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*Review Article*

# Developments And Difficulties Of Messenger Rna Vaccines In Nsclc Therapy.

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**Abstract**

The introduction of immune checkpoint inhibitors in the therapeutics of non-small celllung cancer (NSCLC) has been a game-changer in the management of patients with lung cancer;however, challenges do exist since a non-negligible subset of patients does not respond to therapy. Various immunotherapeutic anticancer strategies have been increasingly developed in recent years,including monoclonal antibodies, adoptive T-cell therapy, and vaccines. Fueled by their rapiddrug development and successful implementation during the COVID-19 pandemic, messenger RNA (mRNA) vaccines represent an emerging therapeutic approach in other fields of medicine,including oncology. Several clinical trials are currently being conducted to assess the safety and efficacy of mRNA vaccines regarding a variety of solid tumors.Additionally, it has been proposed and is presently being researched to combine mRNA vaccines with other immunotherapeutic strategies.Even while the inquiry into NSCLC is still in its early phases, the preliminary findings raise the necessity of educating clinicians about these potential treatments. In light of this, the goal of this study is to provide an overview of recent developments in mRNA vaccine development for NSCLC treatments, as well as to address practical issues pertaining to their medication creation and various implementation prospects.

**Simple Summary:** Adoptive T-cells, mRNA vaccines, and monoclonal antibodies are all part of the fast evolving field of cancer immunotherapy. Because of their widespread application during the COVID-19 pandemic, mRNA vaccines are showing promise as a treatment approach for a number of medical specialties, including oncology. The purpose of several clinical trials is to assess the effectiveness and safety of these vaccinations in the management of solid tumors. Numerous investigations are underway to examine the potential of mRNA vaccines in conjunction with other immunotherapeutic medications and techniques. Research on NSCLC has not yet produced outcomes that will change practice. Nonetheless, given the current findings of the ongoing research, it is imperative that clinicians become more knowledgeable about this therapeutic method.Thus, the purpose of this review is to outline the advancements and challenges in the creation of mRNA vaccines for the treatment of non-small cell lung cancer (NSCLC) as well as potential applications in clinical settings.

**Keywords** : *Lung cancer, NSCLC, messenger RNA, mRNA vaccines, and anticancer vaccinations.*

## INTRODUCTION

The management of patients with lung cancer has changed dramatically in the past 10 years with the advent of immune checkpoint inhibitors (ICIs) in the therapy of nonsmall cell lung cancer (NSCLC), which has resulted in considerable survival advantages and long-lasting responses [1–4]. Because of its immunogenic properties, NSCLC has proven to be an effective model of adding ICIs to the disease's treatment arsenal, beginning with the more advanced stages, and was only introduced to treat early-stage non-small cell lung cancer [5,6].Surgical resection combined with (neo)adjuvant chemotherapy and/or immunotherapy is the accepted treatment for high-risk patients with early-stage non-oncogenic-driven non-small cell lung cancer. Chemo-radiotherapy and maintenance are used to treat locally advanced illness.immunotherapy, although in certain situations, ICI monotherapy or combined chemotherapy and immunotherapy constitute the standard of care for metastatic illness [1–6]. However, there are drawbacks to ICIs, including a subgroup of patients experiencing toxicities known as immune-related adverse events (irAEs) [7, 8]. Any system in the human body could be affected by the erratic development of irAEs [8].

The majority can be controlled by employing immunosuppressive medications and stopping treatment. Rarely, life-threatening irAEs such pneumonitis and neurological irAEs may appear [7, 8]. Furthermore,Another

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significant issue is that a non-negligible percentage of patients have acquired or primary ICI resistance [9,10].

Note that in addition to ICIs, different immunotherapy techniques have been created in anticancer research to modify the suppressive tumor microenvironment (TME), activate the host's antitumor immune, and eventually enhancing the anticancer response, such as vaccinations and T-cell treatment [11–13]. Specifically, immunotherapeutic approaches that employ vaccines as carriers of viruses, peptides, cells, and nucleic acids have been put forth as a desirable choice with promise for both prevention and treatment [12,14].

