Recent advances in lung cancer therapy based on nanomaterials: a review

Running title: Lung cancer therapy using nanomaterials

Leila Gholami[1†], Jalil Rouhani Ivari[2†], Niloofar Khandan Nasab[2], Thozhukat Sathyapalan[3], Reza Kazemi Oskuee[4*], Amirhossein Sahebkar[5,6,7,8*]

[1]Nanotechnology Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran

[2]Department of Medical Biotechnology and Nanotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[3]Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, United Kingdom of Great Britain and Northern Ireland

[4]Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

[5]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran

[6]Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

[7]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

[8]Halal Research Center of IRI, FDA, Tehran, Iran

*Corresponding authors:

Amirhossein Sahebkar, Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran. Tel: +985138002299; Fax: +985138002287; E-mail: sahebkara@mums.ac.ir; amir_saheb2000@yahoo.com

Reza Kazemi Oskuee, Pharm.D., Ph.D, Department of Medical Biotechnology and Nanotechnology, School of Medicine, Mashhad University of Medical Sciences, P.O. Box: 91775-1159, Mashhad, Iran. Tel: +985138002291; Fax: +985138002287

†Both authors contributed equally.

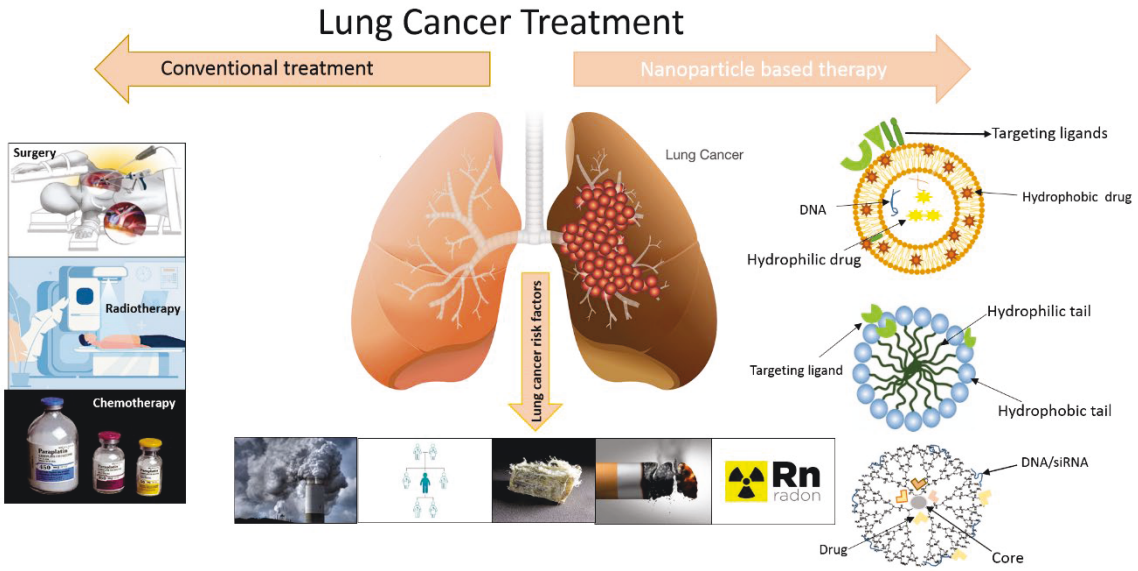

Figure 1. Schematic illustration of various established therapeutic platforms in Lung cancer care.

Abstract

Lung cancer is one of the commonest cancers with a significant mortality rate for both genders, particularly in men. Lung cancer is recognized as one of the leading cause of death worldwide, which threatens the lives of over 1.6 million people every day. Smoking is considered to be the main risk factor for lung cancer. Other factors, including genetic susceptibility, history of respiratory diseases, infections, environmental factors and even diet, are attributed to risk factors. Early diagnosis plays a vital role in medicine to prevent disease, management, and effective treatment. Although cancer is the leading cause of death in industrialized countries, conventional anticancer medications are unlikely to increase patients' life expectancy and quality of life significantly. In recent years, there are significant advances in the development and application of nanotechnology in cancer diagnosis and treatment. The superiority of nanostructured approaches is that they act more selectively than traditional agents. This progress led to the development of a novel field of cancer treatment known as nanomedicine. Various formulations based on nanocarriers, including lipids, polymers, magnetic and porous silica particles, have been investigated to detect, imaging, screen, and treat various primary and metastatic tumors. The application and expansion of nano-agents lead to an exciting and challenging research era in pharmaceutical science, especially for the delivery of emerging anti-cancer agents. The objective of this review is to summarize various lung cancer treatments modalities focusing on nanomedicine.

