Immunopathologia Persa
http immunopathol.com
DOI:10.34172/ipp.2025.43950

The role of immunogenomics in advancing precision immunotherapy for non-small cell lung cancer

Hamed Hekmat Nejad[1], Fatemeh Nezhad Hossein[2], Pooyan Kamalvand[3], Seyed Ali Hosseini[4], Mohsen Farrokhpour[5*]

[1]Department of Basic Sciences, Sari Agricultural Sciences and Natural Resources University, Sari, Iran
[2]Faculty of Veterinary Medicine, Tabriz Medical Sciences, Islamic Azad University, Tabriz, Iran
[3]School of Medicine, Ilam University of Medical Sciences, Ilam, Iran
[4]Student Research Committee, Urmia University of Medical Sciences, Urmia, Iran
[5]Firouzgar Hospital, Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

***Correspondence to**
Mohsen Farrokhpour, Email: Mohsenfrkh@gmail.com, farrokhpour.m@iums.ac.ir

Received 30 Jun. 2025
Revised: 20 Sep. 2025
Accepted 6 Dec. 2025
ePublished 10 Dec. 2025

Keywords: Non-small cell lung cancer, Immunogenomics, Neoantigen, Biomarkers, Next-generation sequencing

Abstract

Among lung cancers, the majority of cases are non-small cell lung cancer (NSCLC), which is the main causes of death is due to molecular complexity and comparative resistance to treatment. Immunogenomics has been able to provide a novel approach to developing targeted immune-based therapies by integrating high-throughput sequencing with immune profiling. The present study investigates the role of immunogenomics tools, including whole exome sequencing, RNA- sequencing, and single-cell analysis to identify tumor-specific mutations, neoantigens, and immune evasion mechanisms in NSCLC. Additionally in this study, key biomarkers including tumor mutation burden (TMB), microsatellite instability (MSI), and programmed death ligand-1 (PD-L1) expression are investigated for their predictive value in response to immune checkpoint inhibitors (ICIs). The development of personalized cancer vaccines, T-cell receptor-based therapies, and chimeric antigen receptor (CAR)-T cell approaches tailored to each patient's genomic profiling and immunologic is enabled by immunogenomics. By reviewing clinical studies, we concluded that patients with high TMB as well as a strong neo-antigen load will show improved responses to ICIs. Integrated genomic analyses will lead to the emergence of new immune targets as well as resistance pathways, thus facilitating combination therapies. Immunogenomics links molecular findings with immune-based precision medicine, thereby defining a new therapeutic paradigm for the treatment of patients with NSCLC. Since we still face serious challenges such as tumor heterogeneity and data standardization, the use of immunogenomics in the context of treatment decisions, overcoming resistance, and improving patient survival outcomes in patients with NSCLC is of great importance.

Citation: Hekmat Nejad H, Nezhad Hossein F, Kamalvand P, Hosseini SA, Farrokhpour M. The role of immunogenomics in advancing precision immunotherapy for non-small cell lung cancer. Immunopathol Persa. 2026;12(2):e43950. DOI:10.34172/ipp.2025.43950.

Introduction

Non-small cell lung cancer is one of the leading causes of cancer-related mortality worldwide, accounting for approximately 80%–85% of all lung cancer cases. Despite significant advances in the diagnosis and treatment of NSCLC (non-small cell lung cancer), it remains a major contributor to global cancer deaths, with a five-year survival rate of less than 20% in advanced stages (1). The primary treatment options traditionally include surgery, chemotherapy, and radiation therapy. However, treatment responses vary widely among individuals due to molecular heterogeneity and immune evasion mechanisms. Furthermore, late-stage diagnosis and the development of resistance to therapy continue to pose significant challenges in the management of lung cancer (2). In recent years, targeted therapies have emerged as promising treatment options. For instance, tyrosine kinase inhibitors, which target specific mutations such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase, have offered new hope for patients. Nevertheless, the development of drug resistance during treatment limits the long-term efficacy of these therapies. Immunotherapy, particularly the administration of immune checkpoint inhibitors (ICIs) like anti-PD-1/PD-L1 agents has also revolutionized the treatment landscape for NSCLC. However, only a subset of patients exhibits a durable response to this approach (3,4). Immunogenomics, an interdisciplinary field combining genomics and immunology, seeks to identify and characterize the genetic and immunological features of individual tumors. This is achieved through advanced technologies such as tumor sequencing and bioinformatics analysis, enabling the development of personalized treatment strategies. Techniques like next-generation sequencing (NGS) are used to assess tumor

