



# Nano-mediated strategy for targeting and treatment of non-small cell lung cancer (NSCLC)

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## Abstract

Lung cancer is the most common type of cancer, with over 2.1 million cases diagnosed annually worldwide. It has a high incidence and mortality rate, leading to extensive research into various treatment options, including the use of nanomaterial-based carriers for drug delivery. With regard to cancer treatment, the distinct biological and physico-chemical features of nano-structures have acquired considerable impetus as drug delivery system (DDS) for delivering medication combinations or combining diagnostics and targeted therapy. This review focuses on the use of nanomedicine-based drug delivery systems in the treatment of lung cancer, including the use of lipid, polymer, and carbon-based nanomaterials for traditional therapies such as chemotherapy, radiotherapy, and phototherapy. The review also discusses the potential of stimuli-responsive nanomaterials for drug delivery in lung cancer, and the limitations and opportunities for improving the design of nano-based materials for the treatment of non-small cell lung cancer (NSCLC).

**Keywords** Nanoparticles · Non-small cell lung cancer (NSCLC) · Polymeric nanoparticles · Stimuli-responsive nanoparticles

## Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths. The complexity and heterogeneity of NSCLC make it difficult to diagnose and treat, leading to a need for ongoing research to better understand the disease. The use of nanotechnology-based tools has resulted in significant improvements in clinical outcomes for NSCLC through retrospective studies of traditional

therapies (García-Fernández et al. 2020; Ferlay et al. 2017). Lung cancer (LC) will surpass breast cancer as the next highly detected cancer worldwide in 2020 with two million new cases. However, lung cancer is the primary reason of death worldwide due to its 1,796,144 fatalities, which accounts for 18% of the total 9,958,133 deaths caused by cancer. Even though smoking is the chief causing factor for lung cancer, geography and racial differences have a big impact on how often the disease occurs (Stabile et al.

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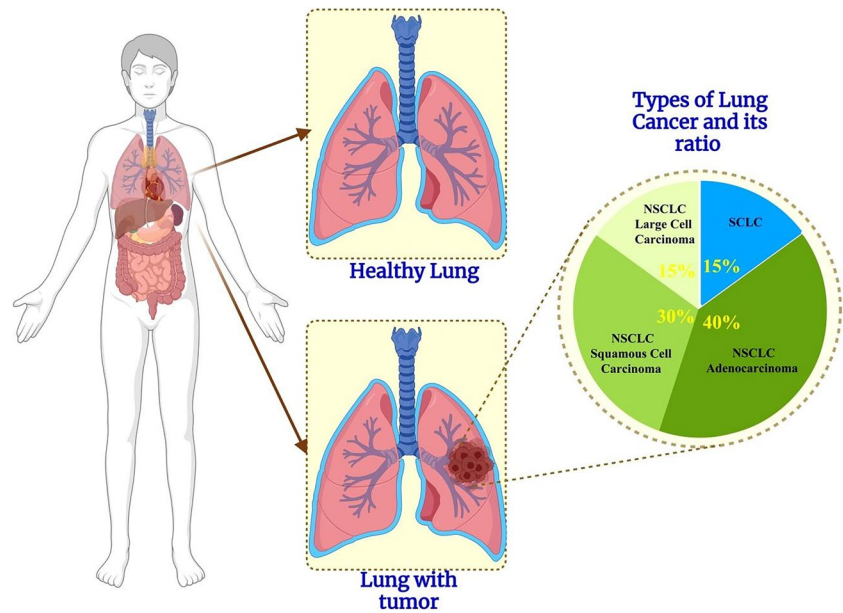
2017; McIntyre and Ganti 2017). There are primarily two types of lung cancer—non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Basically 15% of lung cancers are categorized under SCLC, a fatal tumor, while approximately 80–85% of lung cancers are NSCLC in the form of squamous cell carcinomas, large cell carcinomas, and adenocarcinomas (Roca et al. 2017). This particular kind of lung cancer may develop in non-smokers as well, despite smoking being the primary risk factor (Sun et al. 2007). The middle of the lung is where squamous cell lung cancer often develops from the proximal bronchi. It frequently contributes to 25 to 30% of NSCLC and can manifest in smokers (Socinski et al. 2016). Adenomas and squamous cell lung carcinomas progress more rapidly than large cell lung carcinomas, which may develop anywhere in the lung tissue. Large cell carcinoma makes up around 3% of all lung malignancies, although it has a much lower overall survival rate than the other subtypes (Seong et al. 2020). Chemotherapy, targeted therapy, immunotherapy, surgery, and radiation therapy are currently available treatment options for NSCLC. A huge number of patients under clinical stages Ib-IV require systemic therapies (chemotherapy, targeted therapy, or immunotherapy) (Rochigneux et al. 2020). In general, cisplatin- or carboplatin-based doublet platinum-derived chemotherapy is the first-line treatment for NSCLC (Pai-Scherf et al. 2017). Small-sized EGFR tyrosine kinase inhibitors (EGFR-TKIs) such as erlotinib and gefitinib have recently been introduced as the 2nd-generation therapy for the management of NSCLC (Lynch et al. 2004). EGFR-TKIs have minimal toxicity and considerably enhance quality of life when compared to the conventional chemotherapy regimen. The most current EGFR-TKI, osimertinib, has been routinely employed as first-line treatment for individuals having progressed EGFR-mutant NSCLC since it was approved in April 2018 (Zhou and Zhou 2015). Nanomedicine is a subfield of nanotechnology that uses substances with a size range of 5 to 200 nm for medical and health applications (Chen et al. 2017a). By increasing anticancer drugs' stability and bioavailability, facilitating cancer targeting across biological membranes, expanding circulation and plasma concentration, minimizing enzyme deterioration, and minimizing their toxic effects and antigenicity, a nanoparticle drug delivery system (NDDS) used in nanomedicine has the capabilities to resolve the disadvantages of anticancer drugs (Choi and Han 2018). Through an improved permeability besides enhanced permeation and retention (EPR) effect, nanoparticles are also useful for accelerating the accumulation of therapeutic drugs in cancer tissues. (Børresen et al. 2020). Only a few of the numerous kinds of nanoparticles created for the administration of anticancer drugs have advanced to the clinical stage (Garbuzenko et al. 2019). To our surprise, nanomedicine—which combines treatment and diagnostics—has developed into a workable paradigm

for cancer treatments. It provides the best targeting potential and extremely efficient nanocomposites to carry cargo when coating them with targeted moiety (i.e., ligand, peptide, antibodies) for imaging and therapeutics. The concept led to the creation of several nanoparticles that are ideal for both diagnosis and drug administration, accelerating the development of customized medicine (Fernandez-Fernandez et al. 2011). Nanomedicine has made it possible to create multifunctional systems that can both help with diagnosis and deliver treatments with greater precision to the target spot or tissue. Here, we examine how nanotechnology is being applied to the management of NSCLC. Furthermore, combining drug delivery strategies depending upon the extrinsic stimulation and tumor microenvironment (TME) through other chemotherapeutic and/or immune-modulatory therapies may have synergistic benefits in lung cancer treatment. In the near future, numerous innovations will be required to design the most efficient, intelligent, and smart DDS techniques for the management of lung cancer.

## Lung cancer: an overview

“Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC)” are the two primary subtypes of lung cancer (Fig. 1). Even though SCLC is less frequent than NSCLC, it is more aggressive. Big cell lung cancer, squamous cell carcinoma, and adenocarcinoma are the three primary histological subtypes of NSCLC. Again, each subtype is distinct and responds to available treatments in a different way. The interplay of ecological factors, including cigarette smoke, and genetic predisposition affects lung carcinogenesis. Infrequent germ line transformations such as “epidermal growth factor receptor (EGFR), retinoblastoma, and p53” prominently enhance the risk of developing cancer. Decreased DNA healing effectiveness can correspondingly be a substantial aspect in the development of lung cancer. According to reports, chemicals in tobacco smoke are highly involved in lung cancer development. Tyrosine kinases are clearly implicated in lung cancer pathogenesis, according to new research. Cancer may develop as a result of constitutive kinase activation, downstream signaling, overexpression, and autocrine paracrine stimulation. Tyrosine kinase oncogenic activation, such as that of MET, PIK3CA, and EGFR is often seen in NSCLC and presents a therapeutic target (Burstain and Schwartz 2008; Paul and Mukhopadhyay 2004). Notwithstanding advances in “non-small cell lung cancer (NSCLC) treatment,” the last 5-year survival rate for carcinogenic progression has increased by fivefold in the past few months. Surgical procedure is a crucial component of treating diseases in their early stages. However, lung cancer surgery is complicated and can have negative effects. Another obstacle to patients receiving good treatment for

**Fig. 1** Lung cancer: types and ration of SCLC and NSCLC



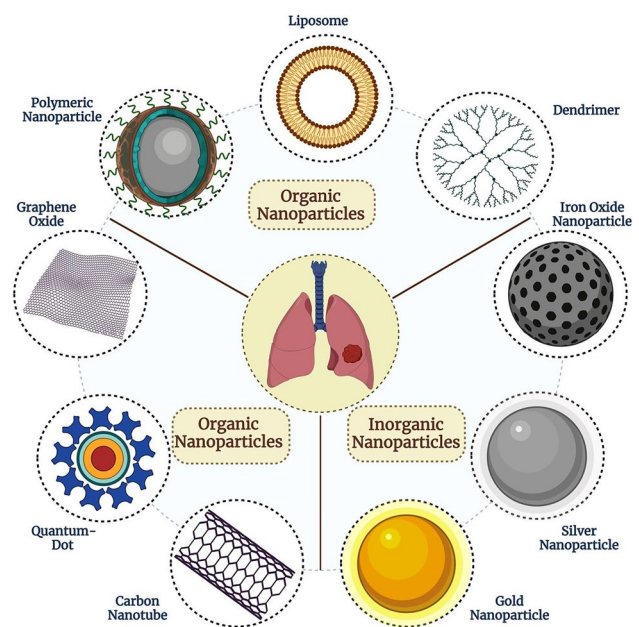
lung cancer is early diagnosis of lung malignant development. Most lung disease patients will have advanced tumor stages when they are detected, and about 75% of these individuals will have symptoms. Radiation therapy and cancer chemotherapy are relatively successful in the early stages of NSCLC treatment. With the advent of large-scale genome-wide association studies and the availability of precise sequencing tools, it is now obvious that molecular heterogeneity occurs especially inside tumor subgroups. Heterogeneity between the initiating malignancy and its metastatic counterpart may occur, even among the tissues of particular cancer, or depending on the tissue that initially gave rise to the tumor. The variety of tumor cells' genetic composition, as well as their propensity to gain adaptive tolerance, makes developing an efficacious treatment difficult (Jamal-Hanjani et al. 2017). A new technique that addressed the biochemical particularities of each participant is required.