Keywords: Lung cancer, Treatment, Nanocarriers, Drug delivery, Nanomedicine

Introduction

Lung carcinoma is one of the leading cause of death, with over 1.6 million death annually worldwide [1, 2]. According to different studies, smoking is considered to be the main risk factor for this lethal cancer. The prevalence of lung cancer in nonsmokers has confirmed that various other risk factors may also play a role in developing lung cancer. Several common genes have been identified in recent years as potential risk factors for lung cancer development. Therefore, integrating possible genetic pathways strengthens the toxic effects of smoking and increases lung cancer risk in an individual[3]. Generally, lung cancer based on the type of cancerous cells could be divided into "small cell lung cancer" (SCLC) and "non-small cell lung cancer" (NSCLC). NSCLC, which accounts for ~ 80% of all lung cancers, is more often classified as adenocarcinoma, squamous cell carcinoma and large cell carcinoma. The likelihood of successful lung cancer treatment in the early stages of diagnosis is more favourable than advanced ones; however, most cases are identified in the later stages [4]. The high mortality of lung cancer is attributed to its tendency to disseminate through the lymphatic and vascular system despite treatment [5]. The main sites of the presence of metastatic LC, apart from lymph nodes, are the brain (47%), bones (36%), liver (22%) and adrenal glands (15%) [6].

Risk factors for lung cancer

- **Environmental factors, smoking and infections**:

Lung cancer has multiple risk factors, and smoking is considered to be the leading risk factor. Other risk factors include genes, environmental pollutants, radiation, diet and viral infections such as HIV [7]. The risk of lung cancer is dose-dependent and could be significantly reduced by stopping smoking [8]. Some studies report that environmental pollutants and air contaminants could contribute to lung cancer, although more than half of non-smoking patients had been exposed to cigarette smoke. They also stated that the environmental risk factors associated with lung cancer are more prevalent among people under 60 years old [9]. Recently, radon gas (Rn) has been identified as the second leading cause of LC. Many studies demonstrated that the incidence of LC was much higher in the areas with higher Rn concentration [10]. By causing DNA mutation on the P53 suppressor gene, radon gas could cause breakage in the DNA chain, acting as the primary step in cancer development [11]. Therefore, individuals who are exposed to high levels of radon should be screened for lung cancer. Older women who live in homes that are exposed to radon are more likely to develop lung adenocarcinomas[9]. There is also a relationship between infection of certain viruses such as "human papillomavirus" (HPV), "human immunodeficiency virus" (HIV) and the Epstein-Barr virus with lung cancer [12]. Kumar et al. reported that smokers infected with HIV were more at risk for lung cancer than nonsmokers. HIV weakens the immune system by reducing the TCD4 + cells. Thereby HIV-infected people are more likely to be harmed by the effects of carcinogens caused by cigarette smoke[13]. Cigarette smoking plays an essential role in developing HIV-related lung cancer. Still, the risk of cancer in people who have HIV is even more than two to four times higher than the general population, even after adjusting for the intensity and duration of smoking [14]. Some studies demonstrate a positive correlation between clinically diagnosed psychological disorders such as depression and anxiety with the surge in the risk of different cancers, including lung cancer [15, 16]. In a study conducted specifically on the Taiwan population, the effects of certain lifestyle factors such as smoking, betel quid chewing, and alcohol consumption on epigenetic alterations and cancer incident were examined. The results showed specific relationships between head and neck, oral, nasopharyngeal carcinoma, lung and gastrointestinal cancers with betel quid, alcohol and tobacco use [17]. In addition to the mentioned factors, environmental carcinogens (*e.g.* arsenic and asbestos), air pollution, and diseases like chronic bronchitis, emphysema, tuberculosis, pneumonia, and asthma also play an essential role either independently or through incremental or combination effects with other risk factors. Lung cancer in nonsmokers is both morphologically and molecularly different from those who smoke, so these findings help the clinician diagnose and manage lung cancer in a more tailored way[5].