Key point

Non-small cell lung cancer accounts for most lung cancer deaths due to its molecular heterogeneity and treatment resistance. Immunogenomics, combining genomics and immune profiling, enables precision immunotherapy by identifying tumor-specific mutations, neo-antigens, and immune evasion mechanisms. Key biomarkers such as tumor mutation burden (TMB), microsatellite instability (MSI), and programmed death ligand-1 expression guide responses to immune checkpoint inhibitors. Emerging biomarkers, including gene expression profiles, tumor-infiltrating lymphocytes, and gut microbiome, enhance prediction accuracy. Personalized vaccines, T-cell receptor-based and chimeric antigen receptor therapies are advancing based on genomic data. Despite challenges like tumor heterogeneity and data standardization, integrating multi-omics and artificial intelligence (AI) holds promise for improved treatment, resistance management, and patient survival in non-small cell lung cancer (NSCLC).

mutation burden (TMB), identify tumor-specific neo-antigens, and evaluate patterns of immune cell infiltration within the tumor microenvironment (5). One of the key advantages of immunogenomics is its potential to predict treatment response using biomarkers such as TMB, microsatellite instability (MSI), and the expression profiles of inflammation-related genes in T-cells (6). In this study, we aim to explore the role of immunogenomics in the evolving landscape of NSCLC treatment, focusing on the biological and immunological aspects of the disease, immunogenomic biomarkers, clinical applications, current challenges, and future directions. Figure 1 shows a general scheme of immunogenomics in the treatment of NSCLC.

Non-small cell lung cancer

NSCLC is a complex and heterogeneous disease that originates in lung epithelial cells and is associated with major genetic and epigenetic alterations. NSCLC includes several histopathological subtypes, the most common of which are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, each characterized by distinct molecular profiles (7). Identification of driver mutations is crucial in cancer diagnosis, as these mutations promote tumor initiation and progression. In approximately one-quarter of NSCLC patients particularly among Asians and non-smokers, mutations in the EGFR gene are observed, most of which occur in the tyrosine kinase domain. These mutations lead to activation of the P13K/AKT and RAS/FAR/MEK signaling pathways, driving cancer cell proliferation and resistance to apoptosis (8). other genetic alterations contributing to NSCLC progression include anaplastic lymphoma kinase and ROS1 gene rearrangements, which trigger aberrant signaling and enhance tumor growth and metastasis. KRAS (Kristen rat sarcoma) mutations are found in roughly 30% of NSCLC cases and are commonly linked to resistance to EGFR inhibitors (9). In addition to driver mutations, epigenetic alterations play a significant role in the development of NSCLC. For instance, methylation of the CDKN2A gene, a well-known tumor suppressor, and dysregulation of microRNAs (miRNAs) contribute to tumor progression. Identifying these molecular changes and underlying mechanisms is essential for the development of targeted therapies. Several targeted agents have been clinically approved, such as erlotinib and osimertinib for EGFR mutations, crizotinib for anaplastic lymphoma kinase rearrangements, and sotorasib for KRAS G12C mutations. These therapies provide more effective and personalized responses compared to conventional NSCLC treatments (10). Cigarette smoking is implicated in approximately 90% of lung cancer cases (11). Other risk factors include exposure to carcinogenic substances such as drug smoke, genetic predisposition, and heavy metals like nickel, arsenic, and chromium (12). Additional contributors to lung cancer include HIV infection, alcohol consumption, and pulmonary fibrosis (13).

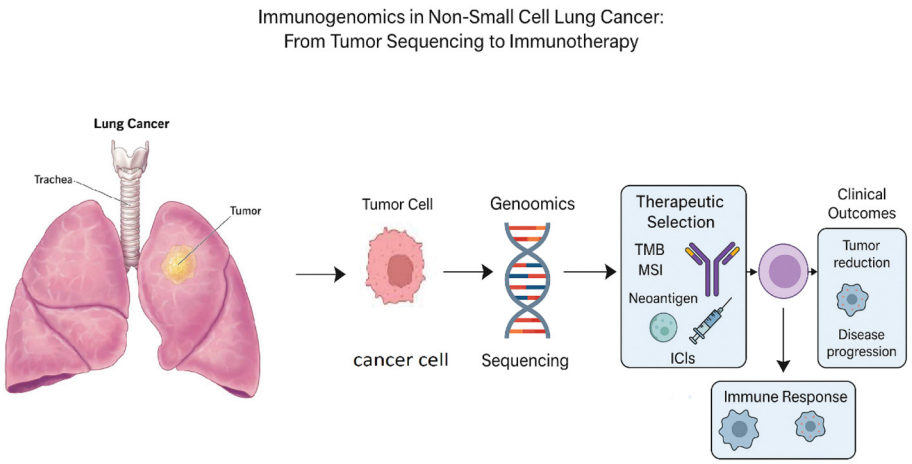

Figure 1. This figure shows the general process of using immunogenomics in the treatment of NSCLC. Tumor cells are extracted from the patient and then sequenced. Through biomarkers (such as TMB and MSI), the selection of appropriate treatment (such as immunosuppressants or ICIs) is made. As a result, an effective immune response is generated, which will reduce tumor progression.

