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Comprehensive Advances in Non-Small Cell Lung Cancer: From Molecular Mechanisms to Precision Therapy

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Abstract:

Accounting for the highest cancer-related death burden worldwide, NSCLC, presents a significant public health challenge due to its high incidence and persistently low survival rates. Despite progress in low-dose spiral CT screening and smoking cessation campaigns, the five-year survival rate for patients diagnosed at advanced stages remains below 20%, underscoring the urgent need for optimized treatment strategies. This article synthesizes recent research advances concerning pathogenic mechanisms, diagnostic classification, and therapeutic innovations. It begins by dissecting the interaction networks between driver gene mutations and the tumor immune microenvironment, elucidating the critical role of epigenetic dysregulation in tumor progression. It subsequently reviews how the integration of liquid biopsy with artificial intelligence (AI)-enhanced imaging techniques is refining molecular subtyping. The article then provides a systematic evaluation of breakthrough clinical developments, including the iterative evolution of targeted agents (such as fourth-generation EGFR inhibitors), the expansion of immunotherapy across all treatment lines (from neoadjuvant settings to advanced disease), and the emergence of antibody-drug conjugates (ADCs) targeting HER3 and TROP2. These transformative approaches have propelled the median survival of advanced patients beyond 30 months and increased the pathological complete response rate in early-stage patients by tenfold. Studies demonstrate that biomarker-directed precision therapy is profoundly reshaping clinical practice. Future efforts must prioritize unraveling complex resistance mechanisms to further extend therapeutic benefits to all patient populations through multi-omics-guided personalized combination strategies.

Keywords:-Non-small cell lung cancer (NSCLC); Drug resistance; Antibody-drug conjugates; Precision medicine

I. Introduction

Lung cancer remains one of the most prevalent and lethal malignancies globally, posing a severe threat to human health. According to the GLOBOCAN 2022 data released by the World Health Organization (WHO) International Agency for Research on Cancer (IARC), lung cancer accounts for approximately 2.47 million new cases and 1.76 million deaths annually, ranking first in both incidence and mortality among all cancers [1]. Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer cases [2], primarily including subtypes such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Although the promotion of early screening initiatives, such as low-dose spiral computed tomography (CT), and smoking cessation campaigns have contributed to declining lung cancer mortality rates in some countries, Over 60% of NSCLC cases present with stage III-IV disease at initial detection, where the 5-year survival rate remains below 20% [3,4] .Consequently, exploring more effective therapeutic strategies, particularly systemic treatments for advanced NSCLC, represents a critical direction in contemporary oncology research.

The treatment paradigm for NSCLC has undergone revolutionary changes in recent years, evolving from conventional chemotherapy, radiotherapy, and surgery towards precision targeted therapy and immunotherapy. The emergence of immune checkpoint inhibitors (ICIs) has fundamentally reshaped the therapeutic landscape for advanced NSCLC [5]. The core principle of immunotherapy involves reactivating the anti-tumor activity of T cells by overcoming tumor-induced suppression of the immune system. Currently, inhibitors inhibition of PD-1/PD-L1/CTLA-4 immune checkpoints, such as pembrolizumab, nivolumab, and atezolizumab, are widely used in clinical practice. Pivotal phase III clinical trials, including KEYNOTE-024 and CheckMate 227, have demonstrated superior survival superior efficacy of anti-PD-(L)1 single-agent regimens versus chemotherapy in patients with high PD-L1 expression (≥50%). Furthermore, the combination of immunotherapy and chemotherapy (e.g., KEYNOTE-189) has extended these benefits to patients with low or even negative PD-L1 expression. Additionally, dual immunotherapy strategies combining combined PD-1/CTLA-4 blockade (exemplified by nivolumab-ipilimumab) have shown long-term survival advantages in specific patient subsets [6]. These breakthroughs in immunotherapy have elevated long-term survival in advanced cohorts from approximately 5% in the era of traditional chemotherapy to over 20%, with some patients achieving long-term survival, approaching a state of "clinical cure."

Despite these significant advances, the clinical application of immunotherapy faces numerous challenges. Primarily, the response rate to immunotherapy is limited, with only about 20%-30% of patients deriving substantial benefit. Furthermore, the predictive value of current biomarkers such as PD-L1 expression and tumor mutational burden (TMB) remains imperfect [7]. Therefore, optimizing immunotherapy strategies – for instance, through combinations with targeted therapies, radiotherapy, or novel immunomodulators – exploring more reliable predictive biomarkers, and overcoming resistance mechanisms constitute major focuses of current research.