## Nanomedicine as an alternative theranostics

Nanotechnology, which has been utilized to treat and diagnose a number of biological disorders, is one of the rapidly increasing subjects in biomedical research. Nanotechnology has witnessed a tremendous surge in its usage in treating a variety of ailments in recent years for instance, cancer, diabetes, bacterial infections, cardiovascular disease, and others (DiSanto et al. 2015). Because traditional therapy techniques for lung cancer have significant drawbacks, researchers and scientists have concentrated on creating nanoscale chemotherapeutic drugs using delivery systems that include polymeric nanoparticles, liposomal nanoparticles, metal nanoparticles, inorganic nanoparticles, and biointegrated

nanoparticles. The number of nanostructures is depicted in Fig. 2, which are commonly employed in tumor targeting.

Because of their small dimension, the nanoparticles have been shown to be efficient theranostic agents for treating lung cancer. This allows them to preferentially concentrate in tumor cells owing to an “EPR effect.” Furthermore, nanoparticles have a significant drug loading capacity owing to their large surface area to volume ratio and accessibility of functionalization (Mukherjee and Patra 2016; Ashique et al. 2022a). Because of their increased biocompatibility and ability to evade renal clearance, nanoparticles outperform



**Fig. 2** Nanoparticles used in drug delivery and tumor targeting

traditional medicinal procedures. Because they have exhibited diverse characteristics including diagnostics imaging, sensing, and treatments, researchers may employ a range of nanoparticles for several applications in lung cancer theranostics. The diversified applications of various nanocarrier systems are explained in Fig. 3. This study concentrated on theranostic uses of a range of nanocomposite types that have demonstrated immense ability to be used in the therapeutic based as well as detection of lung cancer that included (i) polymeric nanoparticles, (ii) liposomal nanoparticles, (iii) metal nanoparticles; (iv) bio-nanoparticles (Ashique et al. 2022b).

## Routes of administration of NDDS for NSCLC

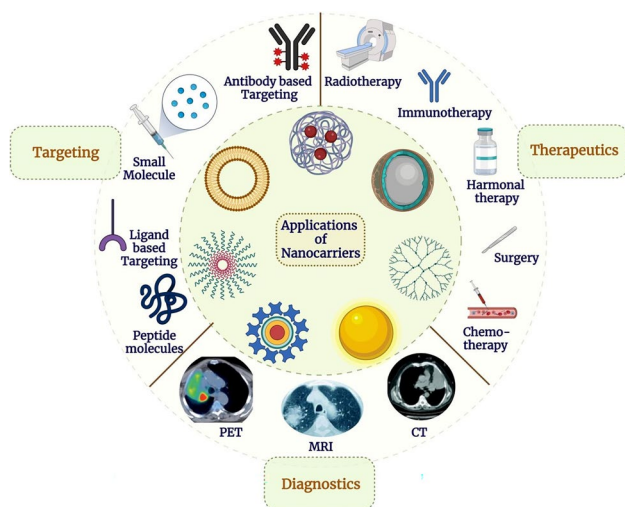
It has been difficult to deliver a novel drug delivery system (NDDS) for lung-related disorders, but it has a lot of potential. The literature contains several reports of attempts to identify the most effective strategy, path, resource, and method for achieving the intended treatment objectives. In general, regional (inhalation) or systemic (intravenous) administration can be used to deliver medication specifically to the lungs. The preferred delivery strategy, systemic administration, has a number of limitations, including toxicities on healthy cells and an effective drug concentration at the site of tumor (Lee et al. 2015). Localized delivery is still preferable since it reduces the possibility of adverse effects brought on by systemic dispersion. The drug administration via inhalation is beneficial and promising for both its local and potential systemic effects, when drug molecules may get gather in the lymphatic circulatory system after administration (Mangal et al. 2017). A NDDS may decrease the toxicities associated with pharmaceuticals by encapsulating

them suggesting that a novel drug delivery approach may also have the potential to minimize the widespread toxicity of medications like doxorubicin (Roa et al. 2011) and cisplatin (Devarajan et al. 2004), when they are delivered through the pulmonary route. It is probable that the pulmonary administration of NDDS and the EPR effect are incompatible. Further research has been done on an active targeted approach for NDDS lung delivery. According to research accomplished by Tseng and his coworkers, the “bEGF-decorated” nano-system has proficiently absorbed by/interacted with tumors overexpressed with EGFR found in animal studies, and large dosages of cisplatin were effectively administered to the malignant lung cells (Tseng et al. 2009.) There are particular issues that must be taken into consideration in order to ensure that NDDS is adequately administered to the lungs. The design of the pulmonary mechanism as well as the lung clearing process may make it more difficult to accumulate a substantial measure of drug-encapsulated NDDS at the site of tumor (Razak et al. 2021). The size of NDDS is concerning because nanometer-sized particles are generally expelled during normal breathing. The appropriate construction of nanostructures is also necessary to enable the collection as well as distribution of the drugs they carry on cancerous cells while preventing damage to normal cells. This minimizes the risk of complications while increasing the efficacy of the treatment. Numerous methods have reportedly been researched, including pH-triggered medication discharge from NDDS (Joshi et al. 2014). Understanding the microenvironment is essential for developing a successful NDDS for tumor targeting, in lung cancer.

## Nanomedicine-based treatment strategy for NSCLC

Their function and consequent therapeutic effects are largely determined by the functionalization of nanoparticles as well as their geometry and materials (Shi et al. 2017a). Additionally, by altering these characteristics, it is conceivable to employ them as contrast agents for PET or CT imaging procedures, effectively creating dual theranostic platforms (Li et al. 2016a). For a variety of NSCLC treatments, numerous nanocarrier systems are really being evaluated as prospective medication delivery strategies. Lipidic, polymeric, and metal-based nanoparticles are the competent classes of nanocarriers that are extensively researched for lung cancer.

The use of ACE-2 and nanotechnology in the treatment of NSCLC was discussed in a prominent publication by Sivalingam and Singh (2023). The most common, deadly, and severe subgroup of NSCLC is “lung adenocarcinoma and squamous cell carcinoma (SCC).” It often develops in scar tissues with regions of persistent irritation toward the lung’s periphery. It has a low mortality rate of fewer than 5% and a



**Fig. 3** Biomedical applications of nanoparticles



greater amount of genetic alteration. (Dong et al. 2020) ACE-2 levels are higher in SCC than in healthy tissue regardless of the stage of the malignancy. It has been suggested that “DNA methylation,” which functions as a cancer regulator, is the cause of elevated ACE-2 expression (Zhang et al. 2020). Samad et al. demonstrated that ACE-2 is upregulated in lung adenocarcinoma and squamous cell carcinoma, with ACE-2 suppressing mortality in “human rat alveolar epithelial cells,” lowering cell migration, and mitigating NSCLC (Samad et al. 2020). In another study, Kim et al. (2022), investigated the antitumor and immunological modulatory properties of the “scL-RB94 nanocomplex” in experimental models of “human non-small cell lung cancer (NSCLC).” Mice with human NSCLC tumors were given systemic therapy with “scL-RB94,” which dramatically reduced tumor development by boosting death and reducing cancer cell development in vivo. Treatment with scL-RB94 also improved antitumor immune function by increasing immunological identification markers and attracting innate immune cells like natural killer (NK) cells (Kim et al. 2022). The “NSCLC cell line H460” was used to investigate the efficacy of “anti-Bcl-xL siRNA” included in an “EGFR-targeted nanomedicine with scFv ligands (NM-scFv)” created by Nguyen and his colleague. “Anti-EGFR scFv ligand”-modified nanostructure was demonstrated to enable active gene transport into “H460 cells” and resulted in roughly 63% of genes being silenced at both the mRNA and protein levels and concluded that “anti-Bcl-xL NM-scFv” variant enhanced the apoptotic activity of cisplatin (Nguyen et al. 2022). Polymeric micelle loaded with paclitaxel for treatment for NSCLC was created by Lu and his group in 2022. They discovered the first indication that “Pm-Pac (polymeric micelle-paclitaxel)” may have extended overall survival in NSCLC patients without pleural metastases while maintaining a favorable safety profile. Overall, this research presents a fresh viewpoint on how nanomedicine is being developed to examine chemotherapy effectiveness (Lu et al. 2022). For the purpose of delivering therapeutic “p53-mRNA” into “p53-null hepatocellular carcinoma (HCC) and non-small cell lung cancer (NSCLC) cells,” Cerami et al. (2012) constructed self-assembling lipid-polymer hybrid nanoparticles. Thirty-six percent of individuals with HCC and 68% of those with NSCLC had defects in the p53 tumor suppressor gene (Cerami et al. 2012). The nanostructures were suggested as effective methods for enhancing macrophage-mediated phagocytosis by Moradinasab et al. 2022. In the interest of achieving an improved antitumor activity in the management of NSCLC, the current study proposes CAR-macrophage as the cutting-edge method and it acts as a bridge between the innate and adaptive immune systems (Moradinasab et al. 2022). Kim et al. investigated whether p53 genetic therapy delivered by a cancer-targeting nanostructure (called SGT-53) can