Basic concepts of immunogenomics

Immunogenomics uses modern sequencing technologies and bioinformatics algorithms to study the interactions between the immune system and the genome, and is a combination of immunology, genomics, and bioinformatics. Therefore, the goal of immunogenomics is to identify and study molecular and genetic patterns that determine a patient's immune response to pathogens or cancer cells (14). The availability of whole-genome data has advanced significantly over the past two decades, with the development of NGS, which includes whole-genome sequencing, whole-exome sequencing (WES), and RNA sequencing (RNA-seq). NGS has high throughput compared to Sanger sequencing in generating genomic and transcriptomic data, thus providing a multi-step basis for investigating immune responses and to identify mutations encoding neo-antigenic peptides, data obtained from sequencing will be used. The resulting data will be predictive through bioinformatics algorithms (15). Neo-antigens are introduced to T lymphocytes via antigen-presenting cells. Through the identification of neo-antigens, it is possible to create personalized anti-cancer vaccines as well as targeted immune therapies on tumor cells (16). The use of the adaptive immune receptor repertoire to examine B and T cell responses allows receptor diversity to be analyzed in more detail (17). Meanwhile, TMB is another important indicator in immunogenomics, which expresses the number of genomic mutations in a tumor sample. High TMB levels will lead to increased production of neoantigens, resulting in a better response to ICIs (18). Immunogenomics also examines the diversity of antigen receptors among immune cell colonies, which will provide a better understanding of the range of antitumor and antiviral immune responses in different individuals (19). Therefore, through immunogenomics, we will go beyond traditional cancer treatments and can perform targeted immunotherapy treatments on cancer patients.

Neoantigens and the immune response

Neoantigens are actually peptides that are not expressed in normal tissues and arise only following somatic mutations in tumors, and are completely new to the immune system, while tumor antigens may be present in very small amounts in normal cells (20). Cancer cell antigens are presented to the cell surface after processing by protease complexes and then presented to $CD8^+$ and $CD4^+$ by MHC class I and sometimes MHC class II. Therefore, after recognizing tumor antigens, T cells will begin to destroy tumor cells containing neoantigens. Tumors with high TMB produce more neoantigens, and as a result, the response to ICIs is more efficient in these individuals (21). In NSCLC, many somatic mutations occur and therefore the high frequency of neoantigens stimulates the immune system, which could help in the development of personalized neoantigen-based vaccines. Indeed, tumor-specific neoantigens are identified through exome sequencing and RNA sequencing and used in vaccine development (22). However, cancerous tumors can escape the appropriate immune system response through mechanisms such as immune evasion (decreased MHC expression) or the creation of a suppressive immune environment (presence of Tregs and myeloid-derived suppressor cells). Therefore, combining immunotherapy and inhibitors of immune response pathways can increase the anti-neoantigen response (Figure 2).

Predictive biomarkers in NSCLC

As you know, biomarkers are molecules, genes or proteins that play an important role in the diagnosis of a disease and contain important information about the response to treatment, physiology and pathology of the patient. In fact, as biomarkers, they provide the conditions to diagnose the disease, then assess its prognosis, and track the effects of treatment. Biomarkers are of four types which include diagnostic biomarker, prognostic biomarker, predictive biomarker, monitoring biomarker. Predictive biomarkers will be used in the treatment of NSCLC and will help determine whether a patient will respond to a particular treatment (23).

