Short communication

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Current status of molecular markers in diagnosis, treatment, and prognosis of non-small cell lung cancer (NSCLC)

Abstract

Non-small cell lung cancer (NSCLC) accounts for the vast majority of lung cancer cases and remains a leading cause of cancer mortality worldwide. Advances in molecular biology have revolutionized the diagnosis, treatment, and prognosis of NSCLC through the identification of key molecular markers. These markers, including driver mutations (such as EGFR, ALK, ROS1, BRAF, KRAS, MET, RET, and HER2) and immune-related biomarkers (like PD-L1 and tumor mutational burden), enable personalized therapeutic strategies and improved patient outcomes. Comprehensive molecular profiling using techniques such as next-generation sequencing, immunohistochemistry, and liquid biopsy is now standard in clinical practice. Targeted therapies and immunotherapies have significantly increased response rates and survival, particularly in patients with actionable mutations or high PD-L1 expression. However, most advanced NSCLC cases remain incurable due to the development of resistance mechanisms, although curative outcomes are possible in early-stage disease with surgery and adjuvant targeted therapy. Ongoing research focuses on overcoming resistance, expanding biomarker panels, and integrating novel therapeutic approaches. The future of NSCLC management lies in precision medicine, multidisciplinary care, and continued innovation in molecular diagnostics and targeted treatment.

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Epidemiology of NSCLC

Non-small cell lung cancer (NSCLC) represents about 85% of all lung cancer cases, with the remainder being small cell lung cancer (SCLC). NSCLC is further subdivided into adenocarcinoma (the most common, especially in non-smokers), squamous cell carcinoma, and large cell carcinoma. Lung cancer is the leading cause of cancer death worldwide, accounting for nearly 1 in 5 cancer deaths.

Key epidemiological facts

a. Incidence: In 2020, there were over 2.2 million new cases of lung cancer globally, with NSCLC making up the majority.[1]

b. Mortality: Lung cancer caused 1.8 million deaths in 2020.

c. Gender and Age: NSCLC is more common in men, but incidence in women is rising, especially among non-smokers. Median age at diagnosis is around 70 years.

d. Risk Factors: Smoking is the leading cause, but environmental exposures (radon, asbestos, air pollution) and genetic predispositions also play roles.

e. Stage at Diagnosis: Over 60% of NSCLC cases are diagnosed at advanced stages (III/IV), contributing to low 5-year survival rates (~25% for all stages combined) (Table 1) (Figure 1).

Table 1 Epidemiology of NSCLC

Parameter	Value (2020)
Global new cases	2206771
Global deaths	1796144
NSCLC % of lung cancers	~85%
Median age at diagnosis	70 years
5-year survival	25% (all stages)
% diagnosed at stage IV	>50%

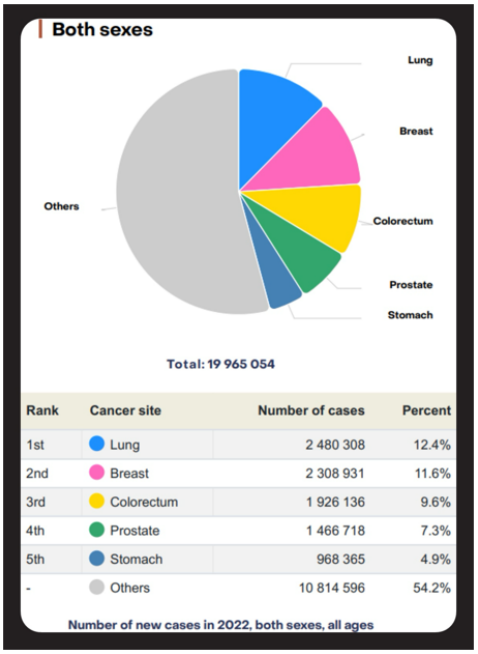

Figure 1 Global Lung Cancer Incidence and Mortality.

(Bar chart illustrating incidence and mortality for lung, breast, colorectal, prostate, and liver cancer worldwide.) GLOBOCAM 2022

Molecular markers in NSCLC

Types and classification

Molecular markers (MM) are genetic, epigenetic, or protein alterations that provide information about tumor biology, prognosis, and potential therapeutic targets. They are classified as:

I. Driver Mutations: Directly involved in tumorigenesis and often actionable.

EGFR, ALK, ROS1, BRAF, KRAS, MET, RET, NTRK, HER2

II. Immune Markers: Predict response to immunotherapy.

PD-L1, Tumor Mutational Burden (TMB), MSI9

III. Other Prognostic/Predictive Markers: Often co-occurring, may influence therapy or prognosis.

TP53, STK11, KEAP1 (Tables 2&3) (Figure 2).