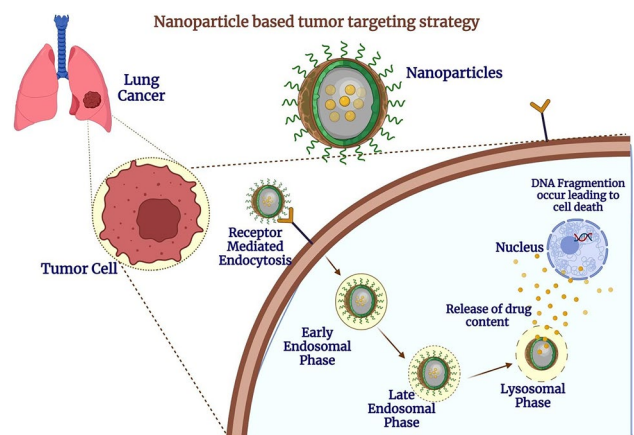
supplement anti-programmed cell death-1 (PD-1) immunotherapy, allowing it to be used in non-responding patients. Utilizing syngeneic mouse models of lung malignancies that are resistant to anti-PD-1, they establish that reinstatement of natural p53 expression stimulates anti-PD-1 to reduce cancer development and extend the lifespan of malignant cells bearing animals. The findings showed that SGT-53 can improve efficient immune function toward NSCLC by lowering immunosuppression chemicals and immunosuppressive cells (M2 macrophages and regulatory T cells) (Kim et al. 2022). In a similar study by Lu and his researcher group, polymeric micellar paclitaxel-based nanoparticle’s antitumor activity was investigated in both “A549/H226 cells and A549/H226-derived xenograft tumor models.” (Lu et al. 2023) For the treatment of NSCLC, inhibiting “YAP expression” may be a promising therapeutic strategy. Huang et al. (2022) developed a “nano-cocktail” treatment method described by using “amphiphilic and block-dendritic-polymer-based nanoparticles (NPs)” for tailored co-delivery of “EGFR-TKI gefitinib (Gef) and YAP-siRNA” to produce a controlled treatment against NSCLC (Huang et al. 2022). According to Das and his researcher group, polyphenol-based tailored nanostructures have shown to bind with a wide range of protein domains and cellular signal-transduction pathways, having a significant impact on key cellular functions. Nano-constructed dietary polyphenols have a number of molecular processes and potential therapeutic targets for the treatment of lung cancer (Das et al. 2022). Shukla et al. (2022), planned to create and evaluate “nintedanib-loaded niosomes” as inhalable carriers for increasing their therapeutic effectiveness by site-specific drug deposition against NSCLC. In vitro tests showed that nintedanib-loaded niosomes had much greater cytotoxicity, which was further supported by 3D spheroids (Shukla et al. 2022). In a similar way, “Indomethacin-loaded liposomes” were created by Sarvepalli et al. (2022) for the successful management of NSCLC. The 3D spheroid experiment results showed that “IND-Lip” nano-conjugate performed noticeably better in ex vivo tumor reduction (Sarvepalli et al. 2022). For the dual delivery of “pemetrexed disodium (PMX) and siRNA” for the treatment of NSCLC, Xiaoyu et al. (2023), created “poly-glutamic acid-modified cationic liposomes ( $\gamma$ -PGA-CL).” The recent research demonstrated the viability of combining “PMX and siRNA via  $\gamma$ -PGA-CL” as a feasible therapy method for NSCLC after in vivo antitumor trials from the complex group significantly inhibited tumor development (Xiaoyu et al. 2023). In order to combat NSCLC, Dominguez-Martinez and his colleague created “folate-decorated cross-linked cytochrome-C nanoparticles.” The findings show that both in vitro and in vivo, the NPs significantly inhibited the development of tumors in cancerous cells that exhibited FR overexpression (Dominguez-Martinez et al. 2022). Thangavelu and his group

created liposomes that were loaded with “6-gingerol” for the evaluation of its anti-NSCLC therapeutic effectiveness in both *in vitro* and *in vivo*. Whenever compared to “standard Gn, lipo-pharmacological Gn’s” characteristics were considerably enhanced in “BALB/c mice” that had NSCLCs generated. “Lipo-Gn” can therefore be taken into consideration for its expanding uses against lung cancer (Thangavelu et al. 2022). In a similar manner, “amentoflavone-loaded nanoparticles” were created by Zhao et al. (2022) to target NSCLC. The remarkable drug carrying efficiency, excellent water tolerance and dispersion, extended bioavailability, and pH-dependent release of the “AMF@DOX-Fe<sub>3</sub> + -PEG nanoparticles (ADPF NPs)” which is the “coordination of ferric ions (Fe<sup>3+</sup>), amentoflavone (AMF), PEG-polyphenol, and doxorubicin (DOX).” ADPF NPs resulted in targeted drug delivery and improved drug deposition in the cancer site. Furthermore, by lowering the “aldo-keto reductase family-1B10 (AKR1B10)” activity, the ADPF NPs might prevent the development of the A549 tumor and improve the cardiotoxicity caused by free DOX. This nanoplatform that is combined with AMF and DOX offers a wide range of potential applications in the treatment of clinical tumors (Zhao et al. 2022). For the treatment of NSCLC, Patil and his colleague created “inhalable bequaquine (BQ)-loaded cubosome (BQLC) nanocarriers.” Upon nebulization, the “BQLC nanocomposites” displayed good aerodynamic qualities. After 48 h of administration, the “BQLC” demonstrated increased cytotoxicity toward NSCLC (A549) cells compared to plain BQ. Moreover, research using 3D tumor simulations shows that cubosomal nanocarriers are more effective in fighting cancer than free BQ (Patil et al. 2021). Another study for the treatment of NSCLC was achieved by the development of quercetin-loaded micelles by Li et al. (2022). The confluence of “enhanced permeability and retention (EPR) and active targeting impact” may be responsible for the good tumor targeting capabilities and anticancer effectiveness shown by quercetin-loaded PEGMA–PDMAEA–PCL/DSPE–PEG–biotin mixed micelles (Que-MMICs). Together, Que-MMICs showed improved anticancer effect in the NSCLC-harboring mouse model and indicated substantial deposition at the tumor site (Li et al. 2022). The “bevacizumab-coated gefitinib-loaded nanoparticles (BCGN)” with dual-responsive drug release were created by Zhao et al. (2023). These nanoparticles were designed to suppress tumor growth and phosphorylation of “epidermal growth factor receptor (EGFR).” Both the “A549 and the HCC827 human NSCLC models” show considerable tumor growth inhibition when treated with a dual-responsive release of the drugs “bevacizumab and gefitinib.” (Zhao et al. 2023) In another work, Asadollahi et al. (2022) created nanostructured lipid carriers (NLCs) in order to assess the synergistic anticancer effects of co-delivering “erlotinib (ELT) and resveratrol (RES),” a naturally occurring phenol

derived from herbs, on NSCLC (Asadollahi et al. 2022). In the subsections, they are briefly discussed. The targeting strategy of nanoparticles toward NSCLC is explained in Fig. 4.

## Liposomes

When natural or synthesized amphiphilic lipids are spread in water, they spontaneously form vesicles with a bilayer shape known as liposomes. Because of their biocompatibility and advantageous safety profile, they have been extensively researched as drug delivery vehicles ever since they were created (Ashique et al. 2021). Phosphatidylcholine, cholesterol, and other substances make up the bilayer structure of liposomes, which are known to transport a variety of hydrophobic and hydrophilic big and small molecules for therapeutic purposes. Polyethylene glycol (PEG) can be grafted onto their surface to change it, lengthening their half-life in circulation (Moghimi and Szebeni 2003). In 1995 and 1999, respectively, the FDA approved Doxil and Myocet, two of the most popular doxorubicin-based liposomes (Barenholz 2012). Even though there are already sixteen liposomal medications on the market, relatively few formulations are approved as a type of treatment for NSCLC. Here, our group enlisted current instances of liposomal formulations used for therapeutic drug transport to the lungs. In 2014, Cheng et al. used the new peptide GE11’s EGFR binding affinity to study the liposomes’ size distribution (Cheng et al. 2014), and it was discovered that 10% GE11 density in A549 cytotoxicity was ideal. Cellular uptake tests also confirmed the clathrin-mediated endocytosis pathway’s significant role. A dual-ligand-modified triptolide-loaded liposome (dl-TPL-lip) was created, for efficient triptolide (TPL) delivery to NSCLC via pulmonary injection. An apoptosis assay was used to gauge the ability to destroy cells (Lin et al. 2018). Importantly, employing 3D tumor spheroids, the liposomes’ better tumor



**Fig. 4** Tumor targeting strategy of nanoparticles against NSCLC

penetration along with tumor growth suppression efficacy was confirmed. For the treatment of NSCLC, Song et al. (2017) developed a multifunctional targeting liposome in 2017 and got superior *in vivo* results. Octreotide (OCT) was used to decorate the liposome surface (Song et al. 2017). Honokiol, which reduces tumor metastasis and inhibits the creation of vasculogenic mimicking channels, and epirubicin, an anticancer medication, were both co-encapsulated in the liposome. These liposomes were found to be able to downregulate PI3K, MMP-2, and MMP-9, while activating caspase 3. Researchers from all across the world are paying close attention to the pulmonary medication delivery technique, or local distribution via inhalation, as a viable option. This necessitates the use of treatments with low doses of low toxicity. In order to determine the effectiveness and side effects of giving patients with lung metastases aerosolized interleukin (IL)-2 liposomes. The liposome-aerosol was inhaled three times daily for around 20 min. On the basis of earlier research, the dose was selected. Three cohorts of three patients each received different doses of IL-2 three times per day for a total of nine individuals. According to researchers, inhaling IL-2 liposomes is safe and causes less systemic damage (Skubitz and Anderson 2000). Aerosolized liposomal cisplatin in patients with lung cancer showed that cisplatin was well tolerated (Wittgen et al. 2007). Lowery et al. designed doxorubicin encapsulated liposomal complex engrafted with peptide molecules for targeted delivery of drug into the malignancies site (Lowery et al. 2011). After being labeled with Alexa Fluor 750, tagged liposomes were used to follow the biodistribution in a murine Lewis lung cancer model. Liposomes are often employed in lung cancer theranostics because of their exceptional biocompatibility and biodegradability (Sercombe et al. 2015). Additionally, liposomes have an advantage over other nanoparticles since they can easily be managed for sustained drug administration and are effective for loading a large number of therapeutic compounds (Bolhassani et al. 2014). Nanoliposomes often experienced certain drawbacks, such as reduced stability and high construction charges (Maja et al. 2020). IV drug delivery of liposome, having positively charged surface, has also been shown to elevate liver enzymes and pro-inflammatory cytokines in healthy C57BL/6 mice with efficient therapeutic activity (Kedmi et al. 2010).

