Comparative Mechanistic Fitness and Clinical Translation of CAR-T Cells, Immune Checkpoint Inhibitors, and Antibody–Drug Conjugates in NSCLC

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Abstract. Immunotherapy has become a cornerstone of treatment for non-small cell lung cancer (NSCLC). This review summarizes the major immunotherapy strategies: immune checkpoint inhibitors (ICIs), antibody-drug conjugates (ADCs), and chimeric antigen receptor T cell (CAR-T) therapy and analyzes how their mechanisms align with distinct tumor immune phenotypes. Specifically, ICIs, through PD-1/PD-L1 blockade, restore antitumor immunity in "hot" tumors and produce durable survival benefits across multiple stages of NSCLC. In contrast, ADCs deliver cytotoxic payloads via target-specific antibodies, thereby offering immune-independent efficacy in "cold" or ICI-refractory tumors. However, toxicities such as interstitial lung disease may be dose-limiting. Transitioning to CAR-T therapy, although this approach is highly effective in hematologic malignancies, it remains experimental in NSCLC due to antigenic heterogeneity, poor T cell infiltration, and a suppressive tumor microenvironment. Notably, early studies, including intrapleural administration of mesothelin-targeted CAR-T cells combined with PD-1 blockade, have demonstrated local activity and safety. By combining mechanistic insights from ICIs and ADCs with next-generation CAR-T engineering, future development of more adaptable immunotherapies for solid tumors may be guided. Keywords: Non-small cell lung cancer (NSCLC); immune checkpoint inhibitors (ICIs); antibody–drug conjugates (ADCs); CAR-T cell therapy; tumor microenvironment; antigen heterogeneity; immunotherapy resistance.

1 Introduction

Lung cancer is responsible for the highest cancer mortality worldwide, predominantly driven by NSCLC. Conventional approaches such as surgical resection, radiotherapy, and chemotherapy provide only modest survival gains. In contrast, immunotherapy has recently revolutionized the therapeutic landscape of NSCLC.

A wide range of immunotherapeutic strategies promotes immune-mediated tumor eradication through distinct mechanisms. ICIs, for example, restore suppressed T cell responses by disrupting PD-1/PD-L1 interactions. In contrast, ADCs deliver cytotoxic molecules directly to malignant cells using antibody specificity and act with minimal reliance on immune activation. Meanwhile, CAR-T cell therapy employs engineered T lymphocytes that specifically bind tumor-associated antigens and induce targeted tumor destruction.

Each therapeutic approach offers specific benefits and faces unique challenges. ICIs can provide durable responses but are ineffective against immune-cold tumors lacking T cell infiltration. ADCs address this limitation by delivering targeted cytotoxicity, but they can also lead to drug resistance or interstitial lung disease [1]. While CAR-T therapy has shown remarkable efficacy in hematologic malignancies, its success in treating solid tumors is limited by the variety of antigens and the suppressive tumor microenvironment [2].

Optimizing immunotherapy efficacy in NSCLC requires aligning treatment strategies with tumor biology. This review discusses the latest evidence for ICI, ADC, and CAR-T therapies, focusing on how their mechanisms influence clinical outcomes in NSCLC.

2 Evolution and Mechanistic Basis of Immunotherapy in NSCLC

2.1 Immune-Checkpoint Inhibitors

The approval of ICIs in 2015 marked a pivotal moment in NSCLC therapy, as blockade of the PD-1/PD-L1 axis reactivated antitumor T-cell function and improved treatment outcomes [3]. The KEYNOTE-024 trial demonstrated that pembrolizumab monotherapy resulted in higher 5-year survival rates than chemotherapy in patients with PD-L1 expression of at least 50% (31.9% versus 16.3%; HR=0.62;. For low PD-L1 expression, pembrolizumab plus platinum-pemetrexed extended benefit; 5-year KEYNOTE-189 analysis reported an HR of 0.60 for survival versus chemotherapy [4].

ICIs have been integrated into therapeutic regimens for early-stage disease. The CheckMate-816 trial

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demonstrated that incorporating ICIs into neoadjuvant chemotherapy was associated with a substantially higher pathological complete response rate (24.0% versus 2.2%) and prolonged event-free survival. This benefit occurred without increasing surgical risk [5]. In the IMpower010 trial, improved disease-free survival was observed in the adjuvant setting among stage II–IIIA NSCLC patients receiving atezolizumab whose tumors expressed PD-L1 in at least 1% of cells. These findings resulted in FDA approval of the drug on October 15, 2021 [6]. The KEYNOTE-671 trial reported superior two-year event-free survival with perioperative pembrolizumab (62.4%) compared to control treatment (40.6%) (HR = 0.58). However, overall survival did not reach prespecified significance at the first interim analysis [7].

