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Targeted T-cell Immunotherapies for Lung Cancer: Mechanisms, Clinical Applications, and Future Directions

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Abstract. As lung cancer remains one of the most prevalent causes of cancer-related fatalities globally, there continues to be a critical and urgent demand for treatments beyond the current standard of care. This review discusses the current and emerging targeted T-cell immunotherapies for treating lung cancer, as well as how lung tumors cause the development of T cell exhaustion and the corresponding immunotherapies that target these mechanisms. There are currently four major categories of immunotherapies directed toward the activation of T cells: immune checkpoint inhibitors (ICIs), adoptive cell therapies (ACT), bispecific T Cell Engagers (BiTEs), and cancer vaccines. Available clinical trial data are presented for each type of immunotherapy, particularly the clinical trial data for ICIs, demonstrating that these treatments provide an increased survival advantage for patients treated for both Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). Remaining clinical challenges include primary or acquired resistance to the immunotherapy, the incidence of immune-related adverse events (irAEs), and the identification of improved predictive biomarkers. Future immunotherapeutic approaches to lung cancer will rely on the use of combination therapy based on sound molecular rationale, the use of personalized neoantigen-based vaccination, the design of next-generation engineered cellular products, and the enhancement of biomarker development to improve therapeutic efficacy and maximize the usage of these innovative therapies.

Keywords: T-cell immunotherapy, Lung cancer, Immune checkpoint inhibitors, Adoptive cell therapy, Immune evasion

1. Introduction

Lung cancer is a worldwide health issue, while there are limited treatment options for advanced-stage disease, presenting a challenge to the healthcare system. Immunotherapy has revolutionized oncology in the past decade by using the immune system to help eliminate cancer cells. One of the key areas in immunotherapy for lung cancer is T lymphocytes. T lymphocytes are critical to the adaptive immune response and play a major role in fighting tumors. However, their function can be impaired by immune checkpoints like programmed death-ligand 1 (PD-L1) and Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4), which tumors use to create an environment that

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pushes T cells into exhaustion. Understanding and targeting these pathways has reshaped lung cancer treatment and brought new hope to many patients. The importance of this field was underscored by the 2025 Nobel Prize in Physiology or Medicine, which recognized breakthroughs in understanding how regulatory T cells (Tregs) and peripheral immune tolerance shape T-cell-based cancer immunotherapies.

Despite all the advancements made, a good number of patients do not respond appropriately or eventually build up resistance against certain immunotherapies. Moreover, other variables have an influence on how successful T-cell targeting therapy becomes due to the variety of interactions that occur with the tumor and the microenvironment. Different types of lung cancer use various approaches to prevent the immune system from killing them by using combination approaches: either through expression of additional inhibitory checkpoint molecules, recruiting immunosuppressive cells into the tumor environment, or creating a hostile tumor microenvironment (TME) for the function of activated T cells to thrive.

Thus, understanding how tumors escape the immune system is key to improving future treatments. This comprehensive review summarizes the current findings of how lung cancer uses immuno-evasive strategies, a description of different categories of therapeutic approaches that target T cells, including immune checkpoint inhibitors (ICIs), adoptive cell therapies (ACTs), and bispecific T-cell engagers (BiTEs), as well as clinical outcomes from using these methods. In addition to discussing clinical outcomes, the review will also highlight unresolved issues related to both toxicity and resistance, as well as outlining possible directions for future research that could maximally leverage the impact of these therapies on lung cancer patients.

2. Mechanisms of lung cancer development and immune evasion

2.1. Genetic changes and tumor microenvironment

Lung cancer progresses through a series of stages driven by an accumulation of genetic mutations. These changes lead to uncontrolled cell proliferation, the failure of standard cell death mechanisms, and eventually metastasis. Non-Small Cell Lung Cancer (NSCLC) is distinguished by the existence of genetic mutations in oncogenes such as EGFR, ALK, and tumor suppressor genes such as TP53 and STK11 [1]. Small Cell Lung Cancer (SCLC) typically involves bi-allelic dysfunction of TP53 and RB1 in almost all cases [2]. The accumulation of genomic alteration often leads to genomic instability and a high rate of Tumor Mutational Burden (TMB), particularly in cancers associated with smoking, providing a greater chance for the development of neoantigens, or new protein sequences that T cells may react against as foreign [3].