### Polymeric nanoparticles

For the therapy of NSCLC, extensive research has been done on polymeric nanoparticles using polymers for instance, polycaprolactone (PCL), polylactic acid (PLA), and chitosan (Esim et al. 2020). In addition to being widely available, the properties of polymeric nanoparticles can be controlled for steady as well as prolonged release, facile surface functionalization, simple nano-sizing, freely available cellular

internalization, and the ability to enclose a wide range of active compounds (including drugs, peptides, and oligonucleotides) (Senapati et al. 2018). They are also more stable in storage than lipid-based formulations. Despite this fact, the complicated processing approach may make large-scale manufacturing difficult. Nevertheless, numerous *in vitro* (lab-based experimental setup) and *in vivo* (experiment based on small animals) investigations have demonstrated the non-toxicity of the PLGA nanoparticulate system, making it excellent polymeric material for the therapy of NSCLC (Semete et al. 2010). The main drawbacks of the drug delivery procedure, such as the harmful consequences of anti-neoplastic therapy, have been addressed using polymeric NPs (Singh and Nalwa 2007). They demonstrate an increase in the effectiveness of chemotherapeutic and targeted treatments by using polymeric NP to encapsulate hydrophobic pharmaceuticals at large concentrations, extending circulation duration, and improving transportation to the targeted region (Allouche 2013). The FDA has authorized “Abraxane®, an albumin-based nanocarrier” filled with paclitaxel for the management of NSCLC and advanced breast cancer (Ma and Mumper 2013). The use of “PEG-modified NPs” that contain taxanes has been shown to increase the effectiveness of combination chem-radiation treatment for non-small cell lung cancer (Jung et al. 2012). Hu et al. presented the effectiveness of “polycaprolactone nanoparticles” loaded with paclitaxel in conjunction with “chronomodulated chemotherapy” in the year 2017, (Hu et al. 2017) and they also suggested a possible role for “circadian rhythms” in tumor progression. Most significantly, Wang et al. revealed intercellular translocation of NPs to cancer cell with *in vivo* suppressed primary cancer progression using mesenchymal stem cells as a carrier to increase delivery of drug (paclitaxel) from NPs (Wang et al. 2019). “Crizotinib (for EML4-ALK fusion-positive lung cancer) and polylactic tocopheryl PEG 1000 succinate (PLA-TPGS)” were combined in a formulation by Jiang et al. in 2015 that demonstrated sustained release, caused cytotoxic effect in “NCIH3122 lung cancer cells,” and detectable both early and late apoptosis (Jiang et al. 2015). In the interest of overcoming resistance mechanism, erlotinib was loaded onto PLGA. This method has shown improved loading capacity, increased entrapment, and prolonged release (Vaidya et al. 2019). Afatinib and paclitaxel were placed into PLGA inhaled microspheres in another trial. These NPs shown great biological compatibility, prolonged release, and maintained higher concentration toward lung cells than other cell/tissue. These targeted NPs are a suitable therapy for resistant lung cancer because of all these benefits (Yang et al. 2019a). Lipid-based polymeric micelles are a different class of nanoparticles; they are distinguished by an architecture that consists of a hydrophobic core with the ability to transport medicines and a hydrophilic PEG-shell. In South Korea and various European nations,

“Genexol-PM,” a micelle formulation of “PLGA-b-methoxy-PEG nanocarrier” carrying paclitaxel, has been authorized for use in the treatment of cancer (Kim et al. 2007). Positive anti-neoplastic outcomes were shown in a phase II study with “Genexol-PM combined with gemcitabine” in those suffering from advanced NSCLC; however, frequent level III–IV toxicities were seen (Ahn et al. 2014). When added to “PEG polymeric nanoparticles,” cisplatin has improved anti-cancer activity toward cancer cells *in vitro* (Li 2018). In the treatment of NSCLC, co-encapsulated micelles encapsulating “itraconazole and paclitaxel” have shown reduced cytotoxicity (Zhang et al. 2018). Using modified micelles coated with “a-conotoxin,” it is also able to deliver additional medications, such as “docetaxel,” to the A549 NSCLC cell line (Mei et al. 2018). A new “polyurethane micelle” with promise for MRI diagnostic and chemotherapeutic treatment was created by Ding and his group (Ding et al. 2014). As a potential remedy for drug resistance, the utilization of NPs in the distribution of anticancer drugs has also been investigated. In order to create biocompatible NPs that were extremely efficient in resistant A549 cells and might suppress the production of certain multidrug-resistance proteins, galactoxylglucan and paclitaxel were utilized (Reshma et al. 2019). Drugs containing polymeric NPs in the form of aerosols may lessen cytotoxic effects (Abdelaziz et al. 2018). Significant anticancer efficacy of cisplatin was reported in “A549 lung adenocarcinoma cells” after lung injection of “gelatin-based NPs.” (Elzoghby 2013) NPs of doxorubicin released from polyisobutyl cyanoacrylate used for the treatment of macrophages resulted in secondary cytotoxicity to lung cancer cells after 8 and 24 h (Al-Hallak et al. 2010). In a different investigation, pulmonary administration of the hyaluronan-cisplatin compound demonstrated enhanced lung drug concentration compared to intravenous cisplatin after 24 h, with reduced tissue/plasma ratio both in kidneys and the central nervous system, lowering dose-limiting toxicities (Xie et al. 2010). Amreddy et al. created and assessed an NP approach based on a “folic acid (FA)–coupled PAMAM-dendrimer-polyethyleneimine” platform for the simultaneous delivery of “cisplatin, siRNA, and human receptor-R” for the treatment of lung cancer and they revealed that composite treatment utilizing “FA receptor (FAR)–targeted dendrimer nanoparticles demonstrated precision and specificity toward FAR–expressing cancer cells, improving the therapeutic effectiveness and also reducing the cytotoxic effects against healthy cells (Amreddy et al. 2018).

### Nanostructured lipid carriers

Nanostructured lipid carriers are composed of emulsifier dispersion in aqueous medium and partially liquid and solidified solid lipids; nanoscale lipid particles are distributed (Makled et al. 2017). This loosely packed crystalline

structure permits drug molecule entrapment, lowers drug leakage during storage, and permits regulated drug release (Iqbal et al. 2012). Additionally, it has been discovered that NLCs are distributed favorably in the organs, including the lungs, which may enhance cancer therapy other than lung cancer. The NLC system’s primary drawbacks are its limited drug loading capacity (Poonia et al. 2016).

NLCs are considered as potential vehicles for the fabrication of efficient individualized cancer chemotherapy therapies against NLC. These lipid-based nanoparticles that are biocompatible and/or biodegradable have a core matrix made of both solid and liquid lipids that is disseminated in a surfactant solution. Most hydrophobic cancer treatments are more soluble in water after NLC. Their surface modification can be employed to produce site-specific tailoring for enhanced efficiency as well as for decreased toxicities related to doses administered, which would help cancer treatment overcome drug resistance. The necessity of an early diagnosis in order to offer an appropriate prognosis and treatment options justifies the significance of a thorough lung cancer assessment. The first lung cancer categorization was offered at the beginning of the twentieth century, and it has been regularly updated to reflect both the rise in cases and the discovery of new subgroups of cell lung cancer (Travis et al. 2015). Many anticancer moieties have so far been effectively created as NLCs. The enhancement in the anticancer effectiveness of cytotoxic medications with fewer side effects has been demonstrated in preclinical research employing cell lines or animal models. Since they lack tumor selectivity characteristics, the majority of cytotoxic medicines have a limited therapeutic window that was previously indicated. The chosen dose is extremely close to the maximum tolerated dose, which makes it difficult to distribute the medication effectively. NLCs have recently demonstrated tremendous potential to target cancerous cells. Drug targeting that is passive or active can target tumor cells (Torchilin 2011). NLCs were recently designed to incorporate or connect multipurpose compounds including anticancer drugs, antibodies as well as ligands addressing MDR cancer cells, nucleic acids, or P-gp inhibitors to block different MDR contributors. The surface of MCF-7 cell line has overexpressed “breast cancer resistance protein (BCRP),” which promotes higher uptake of mitoxantrone hydrochloride (MTO) encapsulated dextran-conjugated NLCs than basic drug solution (Zhang et al. 2008, 2012). The exceptional drug uptake suggests that drug efflux, which is mediated by the breast cancer resistance protein (BCRP), has been inhibited. Docosahexaenoic acid (DHA)– and doxorubicin (DOX)–based NLCs with the resistant “MCF-7/ADR” cell line also demonstrated cytotoxicity at relatively low concentrations (16  $\mu$ M of doxorubicin and 112  $\mu$ M of DHA) (Mussi et al. 2014). Lipid nanoparticle carriers for bioimaging as well as for



anticancer treatments that are loaded with camptothecin and quantum dots were developed and tested by Hsu et al (Hsu et al. 2013). Excellent fluorescence labelling of cancer cells was seen in *in vivo* real-time tumor monitoring using fluorescent imaging. In comparison to the free drug solution, the produced theranostic NLC showed increased cytotoxicity to the B16-F0 melanoma cell line and camptothecin accumulations that were 6.4 times higher. For the therapy of lung cancer, Patel et al. created DIM-CpPhC<sub>6</sub>H<sub>5</sub> (DIM-P) and a tumor-homing PEGylated VEGF peptide (CREKA peptide) encapsulated theranostic NLC system (Patel et al. 2014). When compared to unconjugated NLCs, the developed system showed a threefold increase in attachment with protein molecules present in the tumor plasma site. Studies revealed that CREKA peptide-conjugated designed systems moved through tumor vasculature 40 times more than peptide-unconjugated NLCs. The NLC-based theranostic preparation of MgO NPs (manganese oxide nanoparticles) loaded with MMP2 cleavable peptide and cancer-targeting compound exhibited superior deposition inside the tumor and improved the MRI signaling (Patel et al. 2014; Savla et al. 2014). Remarkable antitumor effectiveness was seen *in vitro* with the BRAF (gene) inhibitor vemurafenib, which has been loaded into NLCs using Chinese hamster ovary cells (CHOK1), human lung (A549), ovarian (A2780), and melanoma (COLO 829) cancer cells, as well as *in vivo* using various cancer models. The development of well-organized means for delivering foreign genes, including siRNA or DNA, to tumor cells is a key component of gene therapy techniques. Recently, there has been a lot of interest in the potential of NLCs as a means of delivering genes (Xue and Wong 2011; Han et al. 2014a). The human lung cell line (A549 cells) *in vitro* cell viability study demonstrated more than 80% of cell viability against control. Shao and his colleague constructed paclitaxel (PTX)-loaded transferrin (Tf) NLCs (Shao et al. 2015). *In vitro* cytotoxicity study illustrated more than fourfold decline in the IC<sub>50</sub> value especially in comparison with PTX solution in limiting the viability of carcinoma cells, taking into account the maximum antitumor activity. Furthermore, the system demonstrated high *in vivo* and *in vitro* gene transfection efficacy. Similar to this, Chen et al. developed multifunctional NLCs for simultaneous DNA and temozolomide (TMZ) delivery (Chen et al. 2016). In an *in vitro* cytotoxicity research using U87MG cells, the formulation showed over fourfold decrement in IC<sub>50</sub> value compared to plain temozolomide, indicating that malignant glioma cells have the strongest anticancer effects. NLCs have several benefits as a potential delivery system for genetic material (i.e., DNA) with their increased transfection proficiency, such as lower cytotoxic nature along with higher gene loading efficiency (Han et al. 2016).