Programmed death ligand-1

In NSCLC, the first clinical indicator to be approved in

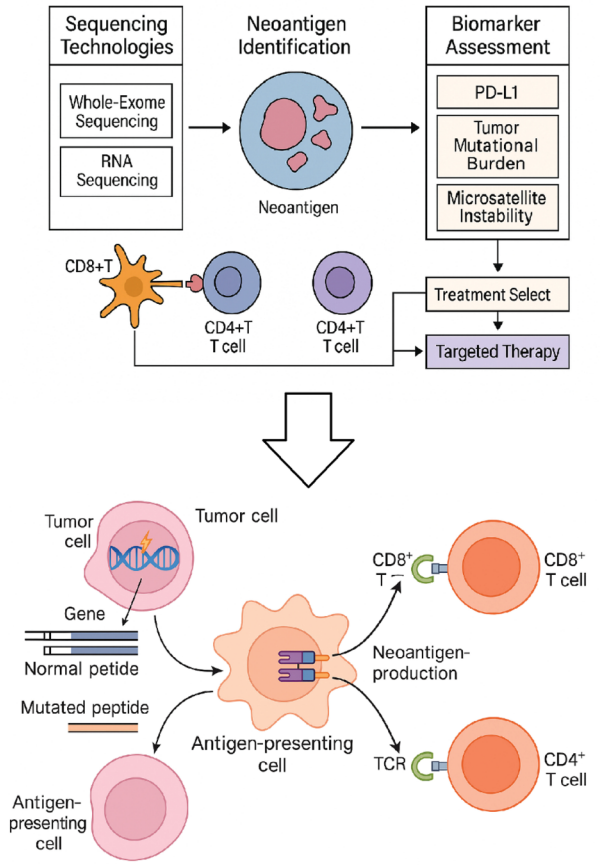

Figure 2. Pathway to identify neoantigens and their use in immunotherapy: Initially, whole exome sequencing (WES) and RNA are performed to identify neoantigens. These neoantigens will be used as predictive biomarkers that will stimulate immune cells (CD4+ and CD8+ T cells) against the tumor.

predicting response to PD-1/PD-L1 inhibitors is the PD-L1 biomarker. Immunohistochemical (IHC) tests are used to examine the presence and expression level of PD-L1 in tumor tissues with clones 28-8, 22C3, and SP263. In fact, each of these clones is a specific type of monoclonal antibody that binds to a specific region of PD-L1. Studies conducted in the phase III study (KEYNOTE-024), which is one of the most important studies in the field of NSCLC immunotherapy, compare the treatment method with PD-L1 inhibitors (pembrolizumab) and treatment with chemotherapy. These studies show that in patients with ≥ 50% PD-L1 expression who do not carry EGFR and anaplastic lymphoma kinase mutations, treatment with pembrolizumab can be much more efficient and effective compared to standard chemotherapy, and it also will have fewer side effects (23). It should be noted that sometimes some patients with a low level of PD-L1 have received a good response to treatment, so PD-L1 is not just a biomarker and is known as an imperfect biomarker.

Tumor mutation burden

Another biomarker predicting response to immunotherapy in NSCLC is TMB, which is one of the strongest biomarkers predicting response to ICIs. Systematic studies of patients with NSCLC indicate that patients with high TMB levels at a threshold of 10 or more mutations per megabase (mut/Mb) are four times more likely to respond and have better progression-free survival than other patients, but the effect on overall survival is variable. (24). TMB can be calculated through whole exome sequencing (WES) as well as targeted panels such as FoundationOne CDx, and the Food and Drug Administration (FDA) has approved it for pembrolizumab. Blood tumor mutation burden (bTMB), a ctDNA-based version, is less invasive and high levels of it are associated with good clinical response (25).

Microsatellite instability

Microsatellite instability actually means a change in the length of microsatellite sequences in DNA that occurs as a result of a defect in the Mismatch Repair (MMR) system (26). This will increase the rate of mutations and consequently increase the rate of neoantigens (27). Microsatellite instability (MSI) is very rare in NSCLC and can be useful in some patients with NSCLC. This biomarker shows a better response to ICIs in other tumors such as colon cancer. MSI is divided into two categories; MSI-high (MSI-H) and MSI-low or microsatellite stable (MSS). In MSI-H, instability is high and responds better to immunotherapy, while in MSS instability is low or nonexistent. In addition, MSI-H can be detected using three methods; NGS, PCR, and IHC. Moreover, MSI-H patients have a high tumor mutational burden (TMB-high) and will respond well to pembrolizumab. With FDA approval in 2017, MSI-H became the first genetic biomarker to be used in tumor-agnostic treatment with pembrolizumab (28).

Combining biomarkers with new biomarkers

Since the aforementioned biomarkers have limitations on their own, their combined use can increase the accuracy of prediction of immunotherapy. For instance, low PD-L1 expression in some patients results in a positive response to immunotherapy, while high expression levels result in a poor response in others. Therefore, the combination of TMB and PD-L1 (TMB+PDL-1) biomarkers or TMB and MSI (TMB+MSI) produces a higher immunotherapy response compared to using a single biomarker (29). The prediction of response to ICIs in TIL/PD-L1 is greater than that of PD-L1 alone. The ability to predict progression-free survival and PBS in patients is improved by combined examination of TP53 and KMT2C (KRAS) mutations (30).

Emerging biomarkers

Emerging biomarkers are important in the treatment of NSCLC as they can predict response to treatment and guide personalized therapies. These biomarkers include gene expression profiling (GEP), tumor-infiltrating lymphocytes (TILs), neoantigen quality, gut microbiome and peripheral blood biomarkers. Notably, GEP emphasizes inflammatory pathways such as interferon-γ (IFN-γ) signature and is considered an indicator of immune activation within the tumor. Therefore, patients with a high inflammatory gene signature have a better response to ICIs. In relation to TILs, a more appropriate immunotherapeutic response will be elicited if cytotoxic T cells (CD8+) are present in the peripheral areas as well as in the TME (31). In accurately predicting response to ICIs, the quality of neoantigens (such as their degree of adhesion to HLA and their similarity to viral pathogens) is more important than their number (32). Interestingly, the gut microbiome can be implicated as a regulator of immunotherapy response. As an example, *Akkermansia muciniphila* microbial specie induce a higher immunotherapy response (33). Finally, peripheral blood biomarkers include neutrophil to lymphocyte ratio (NLR) and circulating tumor DNA (ctDNA). A high NLR level is associated with poor prognosis, while a low ctDNA level is an indicator of a positive response (34). Table 1 summarized the most well-known biomarkers predicting response to immunotherapy in NSCLC.