- **Lung cancer-related genes:**

Changes in the various genes involved in the metabolism of peripheral cancers, nucleotide and base excision repair genes, and genes interfering with the cell cycle control have a significant impact on lung cancer development. Available data suggest that 1.7% of LC patients have a hereditary pattern for up to 68 years. Potentially highly

penetrating genes or genes that affect the metabolism of carcinogens such as tobacco are responsible for this effect [18].

According to different studies, lung cancer has a genetic alteration profile with a pattern of expression of thousands of genes expression altered (Table1). Due to the importance of genes as a risk factor in lung cancer prevalence, various pharmacological treatments targeted the candidate genes encompassing *EGFR, ALK, BRAF, KRAS, VEGF* and so forth to inhibit or stimulate the genetic pathways to impact the development of lung cancer [19].

Table 1. List of some lung cancer-related genes

Gene name	***Abbreviation name***	***Function***	***Reference***
"Epidermal Growth Factor Receptor"	*(EGFR)*	Has a tyrosine kinase activity and involved in some cellular program such as proliferation/growth/survival	[20-23]
"Echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase."	*(EML4-ALK)*	(EML4): is an echinoderm, microtubule-associated protein-like family member encodes a receptor tyrosine kinase:(ALK) The occurrence of EML4-ALK translocation observed in some lung cancer cases	[20]
"Tumor Protein 53"	*(TP53)*	It is a tumor suppressor and a vital regulator gene for energy metabolism/apoptosis/cell growth. TP53 considered an inhibitor of cancer development	[24]
"Baculoviral IAP Repeat Containing 5" (Survivin)	*(BIRC5)*	Survivin is a member of the "inhibitor apoptosis protein" (IAP) family that has a role as an apoptosis inhibitor and control the cell cycle. Overexpression has been reported in human lung cancer	[25]
"Mini Chromosome Maintenance Complex Component 4"	*(MCM4)*	Crucial roles in the start of DNA replication High MCM4 expression was reported in NSCLC	[26]
T-Box 2	*(TBX2)*	Is a phylogenetically conserved family member that share a common DNA-binding domain, the T-box TBX2 involved in cell proliferation / differentiation	[27]
"Solute Carrier Family 2 Member 1"	*(SLC2A1)*	This gene encodes a glucose transporter (GLUT1) protein, and high expression of SLC2A1 is related to lung cancer tumors.	[24]
"Lactate Dehydrogenase A"	*(LDHA)*	Has a role in the control of the glycolysis pathway. This gene is overexpressed in certain types of lung cancers	[24]
"MYC Proto-Oncogene"	*(MYC)*	Considered as cell growth / cell cycle progression/ apoptosis / metabolism regulator. Amplification of the MYC gene is observed in some cancers.	[24]
"Cell Division Cycle 20"	*(CDC20)*	Cdc20 is an Anaphase Promoting Complex (APC) regulator and is involved in the control of cell division	[28]
"Vascular Endothelial Growth Factor"	*(VEGF)*	It is a growth factor that induces proliferation/migration of vascular endothelial cells and is essential for angiogenesis and vascular angiogenesis	[29]
"Ataxia Telangiectasia Mutated"	*(ATM)*	It encodes an apical kinase and takes part in cell cycle regulation and DNA damage repairing and has recently been shown to play	[30]