## Solid lipid nanoparticles

Colloidal nanocarriers called solid lipid nanoparticles (SLNs) circumvent the problems associated with liposomes, emulsions, etc. (Naseri et al. 2015). The medication is either embedded within the solid core of SLNs or is positioned on the exterior portion of the solid lipid that makes up SLNs. They are less susceptible to enzyme breakdown than other nanostructured systems, can resist mild pressure (such as nebulization), and are biocompatible (Duan et al. 2010). Additionally, the technology does not need organic solvents, which makes it easier to pilot scale-up production and gives the enclosed chemotherapeutic drug improved protection (Mishra et al. 2018). Unfortunately, the SLNs share the problem of inadequate drug entrapment with other colloidal systems. SLNs are recently developed substitutes for conventional colloidal delivery systems. SLNs demonstrate substantial potential for drug localization and retention at the actionable site via both passive and active targeting owing to their unique abilities to encapsulate hydrophilic as well as hydrophobic payloads in conjunction with nucleic acids and proteins. For sustained and precise medication and gene delivery, SLNs promise new vistas. Polymeric nanoparticles and liposomes are combined in SLNs, which avoids both acute and long-term toxicity (Scioli Montoto et al. 2020; Chen et al. 2017b). The biocompatible lipids in SLNs, which the body and lungs find bearable, were thought to contribute to their superior safety profile (Dolatabadi et al. 2015). They are therefore highly advised for the delivery of pulmonary drugs, whether in the form of suspension or dry powder, without causing inflammation (Liu et al. 2018). Physiological solid lipids, which are solid at body and room temperatures, have a major contribution to the formation of SLNs. These lipids are stable in surfactant-incorporated water, which aid in blending the aqueous phase (external) with internal lipid phase and preventing particle accumulation (Weber et al. 2014). Scalable nanocarriers with a large surface area and tiny particle size are known as SLNs. By optimizing absorption as well as retention (EPR) based on aberrations in tumor cell behavior including extreme vascularization and inadequate lymph drainage, small particle size of SLNs enables passive targeting, which is critical for improving drug localization at the site of action (Shen et al. 2015). Additionally, the surface of SLNs might be easily customized and embellished by A.O. Elzoghby et al. (2017) (Elzoghby et al. 2017). Additionally, utilizing the proper targeting moiety, which encourages the receptor-mediated endocytosis of nanocarrier toward tumor cells via active targeting based on fusion with receptors overexpressed in the cell surface, the surface of SLNs might be easily tweaked and embellished (Tolosa et al. 2006). In addition to proteins and nucleic acids, the solid-lipid nanostructure has the capacity to incorporate both lipophilic and hydrophilic

drugs. The entrapment efficiency depends on a number of factors, including the drug's solubility in lipid, polymorphous state of lipid, lipid-matrix physico-chemical structure, and its miscibility with lipid (Gaber et al. 2017). SLNs are considered a good option for lipophilic drugs for improving the aqueous solubility and bioavailability and ultimately maximize the therapeutic efficacy like chemotherapeutic agents as etoposide, doxorubicin, and paclitaxel. Decoration of targeting ligands on the surface of SLNs by using PEG is also a facile approach preferentially accumulation at the site of action (Yu et al. 2010; Sahu et al. 2015). PEGylation, on the other hand, consequently increases the ability of SLNs to penetrate and accumulate at the tumor site. Cationic SLNs are one of the types that may be considered for enhancing tumor permeability and enhancing therapeutic effectiveness (Elzoghby et al. 2016). In comparison to bigger particles, SLNs offer superior internalization and higher transfection because of their smaller particle size (below 100 nm). Additionally, negatively charged DNA interacts electrostatically with positively charged SLNs to form lipoplex, which enhances cellular uptake. In several lung cancer cell lines, the wildtype p53 gene plays a critical role in tumor suppression (Choi et al. 2008). Unfortunately, p53 mutations are linked to more than 50% of NSCLCs. In order to defeat lung cancer, it is essential to reintroduce or overexpress the p53 gene in mutant cells. Adenovirus vectors that express p53 were successfully transduced into NSCLC patients by Roth et al. Phase I/II of a clinical trial saw the introduction of this tactic with success. These results corroborated other studies that demonstrated the efficacy and safety of transfecting p53 genes to inhibit the spread of cancer (Choi et al. 2008). Utilizing the melt homogenization approach, a brand-new, stable cationic SLN formulation was created to effectively transport p53 to NSCLC mutant cells. Tricaprin (TC) was the core forming lipid bilayer in this study, with cationic lipid “3b [N-(N0, N0-dimethylaminoethane)carbamoyl] cholesterol (DC-cho),” helper lipid “dioleoylphosphatidylethanolamine (DOPE),” and surfactant “Tween-80” being used. Overexpression of typical oncogenes such as “signal transducer and activator of transcription-3” which operate as apoptosis inhibitors caused multidrug-resistance (MDR) STAT3. Overexpression of STAT3 in NSCLC was a sign of poor prognosis. To inhibit the STAT3 and enhance the effect of anticancer drugs, numerous strategies are used, such as use of chemotherapeutic moiety, STAT3 inhibitors, and siRNA (small interfering RNAs). MDR can be defeated by STAT3 suppression at the mRNA level (RNA interference, RNAi) (Kotmakçı et al. 2017). However, since nucleic acids are susceptible to nuclease enzyme breakdown, direct administration of nucleic acids is not practical. A cationic SLN loaded with “plasmid encoding antiSTAT3-short hairpin RNA (STAT3-shRNA)” was synthesized. MicroRNAs (miRNAs) are small (18e24 nucleotide) endogenous

noncoding RNAs that operate post-transcriptionally. As an oncogene, microRNA21 (miR-21) is a well-known miRNA that has been linked to tumor metastasis in lung cancer. When overexpressed, miR-21 inhibits apoptosis and promotes proliferation. The “anti-miRNA oligonucleotide (AMO)” has enormous potential for preventing cancer (Shi et al. 2012). One promising method for overcoming MDR and improving therapeutic outcomes in lung cancer patients is to combine chemotherapy and gene (nucleic acid) delivery. Targeting drugs directly to the lungs, whether for localized or systemic treatment, is now possible thanks to pulmonary drug delivery (Elzoghby et al. 2015). Effective pharmacokinetic features, capability of solute exchange, high bioavailability, thin alveolar epithelium, large surface area, and a strong inclination to avoid the first-pass effect are all the facts of this strategy based on the special characteristics of lungs (Uchenna Agu et al. 2001). The biocompatible lipids that are extremely well tolerated by the body and lungs form the foundation of the SLNs safety profile. Proteins and nucleic acids can be included into SLNs together with hydrophilic and lipophilic medicines, opening up new possibilities for medication and gene delivery.

## Dendrimers

Dendrimers are polymeric nanoparticles that were initially discovered at the end of the 1970s (Tomalia and Fréchet 2002). Dendrimers are synthesized nano-constructions having three-dimensional architectures that are repeatedly branched and radially symmetrical. The surface of the dendrimers is made up of terminal chemical structures that are covalently bonded to a core of highly repetitive units (Sandoval-Yañez and Castro Rodriguez 2020). Dendrimers are adaptable polymers because of their known molecular weight, nanoscale, and monodisperse nature, as well as their aptitude for encapsulating both hydrophilic and hydrophobic chemotherapeutic drugs (Parajapati et al. 2016). Additionally, their multipurpose surface makes surface modification for targeted distribution simple. Such a smart drug delivery system has the potential to release the drug at a specified site after coming into contact with specific enzymes with the outer functional groups, the medication can also be delivered in a regulated manner in which mAbs and RGD peptide like targeting molecules are employed, and including Doxorubicin (DOX) and paclitaxel (PTX) like hydrophobic medications is commonly used (Hu and Zhang 2012; Mattheolabakis et al. 2012; Lim and Simanek 2012). Drug delivery can also be accomplished using dendrimers that self-assembled into micelles, such as poly(glutamic acid)-b-poly(phenylalanine) copolymers (Webster et al. 2013). Amphiphilic diblock copolymers forming micelles are being used in numerous clinical trials to deliver paclitaxel for the treatment of advanced pancreatic cancer, non-small cell lung

cancer, and breast cancer. Human breast adenocarcinoma (MCF-7), colorectal adenocarcinoma (HT-29), non-small-cell lung carcinoma (NCI-H460), and glioblastoma (SF-268) were utilized to investigate the antitumor proficiency of the dendrimer loaded with camptothecin (Morgan et al. 2006). A study demonstrated the usage of dendrimer-targeting peptide conjugates for NSCLC (Liu et al. 2011). These dendrimer-peptide conjugates were successfully absorbed by the tumor cells when administered to a mouse model with a lung tumor, suggesting their promise as a therapeutic vehicle for the targeting and management of tumor. In a separate investigation, a newly developed “PEGylated dendrimer nanoparticle” showed potential as DDS based on aerosol mechanism (Ryan et al. 2013). While larger dendrimer particles are said to be trapped in the lung for a long time, smaller dendrimer particles are said to enter the bloodstream through inhalation. In the future, injectable medication delivery methods could be replaced by this approach of controlled release drug delivery system (CRDDS) to the lungs.

### Metal-based nanoparticle

As drug delivery techniques in the treatment of NSCLC, various kinds of metal-based nanoparticles, including quantum dot, carbon nanoparticles, gold, and silver nanostructures, have been studied. The acceptable biocompatibility of metal-based nanoparticles and their simplicity in size and surface modification are the main causes of the exponential expansion in this field of research. They are useful for intracellular tracking due to their visible light extinction capabilities (Oerlemans et al. 2012). Due to its greater ability to load drugs due to pi-pi stacking between graphene sheets, in graphene, a monolayer made up of carbon atoms organized in the form of a honeycomb-like hexagonal lattice structure is now receiving a lot of attention (SreeHarsha et al. 2019). To make the most of graphene's use in drug delivery systems, a thorough understanding of its physico-chemical properties is still lacking (Yang et al. 2019b). A thorough analysis of the use of graphene as a versatile platform for the delivery of drug molecules was presented by Hoseini-Ghahfarokhi et al (Hoseini-Ghahfarokhi et al. 2020).