The human papillomavirus (HPV) vaccinations, which offer significant levels of protection against cervical cancer and other HPV-related neoplasms, are the most notable example of anticancer vaccines with prophylactic aim that have mostly been created in the context of a known causal agent [15]. These vaccinations guard against oncogenic virus infection, although they have little effect on malignancies that have already grown. However, despite years of research, therapeutic anticancer vaccines have not yet reached clinical trials because of numerous obstacles, mostly related to pharmaceutical technology [16].

These difficulties mostly entail creating a vaccination that is both safe and effective at the same time [16]. Notably, the efficacy of messenger RNA (mRNA) vaccines against SARS-CoV-2 has sparked a renewed interest in vaccinations [17].

mRNA technology's justification, which was already being researched in anticancer Prior to the pandemic, research was conducted using synthetic mRNA strands (either unbound or coupled with other molecules) that encode cancer cell proteins. The production of these strands triggers immune responses against tumor antigens, including as cytotoxic T-cells and antibodies [18]. In contrast to previous vaccines, mRNA-based vaccines are comparatively easy to produce [12].

For many years, their clinical use was restricted because to the significant obstacle of effectively delivering mRNA in vivo [12]. Their delivery techniques have advanced significantly in recent years, allowing for a more thorough analysis.

Numerous clinical investigations examining the application of mRNA technology vaccines in cancer immunotherapy have been accelerated by their growing and popular use [16,19]. Despite the fact that the majority of these studies are still in the early stages of clinical development, their promising initial findings highlight the necessity for clinicians to be aware of these prospective treatments. After a successful phase 2b trial, a phase III clinical trial utilizing an mRNA vaccine in conjunction with pembrolizumab was just recently initiated in patients with resected melanoma [20].

The creation of mRNA vaccines is in its early stages with respect to NSCLC. The goal of this study is to compile the information from current developments in preclinical research and clinical trials.studies to show how mRNA vaccines can be used to treat NSCLC and to alert physicians to the difficulties that lie ahead.

## MATERIALS AND METHODS

First, a thorough search was conducted in the clinicaltrials.gov database, which was accessed on August 25, 2023. The search term "lung cancer AND mRNA vaccines" was used to retrieve the clinical studies from the clinicaltrials.gov database. Every clinical trial, whether finished or in progress, pertaining to the therapeutic management of non-small cell lung cancer based included vaccinations based on mRNA. Furthermore, a literature study was conducted using combinations of the terms "cancer immunotherapy," "mRNA vaccine," "lung cancer," and "NSCLC" in the PubMed database. Non-English works were not included.We selected current (within the last three years) preclinical research on the examination of mRNA vaccines in relation to NSCLC from the abstracts that were obtained.To find other research, a manual search of the included papers' reference lists was conducted after this search. Lastly, to emphasize the background study in this area, we added representative thorough evaluations of the subject.

### Pharmaceutical Development of mRNA Vaccines

Cell-based, protein/peptide-based, viral vector-based, and gene-based (either DNA or RNA) vaccines are the primary categories of anticancer vaccines. Despite the potential benefits of using mRNA in vaccines, including simple and affordable laboratory synthesis and direct Because of the molecule's instability, translation to protein in the cytoplasm without going through the nucleus was long regarded as a difficult strategy [21,22]. Applying ideal RNA nucleoside changes that impact the coding sequence, the 5-untranslated region (UTR), and the 30-UTR accelerated improvements in the stability, translation efficiency, and innate immunogenicity of mRNA [21,22].RNA chains that have not been altered are extremely immunogenic and prone to breaking down before they can even be translated into the required protein. The implementation of changes in vitro prior to birth, includingas having RNA methylation and pseudouridine, along with modifications to the 50 cap structure and poly(A) tail, are linked to safer and more successful immunization [21].The lengthy single-stranded chain of mRNA makes it challenging to achieve high cellular encapsulation efficiency and drug loading, which is another problem with mRNA vaccine technology. As a result, appropriate formulation procedures are typically needed for effective delivery [22].Both the delivery methods and the identification of the proper targeted tumor antigen or antigens to maximize the immune response have advanced significantly in recent years [16, 23].In