Clinical applications and future prospect

Each of the biomarkers mentioned above has different clinical applications. For instance, they are used in predicting response to immunotherapy, selecting combination therapies, monitoring response to treatment, etc. The collection of information obtained by these biomarkers will help to design a personalized therapeutic approach and thus create a more accurate prediction of response to drugs, which will result in avoiding unnecessary treatments and saving costs. On the other hand, the effectiveness of treatment will increase, which will increase life expectancy and quality of life. In other

Table 1. Biomarkers predicting response to immunotherapy in NSCLC

Biomarkers	Type	Evaluation method	Clinical application	Advantages	Limitations	Reference
PD-L1	Protein	IHC (22C3, 28-8, SP263)	Selecting patients for PD-1/PD-L1 inhibitors	Clinically validated test; available	Non-response in patients with high PD-L1, variability between platforms	(23)
TMB	Genomic	NGS, WES and Targeted panels	Predicting high response to ICIs in patients with TMB≥10	Independent of PD-L1; association with neoantigens	Lack of standardization of thresholds; need for tumor volume	(24)
bTMB	Genomic	ctDNA from plasma	Non-invasive alternative to TMB	Simple sampling; suitable for patients with inaccessible tumors	Less precision than texture; high quality required	(25)
MSI	Genetic/Genomic	PCR or NGS	Strong response to ICIs in MSI-H	High effectiveness in MSI-H	Low prevalence in NSCLC	(28)
TIL/PD-L1 Score	Tissue and immunity	Artificial Intelligence on H&E Slides	Predicting response in PD-L1-/Low patients	More accurate than PD alone; multidimensional analysis	Requires advanced imaging technology and algorithms	(31)
KRAS/TP53 Co-mutation	Molecular	NGS	Predicting sensitivity to ICIs in KRAS mutant	Determinant of inherent resistance or susceptibility	High heterogeneity within subspecies	(35)
Immunogenic Cell Death Siganture	Transcriptomics	RNA-Seq	Marker of sensitivity to ICIs and combination with radiotherapy	Predicting a combination response	In the research phase	(36)
HLA Class1 Loss/ B2M Mutation	Genetic/immune	WES, IHC	Related to primary or acquired resistance	Negative response indicator	Impact on non-recognition by CD8+ T cells	(37)

words, information obtained from biomarkers plays a key role in monitoring drug resistance as well as clinical decision-making in choosing the next lines of treatment (39). Table 2 summarized the recent findings.

Conclusion

Immunogenomics is a new and interdisciplinary science and can play a very important role in the treatment of cancers, especially NSCLC cancer. Therefore, through the use of new technologies in genomic sequencing such as NGS and also immune system analysis, predictive biomarkers such as TMB, PD-L1 and MSI can be identified. These biomarkers play an important role in the selection and success of immunotherapy-based treatments (41). Based on clinical research conducted in recent years, as well as the phase 3 KEYNOTE-024 study, it has been determined that in patients with NSCLC with high PD-L1 expression (expression above 50%), the therapeutic response to immunotherapy with PD-L1 inhibitors is much higher and more appropriate than chemotherapy (42). Using only one biomarker to predict immune response is not sufficient, and therefore, to better predict immunity, combined strategies including multiple biomarkers and integration of multi-emic data (such as transcriptome, epigenetics, and proteome) will be used (43). Following the development of specific neoantigen vaccines as well as the analysis of B and T immune cells based on their genomic information, there has been a dramatic transformation in the design of immune-based therapies. The future prospect of immunogenomics is that using