Strategy and research investigation of metallic nanocarrier, such as silver and gold, aimed toward biomedical and biopharmaceutical characteristics have advanced significantly in recent years. The noble metal gold nanoparticles stand out among these because of their surface-plasmon resonance-enhanced optical capabilities, which have been used recently in biomedical applications with a focus on the detection and treatment of cancer, particularly lung cancer (Huang et al. 2007). Gold nanoparticles have recently been tried with success as sensing agent/diagnostics for identifying and categorizing pathophysiology of various lung cancers. The sensor could differentiate between malignant

and healthy cells, SCLC and NSCLC, and two subtypes of LCs (Barash et al. 2012). In a study on Lewis lung cancer animal model, methotrexate (MTX) linked gold nanoparticle, a medication with excellent hydrophilic nature and minimal tumor retention, demonstrated substantial tumor retention and improved therapeutic efficacy (Chen et al. 2007). Numerous studies have been conducted on magnetic nanoparticles, and they have been used in the detection and therapy of numerous malignancies. The delivery of therapeutic drugs and imaging are both made easier by theranostic nanoparticles. A noninvasive treatment method for lung cancer called magnetic hyperthermia involves the heat-induced ablation of desired tumor tissue. Superparamagnetic iron oxide (SPIO) nanoparticles, for example, are magnetic materials that, when exposed to alternating currents, produce sublethal heat that damages local tissue. One study used a mouse model of NSCLC and found that the tumor-targeted SPIO nanoparticles were very effective at inhibiting tumor development and destroying tumors through hyperthermia (Sadhukha et al. 2013a). Because of their variable drug encapsulation potential, controlled release of drugs characteristic, and versatility, “mesoporous silica nanoparticles (MSNs)” have become more frequently utilized as a novel carrier for the delivery of chemotherapeutic agents. Mesoporous silica nanoparticles (MSNs) were the subject of the first study on their viability in vivo, which was released by the Mou group in 2008 (Wu et al. 2008). For animal magnetic resonance imaging studies and intracellular labelling, multifunctional mesoporous silica nanoparticles have been employed. MSNs are largely internalized by human lung cancer cells via endocytosis (Sun et al. 2008). The development of a cancer-targeted mesoporous silica nanoparticle-associated DDS was created for the inhalation-based treatment of lung cancer. The technology was capable of delivering chemotherapeutic medications (cisplatin and doxorubicin) combined with two categories of siRNA tailored to “MRP1 and BCL2 mRNA” in order to successfully reduce pump and non-pump cellular resistance in NSLC (Taratula et al. 2011). Mesoporous silica nanoparticles were capable of targeting tumor cells because of “LHRH peptide” being conjugated to its surface employing a poly(ethylene glycol) (PEG) as linker.

### Silver nanoparticles

Fluorescence imaging, biosensors, anticancer applications, and other biological uses of silver nanoparticles have all been around for a while (Mukherjee et al. 2014). He et al. recently showed that biosynthesized silver nanoparticles (AgNPs) have anticancer potential (He et al. 2016). By using the trypan blue and MTT assays, the AgNPs showed a powerful cytotoxic effect. Mechanistic investigations revealed that AgNPs led to apoptosis in lung cancer cells. AgNPs'

cytotoxicity is substantially influenced by their morphology, surface chemistry, size, and shape (Stoehr et al. 2011). Jeong and his group of researchers investigated the fundamental phenomenon of hypoxia on silver nanoparticle-induced apoptosis and found that HIF-1 expression was upregulated in both normoxic and hypoxic circumstances. Additionally, whereas normal cells did not experience programmed cell death from the AgNP treatment, lung cancer cells did. Significantly, HIF-1 prevented the AgNP-induced apoptotic phenomenon by regulating the autophagosome flux via the LC3-II, p62, and ATG5. The results of the research suggest that HIF-1 could be a potential candidate for lung cancer treatment by using hypoxia-mediated autophagy to prevent AgNP-mediated apoptosis (Jeong et al. 2016).

### Iron oxide nanoparticles

In addition to their widespread usage as MRI contrast agents, super-magnetic iron oxide nanocarriers may be employed as a delivery mechanism in cancer theranostics applications. Iron oxide nanoparticles have a wide range of medical applications, including long-standing usage in cancer theranostics MRI imaging, magnetic hyperthermia, and medication delivery, in lung cancer (Noh et al. 2009). Wang et al. (2017) have published a study on iron oxide nanoparticle-based targeted ultrasonic ablation therapy for lung cancer (Wang et al. 2017). In a different work, inhalable Fe<sub>2</sub>O<sub>3</sub>NPs that are targeted at the EGFR have been shown by Sadhuka et al. to cause hyperthermia associated with magnetic field in lung cancer (Sadhukha et al. 2013b). The researchers demonstrated that EGFR targeting improved iron oxide nanoparticles' tumor retention. Additionally, EGFR-targeted iron oxide, a nanoparticle, was demonstrated in *in vivo* magnetic hyperthermia treatment in *in vivo* orthotopic lung cancer models by resulting in significant suppression of growth in lung cancer.

### Other metal nanoparticles

For theranostics applications in lung cancer, silica, nano-diamond, and rare earth were utilized, among other nanoparticles (Sadhukha et al. 2013b). *In vitro* and *in vivo* lung cancer imaging using near-infrared tumor targeting and p53 gene therapy was demonstrated by Wu et al. (2015) using a silica-polymer nanocomposite (Wu et al. 2015). When treating lung cancer, paclitaxel was also delivered via a nano-diamond (ND). In a lung cancer cell model, this nanodrug delivery significantly reduced tumor size in immunodeficient animals. According to mechanistic investigations, ND triggered mitotic arrest and apoptosis, which killed lung cancer cells. In a different experiment, Chen et al. showed that Nd<sub>2</sub>O<sub>3</sub> nanoparticles at micromolar concentrations can significantly vacuolate NSCLC cells and trigger

a lot of autophagy (Chen et al. 2005). In order to deliver several siRNAs (EGFR and cyclin B<sub>1</sub>) to lung cancer cells and for bioimaging, Wu et al. (2016) synthesized quantum dot-based carbon nanomaterial with multifunctional moiety attachment on the surface for the establishment of a potential nano-agent (Wu et al. 2016). When activated at 360 nm, this agent creates a visible blue photoluminescence that may be used for bioimaging. Additionally, it was found that this nanodrug preferentially aggregated in cells of lung cancer via endocytosis mediated by the receptor, elevating silencing of gene as well as its anticancer efficacy.

### Carbon nanotubes

Despite numerous attempts by professional teams treating lung cancer, a lot of people continue to pass away every year as a result of this. The prevalence of lung cancer is widely acknowledged as being among the most pervasive malignancies on a global level. Nanotherapy is a novel therapeutic approach that is currently under investigation by experts for the management of non-small cell lung cancer (NSCLC). The disease can be effectively treated by carbon nanotubes (CNTs) themselves by activating the apoptotic pathway by concentrating on the organelle of mitochondria in cancer cells. Accordingly, CNTs coupled to polyethylene glycol may be able to target cancer cell repertoires more effectively, thereby enhancing the effectiveness of nanodrug delivery (Kim et al. 2017). In addition to graphene oxide, the anticancer medication paclitaxel also formed bonds with SWCNTs. This nanostructure improved the efficiency and caused the death of cancer cells A549 and NCI-H460 (Arya et al. 2013). SWCNT modified with chitosan was the subject of a different investigation to deliver this medication and increase *in vivo* compatibility. Hyaluronic acid has also been added to the layer of chitosan to specifically target A549 cells (Yu et al. 2016). Because of the enhanced distribution along with the magnetic localization, doxorubicin delivery by SWCNTs can improve targeting and boost therapeutic effectiveness. The results of boosting the effectiveness of therapy by using MRI technology were in fact validated by this experiment, which was carried out on mice (Al Faraj et al. 2016). In a 2018 study, curcumin was examined in a nano-state using a SWCNT carrier, a substance created with therapeutic promise for A549 cancer cells. The drug's effectiveness was improved by the carrier, which worked with the polysaccharides in chitosan and alginate (Singh et al. 2018). Gemcitabine is one anticancer drug for non-small cell lung cancer. The medication was evaluated employing a SWCNT carrier in a clinical experiment on B6 mice. The A549 cell line, which displays intriguing suppression results, was the subject of this investigation. Because of the substantial loading propensity of the medicine, the extended time of distribution, and the remarkable permeability of the



cell membrane, this study has clearly validated SWCNTs as stimulating carriers for the administration of medications (Razzazan et al. 2016). To reduce drug waste and use it in the intended manner, methotrexate may be conjugated with MWCNTs for the treatment of lung cancer. Animal experiments also showed that this compound had no negative effects on the heart, liver, or kidneys (Das et al. 2013). The anticancer activity of the betulinic acid-loaded MWCNTs with acid functionality can be measured using thermogravimetric and UV light. Actually, certain medication concentrations made lung cancer cells more susceptible (Tan et al. 2014).

### Biological system-based nanoparticles for lung cancer theranostics

The incorporation of a bio-mimicking constituent into medicinal nanostructures emerged as the primary topic of recent investigation. This is because of the excellent biodegradability, stability, and biocompatibility of bio-based nanoparticles, which include apoferritin, aptamers, viral-based nanoparticles, SLNs, polymeric nanoparticles, and protein nanoparticles (Sivarajakumar et al. 2018). These kinds of nanoparticles have been successfully created, manufactured, and applied for cancer theranostics purposes in NSCLC (Rizvi et al. 2008).

#### Viral nanoparticles

Investigators are intrigued by viral nanoparticles (VNPs) produced by viruses or bacteriophages for a variety of biological functions, such as drug delivery, biomedical imaging, biosensing, and vaccine production. This is attributable to the viral nanomaterials' biocompatibility, adaptability in shapes and sizes, and convenience of surface alteration (Li et al. 2020a). In an effort to combat the challenges posed by drug tolerance, a number of investigators have developed a therapeutic strategy for lung cancer that combines chemotherapy and immunotherapy.