This review aims to provide a systematic overview of the clinical progress, mechanisms of action, existing challenges, and future directions of immunotherapy in NSCLC. It will place particular emphasis on examining the working principles and clinical evidence supporting different immunotherapeutic agents (PD-1/PD-L1 inhibitors, CTLA-4 inhibitors), the current application status of immunotherapy across all stages of NSCLC (early-stage, locally advanced, and metastatic), and the limitations of current immunotherapies – including primary and acquired resistance, inadequate biomarkers, and toxicity management – alongside potential solutions such as bispecific antibodies, personalized vaccines, and CAR-T combination strategies. By integrating the latest clinical research findings and fundamental scientific discoveries, this article seeks to provide a theoretical foundation for optimizing NSCLC immunotherapy and to forecast future trends in personalized immunotherapeutic approaches.

II. Pathogenic Mechanisms of NSCLC

A. Driver Gene Mutations and Signaling Pathway Dysregulation

The development and progression of NSCLC are closely linked to specific driver gene mutations that result in the constitutive activation of intracellular signaling pathways. For instance, Oncogenic alterations in EGFR exhibit a remarkably high frequency of 40-50% in Asian non-smoking patients. Among these, exon 19 deletions (constituting approximately 45% of EGFR mutations) and the L858R point mutation in exon 21 (accounting for about 40%) are the most prevalent [8]. These mutations cause persistent activation of the EGFR tyrosine kinase domain, subsequently triggering two key downstream pathways: Two critical downstream cascades are constitutively activated: the PI3K-AKT-mTOR axis enhancing cellular survival/anti-apoptosis, and RAS-RAF-MEK-ERK axis driving aberrant proliferation [9]. Mutations in the KRAS gene occur at a rate of 25-30% in Western populations, with the G12C mutation (representing approximately 40% of all

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KRAS mutations) rendering the KRAS protein deficient in GTPase activity, leading to sustained activation of the MAPK signaling cascade. Notably, recent research has identified a positive correlation between the KRAS G12C mutation and high expression of programmed death-ligand 1 (PD-L1) on tumor cells.

The ALK fusion oncogene, detectable in 3-5% of lung malignancies. The most common EML4-ALK fusion gene produces a constitutively active chimeric protein that promotes tumor metastasis primarily through the JAK-STAT signaling pathway.

B. Immunosuppressive Characteristics of the Tumor Microenvironment (TME)

TME serves as a critical driver of lung cancer progression, with its core components establishing a complex immunosuppressive network. Within the immunosuppressive cellular milieu, regulatory T cells (Tregs) actively suppress effector T cell function through the secretion of interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). M2-polarized tumor-associated macrophages (TAMs) release vascular endothelial growth factor (VEGF), thereby promoting tumor angiogenesis. Myeloid-derived suppressor cells (MDSCs) deplete arginine within the microenvironment via the action of arginase 1.

Metabolic reprogramming represents another key immunosuppressive mechanism. Tumor cells undergo the Warburg effect, producing large quantities of lactate and consequently establishing an acidic microenvironment. This lactate impairs the cytotoxic function of CD8-positive T cells by inhibiting nuclear factor kappa B (NF-κB) signaling. Furthermore, dysregulated glutamine metabolism disrupts the amino acid balance within the TME.

The high expression of immune checkpoint molecules constitutes a major immune evasion strategy. Tumor cell surface expression of PD-L1 engages PD-1 on T cells, delivering an inhibitory signal. Similarly, CTLA-4 functions within lymph nodes to inhibit the activation of T cells.

C. Epigenetic Dysregulation

Epigenetic alterations exert transcriptional control epigenetically while preserving genomic sequence integrity, playing a significant role in NSCLC pathogenesis.

DNA methylation abnormalities are frequently observed. Hypermethylation of the CDKN2A gene promoter leads to the loss of the cell cycle regulator p16. Methylation of the RASSF1A gene promoter results in the inactivation of its tumor-suppressive function.

Dysregulation of non-coding RNA networks is also prominent. Overexpression of microRNA-21 (miR-21) suppresses the PTEN gene, consequently activating the oncogenic PI3K pathway. The long non-coding RNA MALAT1 promotes tumor metastasis by regulating SR splicing factors. Circular RNA circHIPK3 acts as a molecular sponge, sequestering miR-124 and thereby facilitating cellular proliferation.