previous research, dendritic cells (DCs) served as the primary delivery route for mRNA vaccines [24]. Professional antigen-presenting cells (APCs), or DCs, have the capacity to excite naïve T lymphocytes by absorbing biological material from their environment [23]. Compared to in vivo transfection, ex vivo transfection of DCs with mRNA is preferable [19]. Ex vivo creation, however, is laborious and time-consuming [23].

Despite the safety of this platform [23], An alternate delivery method that avoids the need for DC isolation, ex vivo culture, and re-infusion is lipid-based formulations. The components of lipid nanoparticles (LNPs) are lipid-anchored polyethylene glycol (PEG), an ionizable aminolipid-like molecule, a helper phospholipid, and cholesterol [12, 19]. Ionizable lipids are neutral at physiological pH, which increases stability and decreases cytotoxicity. Ionizable lipids are positively charged at low pH levels, which helps the mRNA be encapsulated and released from the endosome into the cytoplasm. They are characterized by high immunogenicity, rapid manufacture, and a high plasticity transfection rate [16].LNPs' elevated effectiveness and relative instability can both be explained by their significant inflammatory responses [25].

Furthermore, protamines are cationic peptides that combine with mRNA to create complexes through electrostatic contact, can be coupled with lipids, and shield mRNA from extracellular RNase destruction. Additionally, these complexes have the ability to trigger the T helper 1-type immune response by activating toll-like receptor 7/8 (TLR7/8) [12]. For RNA distribution, proton is employed as a stabilizing agent [26, 27]. Vaccines based on proteases appear to be safe, practical, well-tolerated, and have minor side effects [23, 27].The thermostability and ability to be maintained without cold-chain storage are two more benefits of protamine-based platforms. However, they appear to be less successful than LNPs or other liposome-basedplatforms [27].

Furthermore, by using one or more tumor antigens, mRNA anticancer vaccines aim to boost the immune system's defenses against cancer. Crucially, there are two primary groups of tumor antigens: Self-antigens known as tumor-associated antigens (TAAs) are aberrantly produced in cancer cells but also Tumor neoantigens are a class of peptides that are expressed on the surface of tumor cells but not in normal tissues. Major Histocompatibility Complex (MHC) molecules work together to help antigen-specific T cell receptors (TCRs) identify these peptides [23].Moreover, mRNA anticancer vaccines seek to strengthen the immune system's defenses against cancer by utilizing one or more tumor antigens. Importantly, tumor antigens fall into two main categories: Cancer cells create self-antigens called tumor-associated antigens (TAAs) abnormally, but they alsoA class of peptides known as tumor neoantigens is expressed on the surface of tumor cells but not in healthy tissues. These peptides are recognized by antigen-specific T cell receptors (TCRs) with the aid of Major Histocompatibility Complex (MHC) molecules [23].According to theory, neoantigens offer a chance for customized immune activation and are not susceptible to central immune tolerance [29]. However, several problems have not yet been looked into,such as the precision of neoantigen prediction systems and the ability of mRNA molecules to encode numerous antigens [30].

## Clinical Trials of mRNA Vaccines Including Patients with NSCLC

The analysis of the trials showed several mRNA anticancer vaccination studies that were either specifically for patients with NSCLC or for patients with a range of solid tumors, including NSCLC. Every study is a clinical phase I or II study. trials. Table 1 summarizes the specifics of the clinical trials that were collected.In order to evaluate the safety and dose-limiting toxicity of a vaccination of DCs loaded with mRNA encoding for CEA, the NCT00004604 trial was carried out in the early 2000s. Patients with lung cancer and other metastatic cancers that expressed CEA were recruited for the study [31]. To be more precise, nine patients with lung cancer that expressed CEA were part of the phase I dose-escalation study.