Despite advances, adaptive resistance limits the efficacy of drugs. Mechanisms include deficiencies in MHC-I/β2 microglobulin, defects in interferon-γ signaling, and immune rejection, all of which reduce antigen presentation and T cell infiltration. Immune-related adverse events, including pneumonitis and colitis, may disrupt treatment and necessitate the use of corticosteroids or alternative immunosuppressive agents [8]. New checkpoint inhibitors such as TIGIT and LAG-3 are currently being investigated. Although extensive research continues, large-scale clinical trials have not established a clear survival advantage in individuals diagnosed with NSCLC. In the SKYSCRAPER-01 trial, unfavorable outcomes were observed for both progression-free survival and overall survival. Single-target escalation alone is therefore unlikely to overcome resistance [9].

2.2 Antibody–Drug Conjugates

Although ADCs emerged after ICIs, their rapid development has focused on targets such as HER2, HER3, TROP2, and c-MET. ADCs combine monoclonal antibodies with cytotoxic drugs for targeted cell killing. This effect is independent of immune activation. ADCs can sometimes induce immunogenic cell death, which promotes secondary T cell activation [10, 11]. Building on these mechanisms, recent trials have explored the clinical activity of ADCs in NSCLC.

Recent trials have highlighted the activity of these ADCs in NSCLC. In the DESTINY-Lung02 trial, trastuzumab deruxtecan (T-DXd) achieved objective response rates of 49% to 56% in those diagnosed with HER2-mutated NSCLC, with a median overall survival reaching about 18.0 months in the 5.4 mg/kg group at the final analysis. In 13%-15% of patients, interstitial lung disease was detected, lending support to the recommendation of a 5.4 mg/kg dose (Jänne et al., 2025). The HERTHENA-Lung02 trial reported that patritumab deruxtecan (HER3-DXd) improved progression-free survival (5.5 vs. 4.3 months; HR = 0.80) while overall survival remained comparable (14.4 vs. 14.1 months; HR = 0.97) in EGFR-mutant NSCLC patients after TKI failure (ESMO 2024). The TROPION-Lung01 trial evaluated datopotomab deruxtecan, a TROP2-directed antibody–drug conjugate, and reported an objective response rate of 26.4% with a median progression-free survival of 4.4 months. In contrast, patients receiving docetaxel achieved an objective response of 12.8% (HR = 0.75), with no significant difference in overall survival (HR = 0.90) [12].

Among individuals whose tumors overexpressed c-MET, telisotuzumab vedotin demonstrated encouraging activity, showing an objective response rate of 36% and a median progression-free survival of 5.9 months, accompanied by acceptable safety profiles (Parisi [12]; [1]).

Collectively, current findings suggest that ADCs can elicit clinical responses in patients with immune checkpoint inhibitor–refractory NSCLC, though their efficacy is limited by antigenic heterogeneity, off-target toxicity, and restricted safety profiles. While ICIs depend on immune activation, ADCs act through direct cytotoxic mechanisms independent of immune modulation. These contrasts emphasize the importance of developing next-generation, programmable strategies such as CAR-T cell–based immunotherapy.

3 Chimeric Antigen Receptor T-cell Therapy in NSCLC

CAR-T–mediated therapy reprograms T cells to recognize tumor-associated antigens in an MHC-independent manner [2]. This approach addresses one of the major mechanisms of ICI resistance, which is the loss of antigen presentation. In CAR-T cell design, the receptor typically consists of an antigen-binding scFv, a CD3ζ activation motif, and a costimulatory component, often CD28 or 4-1BB, that promotes cytolytic activity.

Despite major advancements in CAR-T technology, translating the clinical success of CD19-directed therapies from hematologic cancers to NSCLC remains difficult, largely due to the absence of a well-defined, tumor-specific antigen. Candidate targets such as EGFR, mesothelin, HER2, and MUC1 display heterogeneous expression and are also detected in normal tissues, raising the likelihood of off-target toxicity [13].

In NCT02414269, intrapleural administration of mesothelin-directed CAR-T cells together with pembrolizumab led to localized engraftment and a median overall survival of 23.9 months in the treated cohort, two of whom had NSCLC [14]. Furthermore, preclinical research using piggyBac-engineered EGFR-specific CAR-T cells demonstrated potent antitumor responses with minimal toxicity in NSCLC models.

In summary, these findings indicate that NSCLC lacks an antigen that is both specific and safe. This underscores the necessity to improve delivery methods, enhance persistence, and increase resistance to immunosuppression.