Cancer cells interact with the immune system through complex local ecosystems known as the TME. The TME comprises diverse elements including immune cells, structural cells (stromal cells), cancer cells, blood vessels, and other cellular components, all of which are closely interconnected both structurally and functionally. Given that the TME contributes significantly to determining how cancer will respond to treatment, understanding both the components and their functional state within a given patient's TME is critical for optimal patient care [1]. Lung cancer can generally be divided into three categories of immune-cell infiltration patterns. The first category is commonly referred to as immune-inflamed or “hot” tumors. Immune infiltration into these tumors is characterized by significant levels of T cell activity; therefore, they tend to express high levels of PD-L1 on the tumor cells, as well as a higher-than-average TMB, which allows these tumors to be more effectively treated with ICIs. In contrast, the second category is known as immune-desert or "cold" tumors, in which little T-cell infiltration exists and their TMB is typically resistant to

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checkpoint blockade. The final category is called immune-excluded tumors, in which T cells are present but found at the edge of the tumor and are unable to penetrate the center of the tumor due to physical or biochemical barriers.

2.2. Key mechanisms of immune evasion

To evade immune elimination, lung cancer utilizes a panoply of strategies that effectively shut down the cancer-immunity cycle. Lung cancer employs multiple immune evasion strategies, including inhibitory checkpoints, soluble suppressive mediators, and metabolic reprogramming (Table 1).

Table 1. Key immune evasion mechanisms in lung cancer

Mechanism	Pathways or Components	Functional Outcomes
Inhibitory Checkpoints	TIGIT, PD-1/PD-L1, LAG-3, CTLA-4	T-cell inhibition, anergy, and exhaustion
Soluble Mediators	TGF-β, adenosine, prostaglandin E2, IL-10	Creation of an immunosuppressive microenvironment
Cellular Components	Tregs, MDSCs, Tumor-associated macrophages	Directly suppress effector T cells
Antigen Presentation	Reduced expression of Major Histocompatibility Complex (MHC) molecules	Impair T-cell's capability to recognize tumor cells
Metablic Changes	Tryptophan degradation, depletion of arginine, lactate accumulation	Metabolically suppress T-cell function

A well-characterized immune-evasion mechanism in lung cancer involves the PD-L1 axis. PD-L1 is often observed to be upregulated on lung cancer cells, as well as on antigen-presenting cells in the TME. When PD-L1 binds with PD-1 on activated T cells, it delivers a strong inhibitory signal, which suppresses T-cell function, expansion, and cytokines release, and leading to exhaustion and apoptosis [4]. In addition to PD-1, tumors employ multiple different checkpoint inhibitors that inhibit T-cell activity. Among these, CTLA-4 competes with the co-stimulatory receptor CD28 on the surface of activated T cells for binding to CD80/CD86 on antigen-presenting cells, leading to the dysfunction of T lymphocytes upon initial interaction with their antigen [5]. In addition, other checkpoints, including TIGIT and LAG-3, all have an impact on T-cell inactivation and exhaustion in the TME [6].

Tumors actively recruit and expand Tregs, myeloid-derived suppressor cells (MDSCs) and M2 macrophages. These cells will secrete immunosuppressive cytokines that inhibit effector-T-cell function, but also contribute to a tolerogenic state [1]. Tumors can also downregulate elements of MHC so as to become "invisible" to T cells. The TME is often hostile in terms of metabolism, which can include things like nutrient depletion and waste accumulation, like lactate, which can inhibit T-cell metabolic fitness and effector functions [1].

3. Targeted T-cell immunotherapies for lung cancer

3.1. Immune checkpoint inhibitors

ICIs are the most established T-cell immunotherapy for lung cancer. These monoclonal antibodies block inhibitory receptors on the surface of T cells or their ligands on tumor and immune cells, effectively "releasing the brakes" on antitumor immunity.

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Several anti-PD-1 and anti-PD-L1 drugs, such as pembrolizumab, cemiplimab and durvalumab, are now approved and have shown clear overall-survival (OS) benefits in both first-line and later treatment settings. In the KEYNOTE-024 trial, pembrolizumab was set up as a first-line standard for metastatic NSCLC with PD-L1 expression over 50%, showing better survival than chemotherapy [7].

Ipilimumab, an anti-CTLA-4 therapy, is approved to treat metastatic NSCLC as first-line therapy in combination with nivolumab built upon CheckMate 227, which showed OS improvement in spite of PD-L1 status, with particular benefit in patients who have a high rate of TMB [8].

Next Generation Checkpoints including agents targeting LAG-3 (e.g., relatlimab), TIGIT (e.g., tiragolumab), and TIM-3 are currently being developed and studied with the intention of overcoming resistance to the first-generation ICIs [1].