Despite the fact that all patients had malaise and subcutaneous nodules at the injection site, phase I data indicated that no significant toxicities were seen. Consequently, it was shown that administering DCs transfected with CEA mRNA was safe. The dose that was most practical was 3 × 107 DC per injection. In phase I, 24 patients' responses were assessed. One full response (as determined by the tumor marker), two partial responses, three cases of stable disease, and eighteen cases of progressing disease were observed [31]. This investigation was followed by a phase II trial, although only individuals with colorectal cancer that had been removed were enrolled [31].

In order to evaluate the safety and effectiveness of a DC vaccination in conjunction with cytokine-induced killer (CIK) cells in patients with advanced non-small cell lung cancer (NSCLC) with bone metastases, another phase I/II experiment (NCT02688686) was started in China. Transfection of the cells was done using three fixed tumor antigens encoded by mRNA molecules found in adenovirus type 5 (Ad5) vectors: survivin, MUC1, and suppressor of cytokine signaling (SOCS) 1. Nevertheless, the trial's results have not been made public. Trials looking into mRNA vaccines that target mutations in the Kirsten rat sarcoma viral oncogene homolog (KRAS), which are common genetic changes in a number of neoplasms, are another intriguing idea. NCT03948763 is a phase I experiment that uses an mRNA vaccine (mRNA-5671/V941) developed by LNP, either by alone or in conjunction with pembrolizumab, for patients with pancreatic adenocarcinoma, colorectal cancer, or NSCLC that has a KRAS mutation. In order to improve antigen-specific T-cell responses after immunization,

the tetravalent vaccine contains mRNA molecules that match to G12D, G12V, G13D, or G12C driver mutations in the KRAS gene. Finding the suggested phase 2 dosage is the aim of the research. Seventy individuals were enrolled in the trial, but the findings have not yet been released.Likewise, patients with advanced cancers and KRAS mutations (G12C, G12D, or G12V), including lung cancer, are being recruited for the NCT05202561 trial. The purpose of this phase I single-arm, open-label trial is to assess the safety, tolerability, and anticancer properties of the mRNA tumor vaccine. pharmacokinetics, immunoreactivity, and activity. The safety of the vaccination, either by itself or in conjunction with a PD-1 inhibitor, is being studied.

Additionally, two mRNA-based cancer vaccines, CV9201 and CV9202, were created for non-small cell lung cancer (NSCLC). These vaccines contain mRNAs that encode a variety of tumor antigens in order to elicit an adaptive humoral and cellular immune response. CV9201 was utilized in the NCT00923312 experiment.Five NSCLC-related antigens are encoded by an mRNA-based vaccine that uses free and protamine-complexed full-length mRNAs: trophoblast glycoprotein (5T4), melanoma antigen family C1 and C2, survivin, and New York esophageal squamous cell carcinoma-1 (NY-ESO-1). 46 patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who had at least stable disease following first-line treatment were recruited for a phase I/IIa dose-escalation trial [32]. Five intradermal injections of CV9201 at varying dosage levels were administered to the patients.

The primary goal was to evaluate safety; other goals included estimating T-cell responses to the five antigens and tracking immune cell population changes. In terms of safety, the findings showed that The suggested dosage for phase IIa was 1600 μg, and all CV9201 dose levels were well tolerated. Flu-like symptoms and moderate injection site reactions were the reported adverse events. The study of the immune response revealed that while CV9201 immunogenicity could be identified, immune responses were comparatively infrequent and transient, which clearly suggests that the tested mRNA immunotherapeutic has to be improved [32].