Table 2. Clinical applications of immunogenomics in NSCLC

Type of clinical application	Biomarker/Genomic Profile	Tools/Technology	Clinical advantages	Reference
Predicting response to immunotherapy	PD-L1, TMB, GEP (IFNG, CXCL9)	IHC, WES, RNA-seq	Careful selection of patients for ICIs	(38)
Combination therapy selection	PD-L1+TMB, STK11, KEAP1	NGS, Panel Testing	Identification of ICI resistance, optimization of regimens	(39)
Monitoring response to treatment	ctDNA, neoantigen burden	Liquid biopsy (cfDNA NGS)	Identification of initial response or disease progression	(39)
Personalized neoantigen vaccines	Private neoantigen	WES + bioanformatic	Specific CD stimulation	(39)
Disease prognosis	TILs, IFN- γ signature	Multiplex IHC, GEP	Estimation of overall survival and long-term response	(39)
Identifying innate or acquired resistance	STK11, LKB1, EGFR	NGS, WES	Determination of alternative treatment strategies	(39)
Discovering new drug targets	Novel immune genes (e.g. LAG3, TIM3)	Multi-omics CRISPR screens	Development of new generation ICIs	(39)
Predicting the effect of microbiome compounds	Gut microbiome species	16S rRNA seq, Metagenomics	Understanding modulation of the intestinal immune system	(39)

liquid biopsy as well as combination therapies can lead to more effective treatments with fewer side effects in the field of cancer. Given the many advances, the widespread use of immunogenomics in the clinical field will bring many challenges, one of the most important of which is the lack of appropriate and standardized infrastructure for integrating genomic, immunological, and clinical data at the population level. To increase the accuracy of prognosis and treatment selection, the database must be up-to-date and capable of international exchange. On the other hand, laboratories capable of performing NGS should be developed and neoantigens should be analyzed in clinical settings (44). It is suggested that future research in this area should focus on discovering dynamic biomarkers, using machine learning to predict safety, and designing adaptive therapies. Finally, it should be noted that only by connecting research data with clinical systems can we achieve 100% utilization of immunogenomics in the treatment of NSCLC.

Authors' contribution

Conceptualization: Hamed Hekmat Nejad, Mohsen Farrokhpour.
Data curation: Hamed Hekmat Nejad, Fatemeh Nezhad Hossein, Pooyan Kamalvand, Seyed Ali Hosseini.
Formal analysis: Hamed Hekmat Nejad, , Fatemeh Nezhad Hossein, Seyed Ali Hosseini.
Funding acquisition: Mohsen Farrokhpour.
Investigation: Hamed Hekmat Nejad, Fatemeh Nezhad Hossein, Pooyan Kamalvand.
Methodology: Hamed Hekmat Nejad, Mohsen Farrokhpour.
Project administration: Hamed Hekmat Nejad, Mohsen Farrokhpour.
Resources: Mohsen Farrokhpour.
Software: Fatemeh Nezhad Hossein, Pooyan Kamalvand.
Supervision: Hamed Hekmat Nejad, Mohsen Farrokhpour.
Validation: Hamed Hekmat Nejad, Mohsen Farrokhpour.
Visualization: Hamed Hekmat Nejad, Mohsen Farrokhpour.
Writing–original draft: Hamed Hekmat Nejad, Fatemeh Nezhad Hossein, Pooyan Kamalvand, Seyed Ali Hosseini.
Writing–review & editing: Hamed Hekmat Nejad, Mohsen Farrokhpour, Seyed Ali Hosseini.

Conflicts of interest

The authors have no conflict of interest to declare.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Funding/Support