		an essential role in lung cancer progression. It is suggested that the ATM gene may be a potential new target for the diagnosis and treatment of lung cancer	
"Glutathione S-Transferases"	*(GSTs)*	Glutathione S-transferases are phase II biotransformation enzymes that play an essential role in detoxifying a range of external factors, including carcinogens and anticarcinogenic agents and play a role in the system of cellular defence. It has been shown that GSTs gene polymorphisms play a role in response to treatment	[31]
"RNA Binding Motif Protein 5"	*(RBM5)*	It is a tumor suppressor gene that could stop the cell cycle and induces apoptosis / regulating/inhibiting lung cancer metastasis and often eliminated in the early stages of LC development. Regulating the expression of RBM5 may be a new therapeutic goal for lung cancer. High-expression of RBM5 inhibit human lung cancer growth by increasing apoptosis and inducing cell cycle arrest in the G phase	[32]
"Liver kinase B1 (STK11)	*(LKB1)*	LKB1 is a tumor suppressor gene. Some LKB1 mutations have been reported in sporadic lung tumors. A protein of this gene with serine-threonine kinase activity is related to apoptosis/ cell proliferation/ energy metabolism	[33]
"Kristen Rat Sarcoma"	*(KRAS)*	KRAS protein is a member of the RAS family with GTPase activity and involved in the differentiation/proliferation/survival of cells	[34]
"Glucose Transporter 1"	*(GLUT1)*	GLUT1 play a role in cancer cells glucose transport/metabolism	[35]
"Rearrangement during transfection."	*(RET)*	RET gene is a receptor tyrosine kinase and a protein that involved in produces differentiation/proliferation/migration/survival	[36, 37]
"B-Raf proto-oncogene, serine/threonine kinase."	*(BRAF)*	This gene encodes a protein of RAF family serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ERK signaling pathway, which affects cell division, differentiation, and secretion.	[37]
"MET proto-oncogene."	*(MET)*	This gene encodes a receptor tyrosine kinase family proteins that play a role in mitosis/cell survival/cell motility and was defined as high expression of MET gene involved in lung cancer.	[38-41]
"Phosphatase and tensin homolog."	*(PTEN)*	PTEN Is a tumor suppressor involved in cell survival/cell cycle progression/angiogenesis. Downregulated of PTEN is associated with the development of lung cancer	[39]
"Programmed death-ligand 1"	*(PD-L1)*	(PD-L1), the primary ligand of PD-1 immune checkpoint receptor that expresses on the immune cell surface that involved in tumor immune escape is upregulated in NSCLC and different types of tumors	[42]

- **Lung cancer-related microRNAs (miR)**

MicroRNAs (miRNAs) are small, non-coding RNAs that impact different stages of carcinogenesis and metastasis. Aberrant expression of miRNAs in tissue and plasma has been found in various solid tumors. Due to many studies, dysregulation in the miRNA biogenesis process could result in oncogenesis [43, 44]. So far, numerous studies have been done to provide a miRNA profile of lung tumor tissues. The miRNA changes may also be observed in body fluids such as serum or plasma[45, 46]. Functionally, miRNA could act as tumor suppressors or oncogenes in lung cancer [43]. It had been demonstrated that there is a high expression of miR-10b, miR-14, miR-155, and miR-21 in the serum of patients with lung cancer. Also, miR-29a could be considered as a tumor suppressor in lung cancer. Besides, polymorphisms in miRNA-196a2 are also associated with lung cancer [47]. In contrast with other microRNAs, Let-7 has a lower expression in patients with lung cancer [48]. Dysregulation of the miR-34 family as tumor suppressor miRNAs are reported in the development of lung cancer [49]. The expression of plasma miR-145, miR-20a, and miR-223 was significantly raised in the early-stage NSCLC specimens compared with the control group [50]. Reports suggest that miR-34 and miR-124 loci methylation could be a tumour-associated frequentative incident during NSCLC tumorigenesis and could be used as potent markers for the prognosis of patients with NSCLC [51].