Aberrant histone modifications contribute significantly to tumorigenesis. Overexpression of the EZH2 enzyme increases tri-methylation of lysine 27 on histone H3 (H3K27me3). This H3K27me3 mark acts as a repressive signal, silencing the expression of immune-related genes such as interferon gamma (IFN-γ).

III. III. Diagnosis and Molecular Subtyping of NSCLC

A. Multidimensional Diagnostic Technologies

Liquid biopsy technologies have achieved significant breakthroughs, offering minimally invasive approaches for NSCLC diagnosis and monitoring. Circulating tumor DNA (ctDNA) detection enables the dynamic monitoring of resistance mutations, such as EGFR T790M, with a specificity exceeding 90%. Circulating tumor cell (CTC) capture, facilitated by novel microfluidic chip technologies, allows for single-cell genomic sequencing. Exosome analysis holds promise for early diagnosis, leveraging the microRNA profiles carried within tumor-derived exosomes.

Artificial intelligence (AI) is revolutionizing diagnostic capabilities. AI-powered analysis of CT scans using radiomics can predict gene mutation status based on subtle texture features. Deep learning algorithms applied to pathological slides enable the identification of sub-millimeter micro-metastases [10]. Furthermore, multimodal data fusion models integrate clinical, imaging, and molecular data to significantly enhance diagnostic accuracy.

B. Optimization of Molecular Subtyping Clinical Pathways

Molecular subtyping is essential for guiding precision therapy in NSCLC. Updated guidelines recommend comprehensive testing for key driver genes, as outlined in Table 1.

TABLE I. Essential Genes for Molecular Testing in NSCLCs

Gene	Clinical Significance	Recommended Detection Method
EGFR	Predictive biomarker for sensitivity to EGFR tyrosine kinase inhibitors (TKIs)	Amplification Refractory Mutation System (ARMS)
ALK	Target for ALK TKIs	Fluorescence In Situ Hybridization (FISH)
ROS1	Predictive biomarker for sensitivity to crizotinib	Next-Generation Sequencing (NGS)
KRAS	Prognostic assessment and target for emerging KRAS inhibitors	Digital Polymerase Chain Reaction (dPCR)

Regarding predictive biomarkers for immunotherapy, PD-L1 quantification employs two standardized metrics like Tumor Proportion Score (TPS) or Combined Positive Score [9]. TMB is evaluated via whole-exome sequencing, reported as mutations per megabase. Microsatellite Instability (MSI) status is typically determined by immunohistochemical analysis of mismatch repair (MMR) protein expression.IV.

IV.Therapeutic Strategies and Breakthroughs in NSCLC

A. Breakthroughs in Targeted Therapy

Significant progress has been made in targeting the EGFR pathway. The third-generation inhibitor osimertinib achieves a median progression-free survival (mPFS) of 18.9 months when used as first-line therapy. Fourth-generation inhibitors like BLU-945 show promise in overcoming resistance mediated by the C797S triple mutation. Dual-target inhibitors such as JNJ-6372 simultaneously block EGFR and MET signaling [11].

Targeting the historically "undruggable" KRAS protein represents a major breakthrough. The G12C inhibitor sotorasib (AMG510) demonstrates an objective response rate (ORR) of 37% and a median duration of response (mDOR) of 11.1 months. Adagrasib (MRTX849) shows efficacy against brain metastases, achieving an intracranial disease control rate of 75%.

Effective therapies for rare oncogenic drivers are emerging. The RET inhibitor pralsetinib yields a response rate of 65% in patients with RET fusions [12]. The MET inhibitor tepotinib demonstrates an efficacy rate of 46% in patients harboring MET exon 14 skipping mutations.

B. Innovations in Immunotherapy

Immunotherapy has fundamentally transformed the treatment landscape for advanced NSCLC, as evidenced by key clinical trials summarized in Table 2.