3.2. Adoptive cell therapy

The process of ACT involves drawing immune cells from a patient, which may be genetically altered and multiplied in a lab setting, before being reinfused to the patient's body. Chimeric Antigen Receptor (CAR-T) Cells are T cells that undergo genetic modification to express synthetic receptors. These receptors recognize and connect with the antigens on the surface of tumors, independent of MHC presentation. Though highly efficacious with haematologic malignancies, their use in solid tumors such as lung cancer is hampered by hurdles such as the absence of a unique, ubiquitously expressed surface antigen, a suppressive TME, and poor trafficking [9]. Antigens being evaluated as targets in lung cancer include PD-L1, EGFR, GPC3, HER2, CEA, ROR1, MSLN and MUC-1 [1]. Therapeutic approach testing for improved efficacy include "armoured" CAR-T cells that secrete cytokines or are resistant to TGF-β, and bispecific CARs [1].

Tumor-Infiltrating Lymphocytes (TILs) is a personalized cancer treatment approach where T cells are extracted from a patient’s tumor. These specific T cells are grown and multiplied ex vivo before being infused back the patient’s body. Importantly, TILs are naturally enriched for T cells that detect tumor-specific antigens. This therapy has demonstrated encouraging results in early-stage clinical trials for NSCLC, particularly in individuals whose disease continued to progress despite treatment with PD-1 and PD-L1 inhibitors [10].

3.3. Bispecific T-cell engagers

BiTEs are antibodies that are engineered to bind both CD3 on T cells and a same tumor-associated antigens (TAA) on cancer cells at these two sites. This results in a synthetic immune synapse to redirect and activate any T cell in proximity to promote the killing of the tumor cell, irrespective of TCR specificity. An example relevant in lung cancer is Tarlatamab, a BiTE that targets the TAA DLL3 (which is expressed at high levels on SCLC) and CD3. Initial clinical data provided impressive response rates for Tarlatamab in pretreated SCLC patients [11]. Amivantamab, which is a bispecific antibody designed to target MET and EGFR, has been approved as a therapy for EGFR exon 20 insertion mutated NSCLC [12].

3.4. Cancer vaccines

Therapeutic cancer vaccines are created to provoke preceding T-cell responses against tumor specific antigens or prime them. Peptide and protein vaccines promote TAA (such as NY-ESO-1, MUC-1, MAGE-A3) delivery with an adjuvant. However, early vaccine trials MAGRIT (MAGE-

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A3) and START (Tecemotide) failed to meet primary objectives in unselected populations despite providing useful knowledge and insights [1]. Approval has been granted in select countries for the use of the CIMAvax-EGF vaccine, which works by targeting Epidermal Growth Factor (EGF), in the treatment of advanced NSCLC [13].

4. Clinical outcomes

4.1. Pivotal clinical trials

In the past few years, the number of clinical research evaluating T-cell immunotherapies in both NSCLC and SCLC has grown significantly. ICIs, especially those targeting the PD-1 and PD-L1 pathways, are now among the most frequently used therapies for advanced NSCLC [14].

The 5-year KEYNOTE-024 trial demonstrated that first-line pembrolizumab significantly increased the overall survival (OS) rate (31.9%) compared to chemotherapy (16.3%) for metastatic NSCLC patients with a PD-L1 level of 50% or more [15]. For patients with low or undetected level of PD-L1 expression, combination regimens are preferred. The CheckMate 9LA trial established that a short course of ipilimumab and nivolumab combined with two rounds of chemotherapy would significantly improve OS as compared to chemotherapy with an HR of death equal to 0.72 [16]. In unresectable, locally advanced NSCLC, the PACIFIC trial confirmed durable benefit with durvalumab consolidation after chemoradiotherapy. In particular, the 5-year OS rate was nearly 10 percentage points higher with durvalumab (42.9%) than with the placebo (33.4%) [17].

A recent ACT study demonstrated that utilizing TILs resulted in a 21.4% overall response rate among patients suffering from metastatic NSCLC. The study also revealed that several patients who had encountered disease deterioration on PD-1 inhibitors experienced benefit from TIL therapy, indicating the viability of personalized TIL therapy for these patients [10].

In SCLC, ICIs combined with platinum–etoposide chemotherapy provide modest survival gains, as shown in the CASPIAN and IMpower133 trials, though the benefit is less pronounced than in NSCLC [16,18]. Emerging therapies such as the DLL3-targeting BiTE tarlatamab also show promise, achieving a 40% response rate in heavily pretreated SCLC patients [11].

4.2. Efficacy assessment biomarkers

Clinical trials mainly assess efficacy through objective response rates, OS and progression-free survival. In NSCLC patients who experience positive response to anti-PD-1 treatment, studies show increases in circulating CD4+ and CD8+ T cells, along with higher levels of bioactive T-cell cytokines after treatment, while changes are generally not seen in non-responders [19].