Exosomal serum miR-146a-5p can be a new biomarker to investigate the efficacy of cisplatin for NSCLC patients and real-time monitoring of drug resistance [52]. Overexpression of miR-17/92 cluster in some cancer, including lung cancer, has been confirmed [53]. The study showed that miR-486-5p acts as an oncogene in the development of NSCLC, which affects the PTEN-PI3 K / AKT.PTEN signaling pathway, which is one of the most common pathways for tumor suppression. So it could be concluded that miR-486-5p might be used in the therapeutics of NSCLC [54]. miR-93-5p up-regulation in NSCLC plays an oncogenic role by inhibiting PTEN and RB, suggesting miR-93-5p might be a novel prognostic indicator and a therapeutic target in NSCLC [55], whereas miR-455-3p was downregulated in NSCLC and was associated with the bad prognosis of NSCLC patients. miR-455-3p acts as a tumor suppressor by targeting HOXB5 in NSCLC development and could be a potential target for NSCLC treatment [56]. As mentioned before, the level of miR-770 expression in serum of patients may be a novel diagnostic, prognostic biomarker and a potential target for the treatment of NSCLC [57]. Downregulation of miR-129 has been associated with various cancers, and miR-129-5p has recently been shown to decrease lung cancer proliferation and metastasis [58]. Another study showed that miR-367 could be accompanied by the diffusion and progression of NSCLC by reinforcement of proliferation, invasion and blocking apoptosis in NSCLC cells [59].

Non-Small Cell Lung Cancer treatment strategies

Surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy are the primary approaches for lung cancer treatment, and staging of cancer is fundamental for choosing treatment strategy [60]. In general, lung resection procedures including lobectomy, pneumonectomy, wedge resection and segmentectomy are the optimal options to remove and confine the tumor penetrance, highly dependent on the tumor size, type and location [61, 62]. Another choice for early-stage lung cancer management is radiotherapy, which uses radiation (X-rays) to destroy cancer cells. Radiotherapy includes external beam radiation therapy, stereotactic radiotherapy and internal radiation therapy (brachytherapy). For stage IIIA and IIIB NSCLC patients, radiation therapy, chemotherapy, or combination therapy (chemoradiation) are considered first-line therapies [63]. Chemotherapy based on intravenous (IV) or oral anti-cancer drugs such as Paclitaxel (Taxol) [64], Cisplatin, Doxorubicin [65], Docetaxel [66] and also several types of antibodies[67] remains the basic strategies in the management of lung cancer [68]. Therefore, In the most advanced types of non-small cell lung cancer characterized as the metastatic stage (IV stage), the standard therapeutic options are combination chemotherapy, combination chemotherapy/targeted therapy and radiation therapy [69]. In targeted therapy, the factors involved in the development and spread of the malignancy, including gene or proteins, are targeted. Two types of common drugs in targeted therapy are monoclonal antibodies and small molecule drugs that attack solely on cancer cells than the normal cells [70]. Mutant EGFR tyrosine kinase as a receptor on cancer cells' surface is the most effective target for therapeutic agents such as Afatinib (Gilotrif) [71], Erlotinib (Tarceva), gefitinib and several antibodies including cetuximab, Panitumumab, Matuzumab and NecitumumabiIn [72]. Moreover, targeted therapy could inhibit angiogenesis factors such as “vascular endothelial growth factor receptor 2” (VEGFR2), which are involved in cancer cell proliferation and invasion [73]. The ramucirumab, an anti-VEGFR2 agent, can bind to VEGFR2 and blockade the signaling pathway and inhibit tumor

angiogenesis [71]. Targeting the VEGF receptor-2 pathways demonstrate great promises as a second-line treatment for patients with lung cancer [74, 75]. Another cancer treatment method used for late-stage of lung cancer, s immunotherapy. Immunotherapeutics stimulate the immune system through different agents such as monoclonal antibodies (mAbs), "adoptive cell transfer" (ACT), cancer vaccines (whole-cell vaccines or antigen-specific vaccines) and immunomodulators against checkpoint inhibitor signals to destroy cancer cells [76, 77]. In addition to the mentioned methods, gene therapy is currently being studied to treat cancer [78], although it was initially used to treat monogenic diseases. Gene therapy aims to replace the defective gene with a functional gene to cure diseases, in this case, an increase in the therapeutic efficiency and a reduction in toxicity to normal tissues [79]. According to different studies, *p53* and *TUSC2* are the potential targets that could open new horizons in cancer treatment[78].