Researchers examined whether a comparable lung cancer vaccine (CV9202 or BI1361849) might be safely used in conjunction with local radiation therapy (RT) for the consolidation and maintenance of stage IV treatment in the trial NCT01915524.NSCLC following EGFR tyrosine kinase inhibitor therapy or first-line chemotherapy [33].Six mRNA molecules that encode for fixed tumor-associated antigens—Mucin1 (MUC1), survivin, NY-ESO-1, 5T4, MAGE-C2, and MAGE-C1—that are overexpressed in non-small cell lung cancer (NSCLC) relative to healthy tissue made up the vaccine. It was thought that local radiation therapy, which is commonly used as a palliative treatment for lung, bone, and soft tissue metastases, might increase the vaccine's immunogenic effect. When necessary, maintenance chemotherapy was given in addition to the vaccination. The results showed that the regimen was well tolerated; flu-like symptoms and injection site responses were most typical adverse events. There were increased levels of antigen-specific antibodies and functioning T cells, among other antigen-specific immunological responses. One patient experienced a partial response (PR) in conjunction with pemetrexed maintenance, while 46.2% of patients experienced stable disease (SD), the best overall response in terms of tumor responses [33].An open-label, multicenter, two-armed study (NCT03164772) has assessed the safety and initial effectiveness of combining the same vaccine (CV9202 or BI1361849) with one or two ICIs for non-small cell lung cancer (NSCLC), specifically the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody and the anti-PD-L1 antibody durvalumab.Tremelimumab [34]. Patients in arm B received the vaccine with durvalumab and tremelimumab, while those in arm A received the mRNA vaccine plus durvalumab.The main endpoint, which included dose-limiting toxicity during dose evaluation, was the assessment of safety and acceptability. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and responsiveness were secondary goals. overall survival (OS) and duration. Additionally, to compare the immunological responses, a control group receiving only ICI treatment was included [34]. A total of 61 individuals were included in this experiment, 24 of them were in arm A and 37 in arm B. 57 of the 61 participants received at least one trial treatment dose. In terms of toxicity, treatment-related adverse events of any grade were reported by 55.9% of arm B and 56.5% of arm A.In arm B, the corresponding percentages were 11.1%, 29.6%, and 59.3%, whereas in arm A, 26.3% gave PR as the greatest response, 36.8% SD, and 36.8% progressive disease (PD). Note that there was no randomization in the trial.

The NCT03908671 trial is now testing a customized neoantigen mRNA vaccination. When normal treatment fails for patients with advanced esophageal cancer and non-small cell lung cancer, the vaccination is given as a monotherapy. The trial's primary goal aims to analyze an mRNA tailored tumor vaccine's safety and tolerability, with the secondary goal being a preliminary evaluation of the vaccine's effectiveness in this patient group. Patients are being recruited for the trial.

**Recent Advances in Preclinical Research of mRNA Vaccines for NSCLC**

Numerous recent translational studies have concentrated on determining the best tumor antigens that could be used for mRNA because one of the primary challenges in cancer vaccines is determining the pertinent tumor antigens that will optimize the patient's anticancer immune response and eliminate immune escape possibilities.NSCLC vaccine

development [35]. These investigations, which are mostly bioinformatics-based, examined genomic information from publically accessible datasets on genetic changes associated with non-small cell lung cancer [35].

Candidate targets are often chosen based on their favorable correlation with immune cell filtration and their proven ability to trigger the expression of APCs upon appearance [35–39]. Additionally, researchers look for NSCLC expression patterns that could be improved by mRNA vaccine [35–39]. In a recent investigation, a group of genes linked to lung adenocarcinoma—GPRIN1, MYRF, PLXNB2, SLC9A4, TRIM29, UBA6, and XDH—were identified as potential candidates for mRNA vaccines [35]. Xu et al. looked into the relationship between the expression of APCs and a number of potential tumor antigens associated with lung adenocarcinoma and having prognostic significance [36].

Two genes, KLRG1 and CBFA2T3, were identified by the data as possible antigenic targets that might be employed in the creation of an mRNA vaccine, particularly for lung adenocarcinoma [36]. Additionally, the data suggested that early-stage cancers with a low load of tumor mutations, high immune cell infiltration, and checkpoint expression mightbe appropriate for immunization with mRNA [36]. Five antigens linked to lung cancer (CCNB1, KIAA0101, PBK, OIP5, and PLEK2) were identified in a different study as being significantly linked to immune infiltrating cells and were proposed as possible targets for mRNA vaccines.