This is a self-funded study.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73:17–48. doi: 10.3322/caac.21763.
2. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018;553:446-454. doi: 10.1038/nature25183.
3. Topalian SL, Taube JM, Anders RA, Pardoll DM. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer. 2016;16:275-87. doi: 10.1038/nrc.2016.36.
4. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375:1823-1833. doi: 10.1056/NEJMoa1606774.
5. Thorsson V, Gibbs DL, Brown SD, Wolf D, Bortone DS, Ou Yang TH, et al. The immune landscape of cancer. Immunity. 2018;48:812–830.e14. doi: 10.1016/j.immuni.2018.03.023.
6. Chan TA, Yarchoan M, Jaffee E, Swanton C, Quezada SA, Stenzinger A, et al. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. Ann Oncol. 2019;30:44-56. doi: 10.1093/annonc/mdy495.
7. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018;553:446-454. doi: 10.1038/nature25183.
8. Cho BC, Felip E, Hayashi H, Thomas M, Lu S, Besse B, et al. MARIPOSA: phase 3 study of first-line amivantamab + lazertinib versus osimertinib in EGFR-mutant non-small-cell lung cancer. Future Oncol. 2022;18:639-647. doi: 10.2217/fon-2021-0923.
9. Van Maldegem F, Downward J. Mutant KRAS at the Heart of Tumor Immune Evasion. Immunity. 2020;52:14-16. doi: 10.1016/j.immuni.2019.12.013.
10. Robichaux JP, Le X, Vijayan RSK, Hicks JK, Heeke S, Elamin YY, et al. Structure-based classification predicts drug response in EGFR-mutant NSCLC. Nature. 2021;597:732-737. doi: 10.1038/s41586-021-03898-1.
11. Ellis PA, Smith IE, Hardy JR, Nicolson MC, Talbot DC, Ashley SE, et al. Symptom relief with MVP (mitomycin C, vinblastine and cisplatin) chemotherapy in advanced non-small-cell lung cancer. Br J Cancer. 1995;71:366-70. doi: 10.1038/bjc.1995.74.
12. Bleehen NM, Girling DJ, Machin D, et al. A randomised trial of three or six courses of etoposide cyclophosphamide methotrexate and vincristine or six courses of etoposide and ifosfamide in small cell lung cancer (SCLC). II: quality of life. Medical research council lung cancer working party. Br J Cancer. 1993;68:1157–66.
13. Couraud S, Zalcman G, Milleron B, Morin F, Souquet PJ. Lung cancer in never smokers--a review. Eur J Cancer. 2012;48:1299-311. doi: 10.1016/j.ejca.2012.03.007.
14. Kirk GD, Merlo C, O' Driscoll P, Mehta SH, Galai N, Vlahov D, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Infect Dis. 2007;45:103-10. doi: 10.1086/518606.
15. Miller KE, Mardis ER. Pediatric CNS cancer genomics and immunogenomics. Curr Opin Genet Dev. 2022;75:101918. doi: 10.1016/j.gde.2022.101918.
16. Xu Y, Su GH, Ma D, Xiao Y, Shao ZM, Jiang YZ. Technological advances in cancer immunity: from immunogenomics to single-cell analysis and artificial intelligence. Signal Transduct Target Ther. 2021;6:312. doi: 10.1038/s41392-021-00729-7.
17. Katsikis PD, Ishii KJ, Schliehe C. Challenges in developing personalized neoantigen cancer vaccines. Nat Rev Immunol. 2024;24:213-227. doi: 10.1038/s41577-023-00937-y.
18. Babrak L, Marquez S, Busse CE, Lees WD, Miho E, Ohlin M, et al. Adaptive Immune Receptor Repertoire (AIRR) Community Guide to TR and IG Gene Annotation. Methods Mol Biol. 2022;2453:279-296. doi: 10.1007/978-1-0716-2115-8_16.
19. Hu J, Qiu D, Yu A, Hu J, Deng H, Li H, et al. YTHDF1 Is a Potential Pan-Cancer Biomarker for Prognosis and