Nanomedicine strategy for the treatment of lung cancer

Nanomedicine refers to utilizing nanotechnology in medicine to improve diagnosis, treatment or even monitoring of diseases.
Some nanotechnology applications in medicine consist of targeted drugs, imaging and theranostic (dual-purpose nanomaterials) agents, especially cancer care strategies. These nanosized tools' ability to transfer therapeutic compounds across biological barriers presents a potential avenue for treating cancers[80]. In the recent decade, various nanoparticles with unique properties for identifying different cancer cells, an adequate loading capacity of therapeutic agents, and the possibility of surface manipulation have been developed and investigated[81,82]. Delivery of chemotherapeutic agents to the tumor-specific site more efficiently with less toxicity and better drug activity is the most positive advantage of nanomaterials. Indeed, local delivery of drugs reduces therapeutic agents' side effects on the adjacent healthy tissues [65, 83]. Nowadays, nanomedicine has led to advances in combinational therapy. In combined therapy, two or more drugs can be delivered to several targets by single or multiple sets of nanocarriers. Drug delivery strategies are classified as active targeting, passive targeting, local delivery and triggered drug release [84, 85]. It should be noted that for enhancing the functional specificity of nanovehicles, transferring cargo to target cells, surface modification of nanostructure or nanoformulation with a particular polymer or ligand, even mono or polyclonal antibodies which generate a high tendency to the cells of the target tissue, needs to be developed [86].

Several types of nanoscaled particles have been studied across various cancer types, including liposomes, polymeric nanoparticles, polymeric conjugates, polymeric micelles and dendrimers [85]. By offering different carriers, nanomedicine provides a suitable vehicle for carrying the therapeutic or diagnostic component and improving various treatment modalities (53, 54[87]). The application of nanomedicine as radionanomedicines (radiolabeled nanomedicine) for imaging and cancer therapy has also been developed [88]. These radiolabeled nanomaterials can be applied to visualize tumor tissues in living bodies and imaging the biodistribution and pharmacological index of drug delivery templates in animal tumor models[89, 90]. In the current review, we aim to highlight three versatile types of nanoparticulate cargo delivery systems with insight into specificity to distinct nanoformulation categories **(Figure1).** Liposomes are considered the most promising formulation in clinical settings to date. Many liposomal formulations, FDA-approved products, now prevail in the clinical landscape[91, 92] Novel intelligent polymeric micelles comparable to liposomes due to their unique characteristics such as concentrated tumor-targeting ability and for sequential or simultaneous drug release have made their debut in treatment approaches.[93] Eventually, we discuss dendrimers which could be described as the 3D polymeric structure with plenty of fruitful characteristics over conventional linear polymers[94].

Types of nano-based carrier

Liposomes:

Liposomes as spherical phospholipid structures are the most frequent nanocarriers, owing to their distinctive properties, including biocompatibility, biodegradability, low toxicity and lack of immune system activation. These structures can be exploited for payload and delivery of either lipophilic and hydrophilic drug to various target sites [95, 96]. The liposomal structure could be used for common chemotherapy drugs,[97-99], and other therapeutic agents such as plant-derived exracts in liposomal form have shown acceptable anti-tumour efficiency in lung cancer treatment[100, 101]. Liposomal honokiol (LHK) was used for induction of apoptotic and antitumor activities in different xenograft models generated using NSCLC cell lines such as HCC827 (gefitinib-sensitive) and H1975 (gefitinib-resistant)[101]. Liposomal honokiol was the first drug approved by the China Food and Drug

Administration for clinical trials in NSCLC patients. The liposomal form of baicalin exhibited acceptable and prolonged antitumor efficacy in nude mice bearing orthotopic human lung cancer. Furthermore, the baicalin-loaded nanoliposomes did not bring about lung injury in animal model[100]