The researchers in the same study proposed that the best phenotype for vaccination was immunologically “cold” clusters of lung adenocarcinoma, as determined by their gene expression profiles [37]. Two more genes that have prognostic value, ZC3H12D and TXNDC5, were shown to be correlated with APC infiltration and tumor purity in a research by Zhao et al., suggesting that these could be targets for lung adenocarcinoma vaccines [38]. Last but not least, a study on lung squamous carcinoma revealed that the expression patterns of the genes claudin 5 (CLDN5) and bone morphogenetic protein 5 (BMP5) were positively connected with antigen-presenting cell infiltration, suggesting that these genes could be developed into mRNA cancer vaccines [39].

After tissue-profiling a mouse lung cancer model, Sun et al. identified a set of somatic genetic changes and went on to create a neoantigen–RNA vaccination [40]. In the mouse model, the vaccine was given in addition to modified T cells. The findings showed that the immune system is capable of identifying neoantigens for lung cancer and shown in mouse lung cancer, the treatment was linked to a notable antitumor impact [40]. Remarkably, a recent preclinical investigation of a mouse model of lung cancer with bone metastases looked into an mRNA tumor vaccine [41].

More precisely, the vaccine contained two molecules: monophosphoryl lipid A (mPLA), a toll-like receptor, and an mRNA encoding for MAGE-A1, an immunogenic protein that is highly expressed in lung cancer and involved in tumor proliferation, invasion, and metastasis [42].4 (TLR4) agonist, which can be added to the liposomes’ hydrophobic layer. Because of the large amount of lymphoid tissue, the vaccination was administered by nasal administration. It was found to cross-activate the innate and adaptive immune responses, promote dendritic cell maturation, polarize M2 macrophages into M1 macrophages, and have anticancer efficacy by preventing the formation of metastatic cancers [41].

## DISCUSSION

Although research on mRNA vaccines for NSCLC is still in its infancy, it has advanced recently, according to the current literature review. mRNA vaccines encoding for a single, pre-fixed tumor antigen were mostly used in studies (NCT00004604, NCT02688686) conducted in the previous decades [31]. Over time, mRNA vaccines that encode several antigens [32,33] or with aThe customized neoantigen strategy (NCT03908671) has been presented and investigated. Finding appropriate antigens especially for the NSCLC subtypes of adenocarcinoma and squamous carcinoma is the focus of a noteworthy trend in preclinical research [36–38]. Furthermore, it appears that lipid-based platforms based on nanoparticles are replacing DCs as the method of delivering mRNA (NCT03948763).

The vaccines are being studied in several clinical settings, either alone or in combination with ICIs, chemotherapy, or radiation therapy. However, these studies primarily focus on metastatic NSCLC rather than its early phases.Every trial is in its early stages (phase I and II), with the main goals being to determine the appropriate dosages for additional research, evaluate the toxicity, and gauge the immunological responses. of patients and doing a first efficacy evaluation. In terms of toxicity, mRNA vaccine side effects are often modest and include flu-like symptoms, fever, exhaustion, diarrhea, and injection-site responses including erythema [31, 33].

Although immune responses have been identified, there are few thorough assessments of their type and persistence [32]. Although there has been evidence of antitumor activity in terms of responses and survival endpoints, there is currently insufficient data to make any firm judgments.Perhaps the use of predictive biomarkers and innovative clinical trial design willincrease the likelihood of assessing anticancer activity, even at the earliest phases of clinical research. It is essential to work closely with translational scientists. Overall, the number of clinical studies appears to be little when looking at 20 years of study in this area.Furthermore, research is

not concentrated on a single approach; rather, a number of approaches (pertaining to vaccine formulation or its combination with other agents) are being examined.This may be a result of the prior trials' lack of benefit, particularly those that used mRNA vaccines as monotherapy, which prevented clinical development from moving further. Since not all current trials have been finished, their findings are waited with anticipation.