Table 2 Major Molecular Markers in NSCLC

Marker	Type	Frequency (%)	Associated Subtype	Actionable?	Targeted Therapy Available
EGFR	Driver	10-15 (Caucasian) 40 (Asian)	Adenocarcinoma	Yes	Yes
ALK	Driver	3-7	Adenocarcinoma	Yes	Yes
KRAS	Driver	25-30	Adenocarcinoma	Yes (G12C)	Yes
ROS1	Driver	1-2	Adenocarcinoma	Yes	Yes
BRAF	Driver	1-4	Adenocarcinoma	Yes (V600E)	Yes
MET	Driver	3-4	Adenocarcinoma	Yes	Yes
RET	Driver	1-2	Adenocarcinoma	Yes	Yes
HER2	Driver	1-3	Adenocarcinoma	Yes	Yes
NTRK	Driver	<1	Adenocarcinoma	Yes	Yes
PD-L1	Immune	25-60	All	Yes	Yes
TMB	Immune	Variable	All	Yes	Yes
TP53	Prognostic	50	All	No	No
STK11	Prognostic	10-20	Adenocarcinoma	No	No

Table 3 Molecularly "Hot" vs. "Cold" Tumors in NSCLC

Feature	"Hot" Tumors	"Cold" Tumors
TMB	High	Low
PD-L1	High	Low
Immune Cells	Abundant (CD8+ T cells)	Sparse
Common Mutations	KRAS TP53 smoking-related	EGFR ALK never-smokers
Immunotherapy	High response	Low response

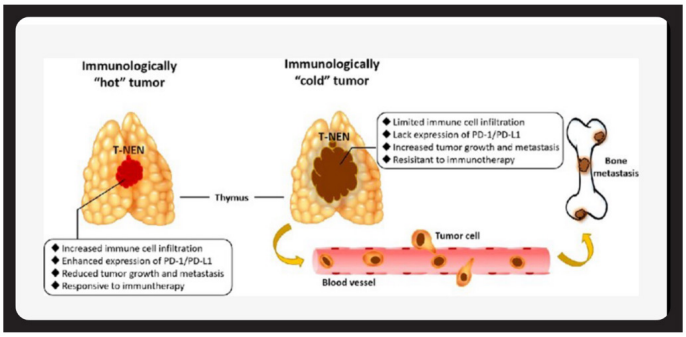

Figure 2 Hot vs. Cold Tumor Microenvironment (Schematic Illustration).

Diagram showing immune cell infiltration and PD-L1 expression in hot vs. cold tumors. (Frontiers in Oncology)

Tumor "Hot" and "Cold" Status

a. "Hot" tumors: High TMB, high PD-L1, abundant immune infiltration; more likely to respond to immunotherapy.

b. "Cold" tumors: Low TMB, low PD-L1, poor immune infiltration; less likely to respond to immunotherapy.

Methodology for determining molecular markers

Diagnostic techniques

a. PCR-based assays: Detect specific point mutations (e.g., EGFR, KRAS, BRAF).

b. Fluorescence In Situ Hybridization (FISH): Identifies gene rearrangements (ALK, ROS1, RET).

c. Immunohistochemistry (IHC): Detects protein expression/ rearrangements (ALK, ROS1, PD-L1).

d. Next-Generation Sequencing (NGS): High-throughput sequencing for multiple genes, fusions, and mutations.

e. Liquid Biopsy: Analysis of circulating tumor DNA (ctDNA) from blood, useful for monitoring and when tissue is scarce (Table 4).

Table 4 Methods for Molecular Marker Detection

Method	Markers	Advantages	Limitations
PCR	EGFR KRAS BRAF	Fast sensitive	Limited to known mutations
FISH	ALK ROS1 RET	Detects rearrangements	Labor-intensive expensive
IHC	ALK ROS1 PD-L1	Widely available inexpensive	Subjective interpretation
NGS	Multiple genes/ fusions	Comprehensive detects rare events	Cost technical expertise needed
Liquid Biopsy	ctDNA (EGFR ALK etc.)	Non-invasive real-time monitoring	Lower sensitivity false negatives

Prognostic and therapeutic value

Prognostic value

a. Favorable prognosis: EGFR and ALK mutations in the context of targeted therapy.

b. Unfavorable prognosis: KRAS, TP53, STK11, KEAP1 mutations, especially when co-occurring.

c. PD-L1 expression: High PD-L1 is associated with better response to immunotherapy, but its prognostic value is less clear.

Therapeutic value

a. Actionable mutations: Enable personalized therapy, improving response rates, progression-free survival (PFS), and overall survival (OS).

b. Resistance mechanisms: Secondary mutations (e.g., EGFR T790M), bypass pathways, and histologic transformation can limit long-term efficacy (Table 5).