As it was mentioned before, the liposomal surface could be tailored by flexible hydrophilic moieties, predominantly polyethylene glycol(PEG)[102, 103], but also polyvinyl pyrrolidones [104] or Poly[N-(2-hydroxypropyl) meth acrylamide [105]. Doxil and Myocet, PEGylated liposomes loaded with doxorubicin (PLD), were considered the first FDA approved nano-drugs to treat lung cancer and some other neoplasms [95, 106, 107]. In the study conducted in 2013, octa-arginine (R8) cell-penetrating peptide is exploited for optimizing the antitumor activity of PLD. The authors reported that the presence of (R8) in the formulation of PEGylated liposomal doxorubicin (R8-PLD) led to the stimulation of apoptol for the efficient accumulation of the drug in lung cancer cells[108]. Cheng et al. studied GE11-modified liposomes loaded with doxorubicin (GE11-LP/DOX) to target A549 tumor-bearing nude mice. GE11 is a peptide with a high tendency to epidermal growth factor receptor (EGFR). The accumulation and retention of the GE-11 modified liposomes were 2.2-fold higher in comparison to unmodified liposomes [109]. In another study, liposomal curcumin dry powder inhaler (LCD) was used to treat lung cancer in the rat as an animal model. LCDs displayed much higher anticancer efficiency than gemcitabine in terms of pathological evidence and the expression of different cancer biomarkers such as VEGF, malondialdehyde, TNF-α, caspase-3 and BCL-2[110]. Dual ligand modified liposomes for a local delivery was investigated by Lin et al. In this study, anti-carbonic anhydrase IX (anti-CA IX) antibody and CPP33 dual-ligand modified triptolide-loaded liposomes (dl-TPL-lip) was used for specific tumor targeting, as well as tumor cell penetration. Their liposomal structure represented an effective inhibitory effect in-vivo and in-vitro studies. In addition, pulmonary administration in the orthotropic lung cancer model exhibited a much higher anti-cancer impact without any significant systemic toxicity[111]. Fu et al. applied linear and cyclic arginine-glycine-aspartate (RGD) peptide-based lipids to manufacture modified liposomal drug delivery systems for active targeting of lung cancer. The modified liposome and enhanced cellular uptake of DOX due to outstanding active targeting ability for integrin $\alpha_v\beta_3$ receptors depicted notable antitumor activity in the in-vitro and in-vivo study[112]. Lu et al. studied the effect of liposomal paclitaxel combined with systemic chemotherapy (carboplatin and gemcitabine) on 48 stage III NSCLC patients. The study demonstrated tolerable toxicity, as well as a significant patient response [64]. Moreover, in several studies, liposomal cisplatin (Lipoplatin) has been evaluated for lung cancer therapy. Cisplatin can crosslink with DNA to disturb mitosis and can be used as a beneficial agent against some types of cancers[65, 113, 114]. Song et al. designed a multifunctional targeting liposome for the treatment of NSCLC. They modified the liposome surface by Octreotide (OCT), a synthetic 8-peptide analog of somatostatin that binds to the overexpressed somatostatin receptors in different cancers and Honokiol and epirubicin were encapsulated in liposomal structure. Their result showed that decorated liposome could decrease the PI3K, MMP-2, MMP-9, VE-Cadherin, and FAK and activate caspase 3, and significant beneficial effects were attained in the animal study[115]. Lin et al. prepared antibody (anti-carbonic anhydrase IX) decorated liposomes (CA IX-TPL-Lips) for targeted delivery of chemotherapeutic agents to treat lung cancer in an animal model via pulmonary administration. They revealed that their nanoformulation showed acceptable results on either A549 tumor spheroids and mice model of orthotopic lung tumors. [116]

All-trans retinoic acid (ATRA) loaded liposomes could be mentioned as another instance for applying liposome structure in cancer therapy. Although ATRA is an effective anti-tumour agent utilized against different cancers, its adverse effects such as the burning of skin and general malaise following systemic administration are the main barriers for its therapeutic application[117] Many studies reports confirmed the anti-metastatic activity of ATRA loaded nanoliposomes on animal models[118, 119]. The liposomal form of IL12 and ATRA in the complex with plasmid DNA, as the dual function nanocarrier for simultaneous drug and gene delivery, was formulated to inhibit the cancer cell proliferation in metastatic lung cancer. Study results demonstrated that liposome form, besides, to prolong the animal model's survival, decrease the number of cancer cells through apoptosis pathway[120]. In another study, the liposomal form of ATRA compared to free ATRA in terms of drug delivery to lung cancer mice. The liposomal form of ATRA displayed a continues and increased therapeutic efficacy on an animal model. Since the cancer-bearing mice endure certain debilitating conditions such as anorexia, cachexia and remarkable weight loss, the liposomal ATRA showed a lower decrease in body weight than free drug[121].

