BiTE that showed antitumor effect in preclinical studies using Xenograft and DLL3+ models. In the interim analysis of the first-in-human dose escalation trial (NCT04429087), among SCLC patients who got the target dose ($n=24$) the ORR was 33%. CRS of any grade occurred in 58% of patients, with grade 3 or higher CRS only occurring in 2% of patients.[76]

QLS31904 is a DLL3/CD3 BiTE that is currently being studied in an ongoing trial (NCT05461287).

HPN328 is a DLL3 tri-specific T-cell activating construct and has a smaller molecular weight than other TCEs. It has a half-life between 2.7 and 3.5 days in preclinical models. In a phase I study, HPN328 resulted in a response rate of 33% of nine enrolled SCLC patients. HPN328 is also being studied in other neuroendocrine cancers.[5,77]

Overview of major adverse effects associated with BiTEs

The main adverse events associated with this type of therapy are similar to those in CAR-T therapy and include CRS and ICANS. These adverse events correlate with dose intensity occurring with initial dose and after a dose increase. CRS manifests as fever, hypotension, tachycardia, and hypoxia and has potentially life-threatening complications such as cardiac dysfunction, renal and/or hepatic failure, and disseminated intravascular coagulation. Management may include infectious work up, the anti-IL6R antibody-tocilizumab, and/or steroids. ICANS is usually preceded by CRS and is characterized by impaired motor skills, aphasia, confusion, and word-finding difficulties. The mainstay treatment of ICANS is corticosteroids and nonsedating antiepileptic agents.[78]

Discussion

ACT and other novel strategies improving the antitumor activity of the immune system are gradually gaining inroads into the treatment of many solid tumors. Several preclinical and early studies have shown the anti-tumor efficacy of ACTs in lung cancer. It appears that some of these therapies (CAR-T and TCR-T) are effective even in immunogenically "cold" tumors where ICIs have proven to be less effective. This may be because engineered cell therapies allow unique antigens to be targeted in these "cold" tumors.

Every type of ACT has its drawbacks. The need for leukapheresis, ex vivo culturing, lymphodepletion using chemotherapy, and the requirement for hospitalization are challenges to incorporating ACTs on a larger scale. The financial and time toxicity in manufacturing ACT products are considerable. The average turnaround time of 4–6 weeks for the production of ACT products can be an issue in patients with advanced disease where urgent treatment options are needed. The associated risk of immunologic toxicity manifested as CRS and ICANS and the management of these remain a challenge. Improvements in the selection of antigens, as well as the development of the constructs of these therapies, will be important in reducing off-tumor, and on-target toxicities and enhancing their efficacy. Other challenges including tumor heterogeneity, TME suppression, and the development of antigen escape variants can impact the clinical efficacy of ACTs. These may be overcome by combining ACT with other types of immunotherapies like checkpoint inhibitors. For example, BiTEs and mRNA vaccines are not considered ACTs, they can be complementary modalities. Combinatorial strategies involving ACT such as CAR-T and TCR therapy with mRNA vaccines may have a synergistic effect, particularly for larger and more extensive tumors. Other combinatorial approaches such as

BiTE expressing CAR-T cells (so called CART. BiTE cells) integrate multiple immune functions and may improve the antitumor activity of ACT. Several questions likely to be the focus of future research include understanding the sequencing of these therapies, leveraging combined modalities of ACTs to optimize treatment response, as well as mitigating the associated side effects, and decreasing production time and cost. However, tarlatamab is now being used in the clinic, and several clinical trials described above have shown signals of efficacy in both NSCLC and SCLC. ACT is increasingly becoming a reality in clinical practice and will hopefully continue to improve durable outcomes for patients with lung cancer.

Conclusion

Adoptive cellular therapy is a treatment modality gaining inroads gradually into the treatment of solid malignancies. Several clinical trials investigating the role of ACT in the treatment of lung cancer are ongoing with some showing promise. The combination of ACT with other treatment types like checkpoint inhibitors may enhance antitumor effect of ACT.

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Author contributions

Faith Abodunrin: Investigation; Writing – original draft.

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Availability of data and materials

Research articles selected for this review were obtained from scientific journals and congress abstracts and presentations, including American Society of Oncology (ASCO), ESMO, World Conference on Lung Cancer, and Society for Immunotherapy of Cancer.

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