Due to their many benefits, mRNA anticancer vaccine development is expected to increase [12]. It should be mentioned that, in comparison to peptide vaccines, the large-scale production of mRNA is easier and faster [22]. Furthermore, mRNA vaccines can encode a tumor antigen in its entirety, in contrast to peptide vaccinations, which possibly shorter in duration [43]. They thereby provide less restriction by the human HLA types, which exhibit variation throughout the human population, and permit the simultaneous presentation of several epitopes to APCs with both class I and class II patient-specific human leukocyte antigen (HLA) [43].A wider T-cell response is stimulated as a result [44].

Since mRNA does not need to be inserted into the genome in order to be translated, it is thought to be safer and less carcinogenic than DNA [22]. By using RNA nucleoside, stability and delivery issues have been partially resolved.alterations and improvements to the delivery systems [21].

Finding the best phenotypes and the right clinical scenario or scenarios is a significant problem with NSCLC therapies in particular, since it may help mRNA vaccines establish a position in the disease's arsenal. Preclinical studies has been centered on identifying potential targets for mRNA vaccines. The goal of these investigations is to direct the synthesis of mRNAs that encode the relevant proteins of the targets under study. Therefore, when combined with effective delivery systems, mRNA molecules may trigger specific T-cell reactions.However, different research have different possible targets for mRNA vaccines, which suggests that the findings of individual studies need to be verified [35–38]. Furthermore, preclinical studies have concentrated on identifying unique phenotypes, primarily based on immune-related gene profiles that may be advantageous.from vaccines made of mRNA. However, the outcomes are unclear. According to some research, mRNA vaccination may be advantageous for immunologically "hot" subtypes with strong T cell infiltration and immune checkpoint expression [36, 38].However, since vaccines elicit an active immune response rather than releasing the brake, as ICIs do, other research suggests that immunologically "cold" phenotypes may be more suited for vaccination [37]. A new preclinical investigation on small-cell lung cancer It was also proposed that the immunologically "cold" subtype of SCLC, which has an immunosuppressive tumor microenvironment and no immune-cell infiltration, might be the candidate phenotype for the application of mRNA vaccination. SCLC is a cancer type that receives little benefit from treatment with ICIs [45].

Lastly, there is still no consensus on the best clinical scenario or scenarios to use the mRNA vaccination for NSCLC, and there may be more than one disease setting (as shown in Figure 1). In spite of recent significant progress, the 5-year overall survival rate of The prognosis for advanced non-oncogenic-driven NSCLC remains bleak [3]. Additionally, between 40 and 50 percent of surgically treated individuals with early illness will experience another relapse within five years [5].

Although the early illness setting should also be addressed, mRNA vaccines are now being studied in the context of NSCLC. It should be mentioned that patients with resected disease are included in the phase III mRNA vaccination clinical trial for melanoma that was just started [20]. Research indicates that additional immunotherapeutic techniques may be used in conjunction with mRNA vaccinations.

Additionally, patients with comorbidities that prevent treatment with ICIs [47–50] and patients who present resistance to ICIs may need a different modality to stimulate the immune response or may need to be re-sensitized to treatment with ICIs [10,46]. For these patients, a more Immune activation that is focused and particular could be studied. The gut and lung microbiome [51,52] are examples of novel immune-related components that may correlate with immune responses and identify the appropriate phenotypes for mRNA vaccination.

## CONCLUSION

In conclusion, it appears that the creation of mRNA vaccines for the therapeutic treatment of non-small cell lung cancer is still in its early stages; yet, recent advances in pre-clinical and clinical research have added fresh perspectives on the subject. mRNA immunization is being investigated as a stand-alone treatment for NSCLC or in conjunction with other therapeutic approaches. The best way to construct mRNA vaccines for solid tumors in general and NSCLC in particular is still being worked out. To optimize the potential new mRNA uses in thoracic oncology, close cooperation between fundamental scientists and clinicians as well as between academia and industry is necessary.

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### Conflicts of Interest

The authors declare no conflict of interest.

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