#### Protein-based nanoparticles

Due to their exceptional biomedical applications, lack of inflammatory response in human pulmonary cell lines, and enhanced cellular uptake, protein nanomaterials having natural polypeptides like legumin, gliadin, albumin, and gelatin have been recently utilized in the delivery of therapeutic agents whether alone or in combination form with biodegradable polymers in the management of lung cancer (Lohcharoenkal et al. 2014). Employing “cationic

bovine serum albumin (CBSA),” siRNA has been administered for the management of metastatic lung cancer (Han et al. 2014b).

#### Apoferritin

Apoferritin is a “ferritin-based multifunctional nanocarrier” utilized to demonstrate the detection of lung cancer in A549 cells by utilizing both fluorescence and MR imaging (Dostalova et al. 2017; Li et al. 2012). This multipurpose apoferritin was employed to image cancer cells with increased  $\alpha v \beta 3$  integrin. Another study done by Luo and his researcher group showed the utilization of daunomycin encapsulated apoferritin nanocages coupled to hyaluronic acid (HA) employed for intracellular distribution and liberation of anticancer drug daunomycin based on a pH-responsive system (Luo et al. 2015).

### Treatment and diagnosis of lung cancer: stimuli-responsive drug delivery systems

#### Light-responsive nanocarriers

Light has indeed frequently been utilized for remote drug regulation because of its generally high level of safety and non-intrusive nature (Li et al. 2020b). For on-demand medication release, photolabile groups can be directly destroyed by short-wavelength light, like visible light or UV. Their inability to penetrate deeply, however, limits their potential for use in biomedicine. Since near-infrared (NIR) light (780–2500 nm) may permeate the tissues more deeply than short-wavelength light, it is necessary for the release of medication in a controlled manner inside the biological system. When activated by light, some nanoparticles can significantly enhance local temperatures or activate/stimulate “reactive oxygen species (ROS),” which might be used to treat malignancies. In addition, external light sources also cause the therapeutic system's structural changes and the quick dissolution of photolabile groups (Ko et al. 2019). These two methods of therapy are referred to as photothermal therapy (PTT) and photodynamic therapy (PDT). For particular, employing oxygen-boosted immunogenic PDT, researchers created core-shell gold nanocage@manganese dioxide (AuNC@MnO<sub>2</sub>) nanoparticles to concurrently eradicate intrinsic triple-negative breast cancer and thereby preventing metastasis of the lung (Liang et al. 2018) and to enhance the antitumor effectiveness while reducing adverse effects by combining various therapeutic modalities (such as PTT, PDT, immunotherapy, and chemotherapy). In the interim, the ROS as well as the heat effects produced by PTT or PDT may possibly cause the drug to be released. Drug release induced by light can potentially be paired with

other stimuli, such as pH, enzyme, and glutathione on the inside and other external stimuli (like radio frequency) on the outside, for improved targeted therapy for lung cancer (Li et al. 2021; Gou et al. 2020; Liu et al. 2019; Pan et al. 2019). Light-responsive therapies, as previously mentioned, have a variety of advantages and show tremendous promise for the therapeutic treatment of lung cancer. Furthermore, during the course of the treatment, light-absorbing molecules that produce temperature or increase “ROS” can emit fluorescence or convert the temperature into something like a photoacoustic (PA) signal. These compounds are used in imaging diagnosis.<sup>181</sup>

### pH-responsive nanocarriers

Tumor cells have a significantly more acidic environment (pH 5.7–6.9) due to the presence of lactic acid and perhaps by some end products formed by lung carcinoma cells that is linked to an unusual accelerated metabolism as well as the proliferation in contrast to normal physiological tissues (Kanamala et al. 2016). Besides increasing the accrual of nanocarrier in tumor cells and strengthening the consistency and protection of therapeutic strategies for the treatment of lung cancer, the release of drug/chemotherapeutics can be controlled inside the tumor microenvironment or even can minimize the drug release to the tumor by employing pH-sensitive nanoparticles. Lee and team discovered that an acidic pH could effectively activate cholesteryl hemisuccinate (CHEMS)-based liposomes, indicating that pH-sensitive nanostructures loaded with anticancer drugs have exceptional anticancer activity against NSCLC. The poor outlook of NSCLC patients was attributed to the folate receptor beta (FR) that was commonly highly expressed in M2 tumor-associated macrophages (TAMs) as well as NSCLC cells (Park et al. 2021). To make pH-sensitive liposomes for regulated drug release, CHEMS (which is unstable in acidic conditions) was coupled to PEG-folate. A mixed micellar system including poly-benzyl-glutamate and d-tocopherol polyethylene glycol succinate may be able to modify the secondary poly-benzyl-glutamate complexes by regulating the release of DOX. The DOX encapsulated conjugated/mixed micelles showed exceptional therapeutic effects against lung cancer when used on naked mice injected with human lung cancer A549 cells (Shih et al. 2020). For the management of lung carcinoma, the acidic pH of the tumor microenvironment could also cause charge reversal to encourage intracellular uptake and nuclear translocation. Despite indiscriminate adsorption, nanocomposites having positive exterior potential often have shorter circulation of blood half-lives. This issue was rectified by using TAT peptide by increasing tumor cells' absorption of the drug. Anhydride (DA) groups can hide TAT's positive charges. After the aggregation of carriers in the tumor's acidic medium, the charge was flipped

from negative to positive, restoring TAT's targeting potential. To combat lung tumors, Jing et al. created a “DA-TAT” vehicle for pH-responsive nuclear targeting and cellular uptake (Jing et al. 2018). Shi et al. constructed pH-triggered nanocomposite utilizing a tri-block copolymer consisting of “poly(sulfadimethoxine), methoxy poly (ethylene glycol)-poly(histidine), and poly(histidine) as mPEG-PHis-PSD.” PSD's charge was immediately changed from negative to neutral by an acidic pH, which caused it to quickly dissociate from the lipid core. This made it possible for NSCLC medication to effectively internalize, accumulate specifically in tumors, and have an anticancer effect (Shi et al. 2018).

### Enzyme-responsive nanocarriers

In order to sustain an organism's regular processes, such as development, growth, disease, metabolism, immunity, and aging, enzymes are crucial biomolecules. Abnormal enzymatic expression was commonly observed in several illnesses' cellular microenvironments, particularly in lung cancer (Chen et al. 2018; Sharma et al. 2018). Hyaluronidase (HAase), matrix metalloproteinases (MMPs), esterase, quinone oxidoreductase, and NADPH are the most commonly overexpressed enzymes (NQO1). Due to the selectivity, efficacy, and speed of enzymatic responses in treating lung cancer, enzyme-responsive nanoparticles have received a lot of interest (Shahriari et al. 2019; Wang et al. 2018). For instance, the MMP family of proteolytic zinc-dependent secreted endopeptidases may precisely break down a range of extracellular matrix components (ECMs). The introduction of drug delivery based on enzyme-responsive devices may take advantage of abnormally high MMP expression in lung carcinoma tissues (Egeblad and Werb 2002). For targeted lung cancer therapy, MMP-responsive peptides or gelatin is typically adhered to the surfaces of nanoparticles (Fan et al. 2017). This is predicated on the notion that collagen as well as basement membrane can be preferentially broken down by MMP-2 and MMP-9. Gianneschi constructed an MMP-9-associated nanostructure for the purpose of delivering the “immunotherapeutic small molecule (1V209)” for stimulation of the immune system. The previously stated platform improved medication efflux and prevented lung tumor spread in vivo (Li et al. 2019). Additionally, gelatin can act as the carrier skeleton and serve as a substrate for MMPs. As the extensive treatment approach of lung tumors, the complexed gelatin and cisplatin create an intelligent inhalable nanocarrier. When subjected to physiological solutions, cisplatin was swapped with chloride ions after gelatin was broken down, which caused the drug to be quickly released at the tumor location (Vaghasiya et al. 2021). To enhance the efficiency of treatment for lung cancer, HAase is typically coupled with multi-responsive nanoparticles. The hydrophilic shell was built using hyaluronic acid (HA), and hydrophobic chemicals

could be added to the HA structure via a conjugation mechanism. In contrast, by employing pH-sensitive hydrazone couplings, Tang and coworkers developed hyaluronic acid (HA) NPs that are both pH and enzymatic responsive (Ren et al. 2019). He and colleagues created HPGBCA nanostructure for the delivery of “afatinib” via carrier-mediated targeting mechanism for the management of NSCLC therapy. Another excellent option is an esterase-sensitive nanocarrier which has been employed to deliver chemotherapeutics toward lung cancer cells based on enzyme-responsive phenomena. For the treatment of lung cancer, Cho and colleagues created the HAPBA nanoparticle, which would release medications in an esterase-rich environment within the tumor tissue. HA was conjugated 4-phenylbutyric acid (PBA) via ester linkage to regulate and control the rapid liberation of PBA-curcumin. PBA served as both the hydrophobic section and an effective histone deacetylase inhibitor in the formation of these nanoparticles (HDAC). When ester bonds were broken, curcumin and PBA were released quickly, effectively slowing down the growth of lung adenocarcinomas (Lee et al. 2019). A curcumin-gold nanorod coupled nanostructure was created by using an “esterase-labile ester link” demonstrated by Ren et al. This compound displayed a curcumin release that was both quick and consistent (Ren et al. 2019). In the absence of esterase, the amount of loaded therapeutic agent was fully constrained within the nanomaterials. Curcumin was released suddenly as esterase concentration increased, indicating that ester hydrolysis was a crucial catalyst for drug release. As a result, the nanorod-associated curcumin-coupled nanocarrier inhibitory potential on human lung cancer cells (A549) was enhanced by the introduction of the ester linkage (Zhu et al. 2018).

## Vaccine-based therapy for NSCLC

Historically, the word “vaccine” has been associated with the medical practice of treating infectious disorders by the induction of humoral immunity toward infectious agents. In the process of developing therapeutic vaccines, several forms of vaccinations have acted as a source of motivation (Banchereau and Palucka 2018). The former are intended to cure a condition by enhancing the cellular and humoral responses of the immune system, particularly those of T cells. The discovery of mutant proteins that are undesirably produced by cancer cells gave birth to the idea of developing a vaccination for cancers. These are recognized by the immune function as “tumor-associated antigens (TAA),” and they are able to be separated into two categories: expressed fetal antigens, which are ordinarily lacking in healthy adults, and overexpressed normal proteins (Cuppens and Vansteenkiste 2014; Cortés-Jofré et al. 2019). The basic operating concept of medicated vaccinations is that they function by

instructing the immune system to detect and react appropriately to certain antigens. Numerous vaccination approaches, such as whole-cell (Xia et al. 2016; Ward et al. 2002) peptide/protein-based (Wada et al. 2017) and mRNA-associated (Sebastian et al. 2011, 2014) vaccines have been investigated as potential treatments for non-small cell lung cancer (NSCLC) (Table 1). In this essay, we will concentrate on mRNA, peptide, and protein, peptide since there have been some noteworthy breakthroughs surrounding the encapsulation of these types of vaccines utilizing nanoparticles.