Immunotherapy. Front Oncol. 2021;11:607224. doi: 10.3389/fonc.2021.607224.
20. Kiyotani K, Toyoshima Y, Nakamura Y. Immunogenomics in personalized cancer treatments. J Hum Genet. 2021;66:901-907. doi: 10.1038/s10038-021-00950-w.
21. Hanada KI, Zhao C, Gil-Hoyos R, Gartner JJ, Chow-Parmer C, Lowery FJ, et al. A phenotypic signature that identifies neoantigen-reactive T cells in fresh human lung cancers. Cancer Cell. 2022;40:479-493.e6. doi: 10.1016/j.ccell.2022.03.012.
22. Veatch JR, Lee SM, Shasha C, Singhi N, Szeto JL, Moshiri AS, et al. Neoantigen-specific CD4+ T cells in human melanoma have diverse differentiation states and correlate with CD8+ T cell, macrophage, and B cell function. Cancer Cell. 2022;40:393-409.e9. doi: 10.1016/j.ccell.2022.03.006.
23. Awad MM, Govindan R, Balogh KN, Spigel DR, Garon EB, Bushway ME, et al. Personalized neoantigen vaccine NEO-PV-01 with chemotherapy and anti-PD-1 as first-line treatment for non-squamous non-small cell lung cancer. Cancer Cell. 2022;40:1010-1026.e11. doi: 10.1016/j.ccell.2022.08.003.
24. Wlosik J, Fattori S, Rochigneux P, Goncalves A, Olive D, Chretien AS. Immune biology of NSCLC revealed by single-cell technologies: implications for the development of biomarkers in patients treated with immunotherapy. Semin Immunopathol. 2023;45:29-41. doi: 10.1007/s00281-022-00973-1.
25. Yu D, Yuan C, Zhang H, Chu W. The association of efficacy with PD-1/PD-L1 inhibition and tumor mutational burden in advanced nonsmall cell lung cancer: A PRISMA-guided literature review and meta-analysis. Medicine (Baltimore). 2022;101:e29676. doi: 10.1097/MD.0000000000029676.
26. Wang Y, Wang W, Zhang T, Yang Y, Wang J, Li C, et al. Dynamic bTMB combined with residual ctDNA improves survival prediction in locally advanced NSCLC patients with chemoradiotherapy and consolidation immunotherapy. J Natl Cancer Cent. 2024;4:177-187. doi: 10.1016/j.jncc.2024.01.008.
27. Willis JA, Reyes-Uribe P, Chang K, Lipkin SM, Vilar E. Immune activation in mismatch repair–deficient carcinogenesis: More than mutational rate. Trends Cancer. 2021;7:608–622. doi: 10.1016/j.trecan.2021.03.006.
28. Yang SR, Gedvilaite E, Ptashkin R, Chang J, Ziegler J, Mata DA, et al. Microsatellite Instability and Mismatch Repair Deficiency Define a Distinct Subset of Lung Cancers Characterized by Smoking Exposure, High Tumor Mutational Burden, and Recurrent Somatic MLH1 Inactivation. J Thorac Oncol. 2024;19:409-424. doi: 10.1016/j.jtho.2023.10.004.
29. Chang L, Chang M, Chang HM, Chang F. Microsatellite Instability: A Predictive Biomarker for Cancer Immunotherapy. Appl Immunohistochem Mol Morphol. 2018;26:e15-e21. doi: 10.1097/PAI.0000000000000575.
30. Goodman AM, Kato S, Bazhenova L, Patel SP, Frampton GM, Miller V, et al. Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. Mol Cancer Ther. 2017;16:2598-2608. doi: 10.1158/1535-7163.MCT-17-0386.
31. Shi Y, Lei Y, Liu L, Zhang S, Wang W, Zhao J, et al. Integration of comprehensive genomic profiling, tumor mutational burden, and PD-L1 expression to identify novel biomarkers of immunotherapy in non-small cell lung cancer. Cancer Med. 2021;10:2216-2231. doi: 10.1002/cam4.3649.
32. Ayers M, Lunceford J, Nebozhyn M, Murphy E, Loboda A, Kaufman DR, et al. IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade. J Clin Invest. 2017;127:2930-2940. doi: 10.1172/JCI91190.
33. Lang F, Schrörs B, Löwer M, Türeci Ö, Sahin U. Identification of neoantigens for individualized therapeutic cancer vaccines. Nat Rev Drug Discov. 2022;21:261-282. doi: 10.1038/s41573-021-00387-y.
34. Jin Y, Jie Z, Fan X. Gut microbes and immunotherapy for non-small cell lung cancer: a systematic review. Front Oncol. 2025;15:1518474. doi: 10.3389/fonc.2025.1518474.
35. Passiglia F, Galvano A, Castiglia M, Incorvaia L, Calò V, Listì A, et al. Monitoring blood biomarkers to predict nivolumab effectiveness in NSCLC patients. Ther Adv Med Oncol. 2019;11:1758835919839928. doi: 10.1177/1758835919839928.
36. Toki MI, Mani N, Smithy JW, Liu Y, Altan M, Wasserman B, et al. Immune Marker Profiling and Programmed Death Ligand 1 Expression Across NSCLC Mutations. J Thorac Oncol. 2018;13:1884-1896. doi: 10.1016/j.jtho.2018.09.012.
37. Zhou S, Lu Y, Chen Y, Gan W. Identification of an immunogenic cell death-related gene signature predicts survival and sensitivity to immunotherapy in clear cell renal carcinoma. Sci Rep. 2023;13:4449. doi: 10.1038/s41598-023-31493-z
38. Perea F, Sánchez-Palencia A, Gómez-Morales M, Bernal M, Concha Á, García MM, et al. HLA class I loss and PD-L1 expression in lung cancer: impact on T-cell infiltration and immune escape. Oncotarget. 2017;9:4120-4133. doi: 10.18632/oncotarget.23469.
39. Wang J, Zhou Y, Yang Y, Wu Z. The expression panel of CXCL9, GBP5, and IFNG is a potential pan-cancer biomarker to predict immunotherapy response. Am J Transl Res. 2023;15:3960-3975.
40. Odintsov I, Sholl LM. Prognostic and predictive biomarkers in non-small cell lung carcinoma. Pathology. 2024;56:192-204. doi: 10.1016/j.pathol.2023.11.006.
41. Kinoshita T, Terai H, Yaguchi T. Clinical Efficacy and Future Prospects of Immunotherapy in Lung Cancer. Life (Basel). 2021;11:1029. doi: 10.3390/life11101029.
42. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol. 2021;39:2339-2349. doi: 10.1200/JCO.21.00174.
43. Strickler JH, Hanks BA, Khasraw M. Tumor Mutational Burden as a Predictor of Immunotherapy Response: Is More Always Better? Clin Cancer Res. 2021;27:1236-1241. doi: 10.1158/1078-0432.CCR-20-3054.
44. Zviran A, Schulman RC, Shah M, Hill STK, Deochand S, Khamnei CC, et al. Genome-wide cell-free DNA mutational integration enables ultra-sensitive cancer monitoring. Nat Med. 2020;26:1114-1124. doi: 10.1038/s41591-020-0915-3.
45. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. N Engl J Med. 2021;377:2500–2501. doi: 10.1056/NEJMc1713444.