The architecture of solid tumors impedes CAR-T cell infiltration. Physical obstacles, including abnormal vessel organization, dense connective stroma, and elevated internal pressure, impede the entry of CAR-T cells into tumor sites. In parallel, an immune-suppressive niche shaped by TGF-β and suppressor immune cells undermines their expansion and functional activity [2, 13].

In response to these barriers, researchers have explored several engineering solutions, including the creation of armored CAR-T cells engineered to secrete IL-12 or IL-15, or to resist TGF-β–mediated inhibition via a dominant-negative receptor.

Building on these approaches, CRISPR-mediated knockout of TGFβRII enhances tumor control and improves memory-like T cell traits in xenograft models [15]. Similarly, TGF-β-resistant CAR-T cells retain effector function in vitro, sustaining anti-tumor activity. Dual-targeted CAR-Ts more effectively address antigenic heterogeneity in tumors, and piggyBac-based viral-free platforms provide scalable, clinically adaptable CAR-T cell production. Regional delivery methods, such as intrathoracic infusion, may enhance CAR-T cell persistence and safety, although these approaches are experimental and have not been widely validated in clinical settings [14].

According to early reports, the heterogeneous biology and dense structure of solid tumors impede CAR-T-cell activity, explaining its limited benefit in NSCLC. However, advances such as armored CAR-Ts, dual-targeting strategies, CRISPR editing, and localized delivery highlight the ongoing evolution of CAR-T therapy toward a more rational, design-oriented framework for lung cancer management.

4 Mechanistic Fit and Translational Insights

Although ICIs, ADCs, and CAR-T cell therapies all aim to eliminate tumor cells, their clinical success in NSCLC depends on how each therapy interacts with the tumor immune environment.

ICIs show the greatest benefit in immunocompetent tumors characterized by strong $CD8^+$ T cell infiltration, intact antigen presentation, and high PD-L1 expression. In these settings, PD-1 blockade can restore T cell function and achieve long-term tumor control, as demonstrated in both late-stage (KEYNOTE-024) and early-stage (CheckMate-816) tumors. However, their activity is diminished in immunologically cold tumors, which have reduced MHC-I expression or defective interferon signaling. These factors limit T cell recruitment and antigen recognition by the immune system.

In contrast, ADCs work differently, delivering cytotoxic drugs directly to antigen-expressing tumor cells without being affected by immune activation. Drugs such as trastuzumab deruxtecan have demonstrated antitumor activity even in ICI-refractory or immune-rejected NSCLC, although their efficacy is limited by antigen heterogeneity, shedding, and dose-related toxicity [1].

Bridging these two modalities, CAR-T therapy lies somewhere between the ICI and ADC approaches. It achieves antigen-specific killing and is not MHC-restricted, but its efficacy in NSCLC is limited by antigenic variability, stromal barriers, and a highly suppressive tumor microenvironment. Early studies, such as intrapleural mesothelin-CAR-T therapy combined with pembrolizumab, have demonstrated safety and durable local persistence; however, they are currently limited to small, exploratory cohorts [14].

Taken together, ICIs restore immunity in a permissive microenvironment, ADCs deliver cytotoxins directly, and CAR-T therapy combines both but faces barriers unique to solid tumors. Future CAR-T development must adapt to NSCLC biology, incorporating regional delivery, resistance to the tumor microenvironment, and rational integration of checkpoint blockade to realize its transformative potential.

5 Conclusions

Even though CAR-T therapy for NSCLC is at an early developmental stage, its limited outcomes point to the persistent difficulties imposed by the solid tumor microenvironment. These obstacles include antigenic heterogeneity, stromal barriers, and immunosuppressive signals that hinder T cell function.

Recent advances have shifted CAR-T design from hematologic models to constructs more closely aligned with the biology of solid tumors. Subsequently, to enhance preclinical NSCLC antitumor activity and durability, researchers have explored approaches such as tandem and armored CAR-T, chemokine receptor modulation, and CRISPR-based checkpoint editing. Furthermore, early trials have shown that regional delivery, including intrapleural infusion with PD-1 blockade, demonstrates localized therapeutic benefit and an acceptable safety profile.

Though clinical results are still preliminary, the programmable nature of CAR-T therapy presents opportunities to overcome the physical and immunological barriers associated with NSCLC. To achieve durable and safe therapeutic effects, future developments will rely on integrating regional drug delivery, tumor-adaptive constructs, and synergistic immune modulation. As translational efforts continue, CAR-T therapy may evolve from an experimental framework into a viable platform for developing immune-based treatments against solid tumors.

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