There has been interest in biomarkers like the PD-L1 expression level, or TMB, in order to predict possible responses to anti-PD-1 and anti-PD-L1 treatments; however, this has varying rigor [20]. Other biomarkers such as mutations in MED12, which inhibit CD8+ T-cell cytotoxicity by regulating activity through the STAT1/TAP2 axis, provide new independent markers of response to ICIs [21]. Therefore, the body of clinical trial work has established efficacy for T-cell-based immunotherapies in lung cancer, while pointing to the need for improved patient stratification of ICI therapy using biomarkers, to improve efficacy and minimize toxicity.

4.3. Immune-related adverse events

Immune-related adverse events (irAEs) are characteristic toxicities of immune checkpoint therapies in lung cancer, commonly manifesting as pneumonitis, skin reactions, or endocrine dysfunction such

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as adrenal insufficiency and thyroiditis [22]. Prompt identification and control of severe immune-related adverse events (irAEs) is essential despite being infrequent occurrences. Some symptoms may appear months after starting treatment, therefore patients need to be watched closely.

The Common Terminology Criteria for Adverse Events (CTCAE) is utilized as a standardized tool for grading the severity and course of action for treatment of irAEs [22]. Corticosteroids are the main treatment modality for the management of irAEs, while infliximab, vedolizumab, and adalimumab are a few second-line treatments typically utilized for the treatment of irAEs that do not respond to steroid therapy, primarily gastroenterological irAEs [23]. Complex cases often warrant the collaboration of various medical specialties [22], and newer medications such as dupilumab are beginning to emerge in patients with crusted cutaneous irAEs who do not respond to traditional corticosteroid therapy [24].

The use of biomarkers to detect and predict irAEs in the early stages may prove beneficial, as suggested by the results from an analysis of serum cytokines and subsets of immune cells [19]. Additionally, management of these toxicities requires prompt identification, patient education, and a coordinated approach to immunotherapies with individualized immunosuppression therapy.

5. Obstacles and prospects

Despite progress, the delivery of T-cell immunotherapies to patients with lung cancer is far from optimal. The most important barriers that limit effective application of this treatment for lung cancer patients include a variety of possible resistance mechanisms (e.g., senescence of T cells, which is defined as decreased ability to proliferate and decreased ability to recognize antigen), leading to diminished response to treatment [25]. Another significant barrier to the effective use of T-cell immunotherapies is the heterogeneity of tumors and the immune escape pathways associated with them, including downregulation of the immunogenicity of MHC class I molecules, which diminishes the efficacy of the treatment by removing the ability of T cells to kill the tumor [26].

One obstacle in addressing resistance during NSCLC's transformation to SCLC is that these patients have a dismal prognosis [27]. To overcome these mechanisms of resistance and restore normal levels of tumor infiltration within the cancerous mass, combinations of T-cell immunotherapies with currently available treatments including chemotherapy and targeted agents need to be developed, along with new immune modulators [28].

Additionally, the development of personalized therapeutic models using biomarker-derived data (tumor-specific T-cell gene expression profiles) and novel molecular target antigens like SAGE-1 and EPC-1/MD-12/USP22 is essential for improving how we classify patients as well as developing optimal therapeutic regimens [21]. Recently identified cellular engineering techniques provide durable T-cell engraftment, increased T-cell persistence against suppression, and the advent of innovative T-cell delivery systems, such as inhalation of 2D Molybdenum disulfide-based for T-cell hyperactivation [29].

Future research should provide a deeper comprehension of the relationships and mechanisms behind autophagy, ferroptosis, and immune evasion so that it can help discover new therapeutic strategies [30]. Ultimately, by developing improved bioengineering techniques, multi-omics studies (transcriptomics, proteomics, metabolomics, etc.), and combination immunotherapies will help overcome current challenges and provide better results for patients receiving T cell immunotherapies for lung cancer.

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6. Conclusion

In conclusion, T-cell immunotherapies are changing the prospect of lung cancer therapy by providing patients with durable survival benefits. For NSCLC and SCLC, ICIs provided the first evidence for this, with some patients achieving a durable response following treatment for up to 5 years. New innovations and applications in the field of immunotherapy, such as BiTEs, tarlatamab for SCLC, and the personalized ACT approach with TILs, are giving us new ways to treat patients with advanced lung cancer. There remains critical issues to be addressed, including the effects of the heterogeneity of tumors, the effects of the immunosuppressive microenvironment, management of irAEs, and the need for reliable predictive biomarkers. The prospect of T-cell immunotherapies, specifically in the field of lung cancer treatment, lies within the elimination of the above barriers through academic collaboration and the development of innovative ideas. Future research should focus on rationally designed combination therapy approaches that target multiple pathways of resistance; development of personalized T cell therapies through the use of neoantigen vaccines and patient-specific T cell products; and advanced bioengineering of T cells to develop "smart" T cells that are more effective and have lower toxicity potential.

Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

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