## Nanoparticle-associated ongoing clinical trials for management of NSCLC

The therapeutic effects of nanoparticles are mostly determined by their function, which is also highly determined by their shape and materials (Shi et al. 2017b). Additionally, by changing these properties, it is feasible to employ them as contrast agents for CT/PET imaging methods, consequently establishing multifunctional theranostic platforms (Li et al. 2016b). The researchers were capable of identifying possible targets for repurposing depending on the mode of action by employing different repurposing methodologies. Nevertheless, there were only a few medications that made it to the level of clinical trials. Glucocorticoids are the most prevalent class of pharmaceuticals in clinical studies exploring prospective therapies for repurposing in the management of non-small cell lung cancer. The recent/ongoing clinical investigation for the treatment of NSCLC based on nanoparticle system is mentioned in Table 2.

## Conclusions and future perspectives

In conclusion, fresh applications for usage in cancer diagnosis, detection, imaging, and treatment are constantly being developed, demonstrating the limitless promise of nanoparticle-based medicine. Nanoparticles are the best delivery systems for the treatment of lung cancer because they may be specifically designed for a personalized medicine approach. Recognizing cancer physiology, tumor’s microenvironment, and the engagement of tumor cells with nanoparticles is essential for the future development of various techniques to specifically deliver medications to lung tumors and lung metastases. Oncologists now have a larger selection of medications at their disposal thanks to polymer conjugates and particulate nanocarriers. These currently rely on passive tissue targeting rather than active cellular targeting, primarily through EPR. Theranostics, or individualized treatment for cancer, is based on a personalized prescription and therefore it is evidence-based to ensure the precise administration of medicines or the effective treatment at the correct time, improving the patient’s

**Table 1** Vaccine-associated ongoing investigation for management of NSCLC

Vaccine system	Title of clinical trial	Clinical trial phase	NSCLC-stage	ClinicalTrials.gov identifier	References
DNA vaccine	“NY-ESO-1 plasmid DNA (pPJV7611)”	I–II	III–IV	NCT00199849	ClinicalTrials.gov Identifier:NCT00199849 (2005)
	“Plasmid encoding neopeptides (VB10. NEO) and Bempegaldesleukin (NKTR-214)”	I–II	III–IV	NCT03548467	ClinicalTrials.gov Identifier:NCT03548467 (2018)
mRNA vaccine	“Autogene Cevumeran (RO7198457) as a Single Agent and in Combination With Atezolizumab”	I	II–IV	NCT03289962	ClinicalTrials.gov Identifier:NCT03289962 (2017)
	“mRNA-5671/V941 as Monotherapy and in Combination With Pembrolizumab (V941-001)”	I	III–IV	NCT03948763	ClinicalTrials.gov Identifier:NCT03948763 (2019)
	“messenger ribonucleic acid (mRNA) Vaccine [BI 1361849] + anti-programmed death ligand 1 (PD-L1) [durvalumab] + anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody”	I–II	III–IV	NCT03164772	ClinicalTrials.gov Identifier:NCT03164772 (2017)
Peptide vaccine	“Phase III Trial of OSE2101 as 2nd or 3rd Line Compared With Standard Treatment (Docetaxel or Pemetrexed) in HLA-A2 Positive Patients”	III	III–IV	NCT02654587	ClinicalTrials.gov Identifier:NCT02654587 (2016)
	“Therapeutic Vaccination Using Telomerase-derives Universal Cancer Peptides in Metastatic Non Small Cell Lung Cancer”	I–II	III	NCT02818426	ClinicalTrials.gov Identifier:NCT02818426 (2016)
	“EMD531444(L-BLP25 or BLP25 Liposome Vaccine)”	I–II	III	NCT00960115	ClinicalTrials.gov Identifier:NCT00960115 (2009)
	“UV1 Vaccination (UV1-hTERT2012L)”	I–II	III	NCT01789099	ClinicalTrials.gov Identifier:NCT01789099 (2013)
	“IDO peptide with With Immune Stimulating Agent Aldara and the Adjuvant Montanide”	I	III–IV	NCT01219348	ClinicalTrials.gov Identifier:NCT01219348 (2010)
Protein vaccine	“Recombinant PRAME protein combined with the AS15 Adjuvant System GSK2302032A”	II	I–IIIA	NCT01853878	ClinicalTrials.gov Identifier:NCT01853878 (2013)
	“Tumor Antigen-loaded Dendritic Cell-derived Exosomes (CSET 1437)”	II	III–IV	NCT01159288	ClinicalTrials.gov Identifier:NCT01159288 (2010)
	“Vaccine gp96-Ig Fusion Protein (Ad100-gp96Ig-HLA A1)”	I	III–IV	NCT00503568	ClinicalTrials.gov Identifier:NCT00503568 (2007)
	“MUC1 Peptide—Poly-ICLC (Polyinosinic-polycytidylic Acid Stabilized With Polylysine and Carboxymethylcellulose) OR HILTONOL™ Adjuvant Vaccine”	I–II	III	NCT01720836	ClinicalTrials.gov Identifier:NCT01720836 (2012)



**Table 1** (continued)

Vaccine system	Title of clinical trial	Clinical trial phase	NSCLC-stage	ClinicalTrials.gov identifier	References
Cellular vaccine	“DCVAC/LuCa Added to Standard First Line ChT With Carboplatin and Paclitaxel ± Immune Enhancers (Interferon- $\alpha$ and Hydroxychloroquine)” (Allostim®)	I–II	IV	NCT02470468	ClinicalTrials.gov Identifier:NCT02470468 (2015)
	“Autologous dendritic cells pulsed with allogenic tumor cells” (MeiCancer-Vac®)	II	III–IV	NCT00442754	ClinicalTrials.gov Identifier:NCT00442754 (2007)
	“Allogenic whole tumor cells” (Lucanix®)	III	III–IV	NCT00676507	ClinicalTrials.gov Identifier:NCT00676507 (2008)
	“MIDRIXNEO-LUNG, an Autologous Neoantigen-targeted Dendritic Cell Immunotherapy”	I	III–IV	NCT04078269	ClinicalTrials.gov Identifier:NCT04078269 (2019)
	“Allogeneic Cellular Vaccine 1650-G”	II	I–II	NCT00654030	ClinicalTrials.gov Identifier:NCT00654030 (2008)

condition and lowering the cost of drugs and services. Using a delivery platform based on nanotechnology, theranostics medicine is used to deliver imaging and therapeutic substances to the predetermined specific location via site-specific targeting (i.e., lung cancer cell). Nanomaterials have shown to be extremely useful tools and are now being used in medical settings. Due to their new physical characteristics, nanostructures can frequently resolve problems with solubility as well as stabilization via interface modifications or supplementary preparations. Targeted drug delivery and diagnostics nanostructures are made possible by the assimilated method of integrating biomacromolecules, carriers, medications, and diagnostic material. The nanometric size range molecules have larger surface area which contributes to the higher therapeutic payload as well. Targeting specific cancer cells with nanoparticles

and delivering therapeutic payloads to cancer areas with precision through “active and passive targeting” can greatly lower nonspecific cytotoxicity. Despite the benefits, there are still many obstacles that need to be resolved, like cost-effective manufacturing, scale-up concerns, imaging approach, and the pharmacokinetics of drugs. To see lung cancer theranostics reach the clinic, more concerns with nanotoxicity and regulatory rules and barriers need to be tackled. Although nanotechnology has made significant progress, it is still not being utilized to its full potential in lung and other cancers. Stronger sequencing, immunohistochemistry, and proteomic techniques are now available, which will lead to a greater understanding of the mechanisms behind cancer as well as the discovery of novel, conclusive biomarkers. The development of key genomic programs like the “human protein atlas, cancer

**Table 2** Nanoparticle-associated ongoing clinical trials for management of NSCLC (Doumat et al. 2023)

Nanoparticles	Drug employed	Condition-stage	Clinical trial phase	ClinicalTrials.gov identifier	References
Liposome	Lurtutecan	NSCLC IIIB	I	NCT00006036	ClinicalTrials.gov Identifier:NCT00006036 (2004)
	Camptothecin	NSCLC IIIB-IV	Preclinical	NCT00277082	ClinicalTrials.gov Identifier:NCT00277082 (2006)
	Doxorubicin	NSCLC IIIB	I	NCT01051362	ClinicalTrials.gov Identifier:NCT01051362 (2010)
	Doxorubicin	NSCLC IIIB-IV	II	NCT00020124	ClinicalTrials.gov Identifier:NCT00020124 (2003)
Polymeric micelle	Paclitaxel	NSCLC IV	II	NCT01023347	ClinicalTrials.gov Identifier:NCT01023347 (2009)
	Paclitaxel	NSCLC	III	NCT02667743	ClinicalTrials.gov Identifier:NCT02667743 (2016)
Nanoparticles	Paclitaxel	NSCLC II	II	NCT01620190	ClinicalTrials.gov Identifier:NCT01620190 (2012)
	Docetaxel	NSCLC	II	NCT02283320	ClinicalTrials.gov Identifier:NCT02283320 (2014)
	Docetaxel	NSCLC	II	NCT01792479	ClinicalTrials.gov Identifier:NCT01792479 (2013)
	Carboplatin	NSCLC IIIB-IV	II	NCT00729612	ClinicalTrials.gov Identifier:NCT00729612 (2008)

proteome studies, and The Cancer Genome Atlas (TCGA)” and increased financing for multi-center cohort research all advanced our understanding of cancer. In a single nanoscale package, multifunctional nanocarriers provide earlier detection, diagnostic capabilities, targeted medication distribution via several pathways, and therapy evaluation. These advantages are especially significant for adenocarcinomas that have MDR, such as NSCLC. It is crucial to explore alternatives to traditional chemotherapeutic therapies because NSCLC is one of the most deadly cancers, with one of the highest fatality rates. Nowadays, nanomedicine is a vital option for the treatment of NSCLC, and it may serve a deciding role in the approaching transformation of a tailored comprehensive therapy.

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**Data availability** This document includes citations for all the data that were analyzed throughout the literature review.

## Declarations

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