Table 5 Prognostic and Predictive Value of Key Markers

Marker	Prognostic Value	Predictive Value	Therapy Impact
EGFR	Favorable (with TKI)	Predicts TKI response	High
ALK	Favorable (with TKI)	Predicts TKI response	High
KRAS	Unfavorable	Predicts G12C inhibitor	Moderate
PD-L1	Variable	Predicts immunotherapy	Moderate-High
STK11	Unfavorable	Poor immunotherapy response	Low

Treatment according to molecular profile

Targeted therapies and immunotherapy

The identification of actionable mutations has revolutionized NSCLC therapy. Patients with specific mutations receive targeted therapies, while those with high PD-L1 or TMB may benefit from immune checkpoint inhibitors (Table 6) (Figure 3).

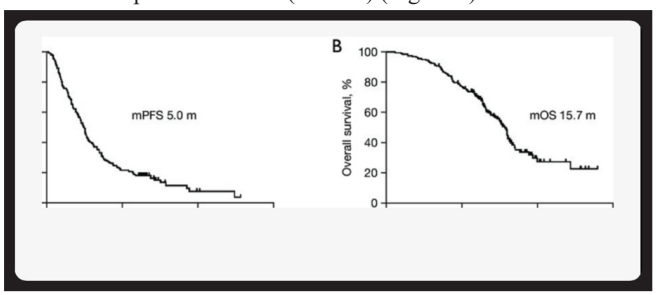

Figure 3 Progression-Free Survival by Molecular Subtype (Kaplan-Meier curves).

Kaplan-Meier curves of PFS (A) and OS (B) of patients with advanced NSCLC who received ICI-based treatment beyond progression with prior immunotherapy. mPFS, median progression-free survival; mOS, median overall survival; NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor.

Table 6 Targeted Therapies and Clinical Outcomes in NSCLC

Marker	Drug(s)	Response Rate (%)	Median PFS (months)	Median os (months)
EGFR	Osimertinib, Erlotinib	60-80	10-19	30-38
ALK	Alectinib, Crizotinib	60-80	10-34	34-57
ROS1	Crizotinib, Entrectinib	70-80	15-20	30-40
BRAF V600E	Dabrafenib+Tra metinib	60-70	9-10	18-24
MET	Capmatinib, Tepotinib	40-50	6-12	17-21
RET	Selpercatinib, Pralsetinib	60-70	17-24	30-40
KRAS G12C	Sotorasib, Adagrasib	30-45	6-8	12-15
PD-L1 >50%	Pembrolizumab (mono)	40-45	7-10	20-26

Are tumors with molecular alterations curable?

In advanced NSCLC, targeted therapies and immunotherapies have greatly improved outcomes, but true cures are rare due to the development of resistance. In early-stage disease, adjuvant targeted therapy (e.g., osimertinib for EGFR-mutant NSCLC) has increased the chance of cure, as shown in the ADAURA trial.[2] However, long-term follow-up is needed to confirm durable cures.[3-7]

a. Advanced/metastatic NSCLC: Not curable, but long-term remissions are possible.

b. Early-stage NSCLC: Cure is possible with surgery ± adjuvant targeted therapy.

Which tumors can be cured?

I. Early-stage (I-II) NSCLC: Surgical resection offers the best chance of cure, especially if the tumor harbors a targetable mutation and adjuvant therapy is given.

II. Locally advanced (III) NSCLC: Multimodal therapy (chemoradiation + immunotherapy) can result in long-term survival in a subset.

III. Metastatic NSCLC: Durable complete responses are rare, but have been reported in select patients (especially with ALK, ROS1, or EGFR mutations treated with modern TKIs, or with high PD-L1 and immunotherapy) (Table 7).

Table 7 Curability by Stage and Molecular Profile

Stage	Curability	Role of Molecular Markers
I-II	High	Adjuvant targeted therapy improves DFS
III	Moderate	Multimodal therapy + immunotherapy
IV	Low	Rare durable responses, not curable

Final considerations

a. Comprehensive molecular profiling is now standard for all advanced NSCLC.

b. Access to testing and targeted therapies varies globally.

c. Resistance remains a major challenge; research is ongoing into overcoming it.

d. Liquid biopsy is emerging as a key tool for real-time monitoring and guiding therapy changes.

e. Multidisciplinary approach is essential for optimal management.[8-10]

Future directions

a. Next-generation inhibitors: To overcome resistance (e.g., EGFR C797S, ALK G1202R).

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b. Combination therapies: Targeted agents + immunotherapy, or dual targeted therapy.

c. Personalized vaccines and adoptive cell therapies: Under investigation.

d. Expansion of biomarker panels: To include rare and emerging targets.

e. Artificial intelligence: For integrating multi-omics data and predicting response.

Conclusions

Molecular markers have transformed the landscape of NSCLC, enabling precision medicine that improves survival and quality of life. While most advanced cases remain incurable, ongoing research into novel targets, resistance mechanisms, and combination strategies offers hope for further progress. Early detection, comprehensive molecular profiling, and access to innovative therapies are key to improving outcomes.

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Conflict of interests

Authors declare no conflict of interest.

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