TABLE II. Evolution of Treatment Paradigms for Advanced NSCLC

Treatment Regimen	Key Clinical Trial	Primary Beneficiary Population	Median Overall Survival (mOS)
Pembrolizumab Monotherapy	KEYNOTE-024	PD-L1≥50%	26.3 months
Chemotherapy + Immunotherapy	KEYNOTE-189	All comers (regardless of PD-L1 status)	22.0 months
Dual Immunotherapy	CheckMate 227	TMB ≥10 mutations per megabase	23.0 months

Significant breakthroughs are also occurring in the perioperative setting. Neoadjuvant therapy combining immunotherapy and chemotherapy (e.g., nivolumab + chemo in CheckMate 816) resulted in a pathological complete response (pCR) rate of 24%. Adjuvant therapy with osimertinib dramatically reduced the risk of disease recurrence by 80% in patients with EGFR-mutant stage IB-IIIA NSCLC (ADAURA study).C. Antibody-Drug Conjugates (ADCs)

This targeted modality demonstrates accelerated clinical translation. Targeting Human Epidermal Growth Factor Receptor 3 (HER3), patritumab deruxtecan (HER3-DXd) has shown promising activity in EGFR inhibitor-resistant patients, achieving an ORR of 40%. Its unique mechanism involves a cleavable linker that releases a potent topoisomerase I inhibitor payload within tumor cells.

Targeting Trophoblast Cell Surface Antigen 2 (TROP2), sacituzumab govitecan demonstrated an ORR of 26% in heavily pretreated patients. Its innovative design utilizes a pH-sensitive linker to achieve precise payload release within the acidic tumor microenvironment.

V. Resistance Mechanisms and Overcoming Strategies

A. Strategies to Overcome Targeted Therapy Resistance

Resistance to targeted agents remains a significant challenge. Management strategies for EGFR inhibitor resistance are categorized based on the underlying mechanism, as outlined in Table 3.

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TABLE III. Classification and Management of EGFR Inhibitor Resistance

Resistance Type	Mechanism	Potential Solution
On-target Secondary Mutation	T790M, C797S mutations	Third-generation or Fourth-generation EGFR TKIs
Bypass Pathway Activation	MET Amplification	Combination therapy with a MET inhibitor
Histologic Transformation	Transformation to SCLC	Platinum-based chemotherapy combined with immunotherapy

Recent discoveries also shed light on resistance mechanisms to KRAS inhibitors [13]. Acquired mutations such as KRAS Y96D can alter the drug-binding pocket, while activating BRAF mutations can lead to downstream signaling escape.B. Strategies to Overcome Immunotherapy Resistance

The conversion of immunologically "cold" tumors (lacking T-cell infiltration) to "hot" tumors is a major focus. Mechanisms maintaining the cold phenotype include dysregulated Wnt/β-catenin signaling and deficiency in the stimulator of interferon genes (STING) signaling pathway. Combination strategies aiming to enhance immunotherapy efficacy are under intense investigation. Radiotherapy can remodel the immune microenvironment by releasing tumor antigens and enhancing immune recognition [5]. Epigenetic modulators, such as histone deacetylase inhibitors (HDACi), can reverse immune-related gene silencing. Targeting immunosuppressive cells, for example, using anti-CCR5 antibodies to block MDSC tumor infiltration, represents another promising approach.

VI. Conclusion

Research in NSCLC has undergone a profound paradigm shift over the past decade, transitioning from traditional chemotherapy towards precision medicine. This review has systematically explored the intricate interplay between driver gene mutations and the tumor microenvironment in NSCLC pathogenesis, elucidating how aberrant activation of key signaling pathways like EGFR and KRAS promotes immune evasion through metabolic reprogramming and epigenetic dysregulation. Furthermore, it has analyzed revolutionary advances in multimodal diagnostic technologies, particularly emphasizing the enhanced value of liquid biopsy and artificial intelligence-driven radiomics for early detection and refined molecular subtyping. Building upon this foundation, the review has detailed breakthrough therapeutic strategies centered on the iterative development of targeted drugs, the comprehensive application of immune checkpoint inhibitors across all disease stages, and the rise of antibody-drug conjugates [14,15]. These collective advances have significantly extended the median survival of patients with advanced disease and crucially moved the therapeutic window forward into the neoadjuvant setting.

Nevertheless, current research confronts persistent limitations, including the complexity of acquired resistance mechanisms and the insufficient predictive power of existing biomarkers, which prevent a substantial proportion of patients from deriving optimal benefit. Looking ahead, the integration of spatial multi-omics to decipher tumor heterogeneity, the development of fourth-generation targeted agents to overcome resistance, the exploration of synergistic radio-immunotherapy combinations, and the advancement of artificial intelligence-assisted personalized treatment decision-making hold immense promise. These concerted efforts pave the way towards the ultimate goal of transforming NSCLC management from a predominantly incurable disease into a controllable chronic condition.

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