Polymeric micelles:

Micelles are self-assembled core–shell-type nanostructures which have been utilized for hydrophobic drugs and nucleic acid delivery. Owing to their characteristic physicochemical properties, drug encapsulation capacity, release profile, prolong systemic circulation, biocompatibility and facile composition, these versatile nanocarriers has drawn immense attention in recent years[122, 123]. So far, several studies have investigated the therapeutic effect of micellar paclitaxel in lung cancer. Kim et al. developed the form of a polymeric micelle of paclitaxel (Genexol-PM). They evaluated the therapeutic effects of their liposome on clinical trial phase II to treat advanced NSCLC patients. The results showed Genexol-PM plus cisplatin combination chemotherapy had significant antitumor properties[124]. In 2010, Guthi et al. developed a theranostic nanoplatforms which consists of PLA polymeric micelle whose surface was engineered with a lung cancer-targeting peptide (RGDLATLRQL) targeted against the overexpression of αvβ6 integrin human NSCLC cell H2009. Also, DOX and "super-paramagnetic iron oxide nanoparticles" (SPIONs) encapsulated in the micelle core for drug delivery and MR imaging simultaneously. Their designed nanoparticle with integrated function showed a promising result in the in vitro evaluation[125]. Besides, Zhang et al. designed a micellar form of PEG-PLA to co-deliver paclitaxel (PTX) and itraconazole (ITA) against NSCLC. The co-encapsulated micelles displayed superb effectiveness in inhibiting tumor proliferation in the orthotropic models and paclitaxel-resistance subcutaneous models [126]. The therapeutic effect of the chitosan-cholesterol micellar platform for combined delivery of siRNA and curcumin as a therapeutic agent (C-CCM/siRNA) were explored by Muddineti et al. The study demonstrated the utility of cholesterol-chitosan as a co-delivery system for both siRNA and a hydrophobic drug in combinational approach for cancer therapy. [127]. NC-6004 is a nanosized micellar polymeric form (about 30nm) of cisplatin composed of polyethylene glycol, which was utilized in combination therapy with Gemcitabine in patients with late-stage solid tumors. Up to now, Phase Ib/II of NC-6004 plus Gemcitabine clinical trial was done for patients, and acceptable results were achieved without any clinically significant neuro-, oto-, or nephrotoxicity [128]. Functionalizing polymeric micelles' surface with chemical moieties, antibodies, targeting ligands, and so forth, arise novel opportunities for more targeted drug delivery in various cancers[129]. Folat decorated self-assembled micelles were prepared for targeting Rapamycin (mTOR) kinase and phosphatidylinositol-3-kinase (PI3K). In this study, platinum (II) linked the dactolisib to the core of the structure of the micelles, which consist of poly (ethylene glycol and poly(acrylic acid) (PEG-b-PAA), to develop a PEG-b-PAA) polymeric micelles. According to their report, the presence of folat on the micelles' surface and enhanced cellular uptake by cancer cells improved the antitumor properties of dactolisib[130]. Zhou and coworkers developed a nanomicellear formulation of polyethylene glycol and polylactic acid-functionalized with aminoglucose to overcome the multidrug resistance in lung cancer patients. Paclitaxel (PTX)-loaded AG-PEG-SS-PLA (AG-PEG-SS-PLA/PTX) nano micelles displayed an efficient cellular internalization, drug release as well as, enhancement in tumor growth inhibition in nude mice bearing A549/ADR xenograft tumors. Therefore, they suggested that AG-PEG-SS-PLA/PTX nano micelles could build a platform to defeat MDR in cancer therapy[131].

Inhalable drug delivery systems are another development in lung cancer treatment. Inhalation route not only do provide a non-invasive route for drug administration but also this type of setting offers the advantage of the localized transfer of anti-cancer agent to lesion site[132]. The mixed polymeric micelles synthesized with succinate-polyethylene glycol 1000 and 5000 Da loaded with paclitaxel (PTX) in the spray-dried form showed a promising in vitro cytotoxicity toward cancer cells in comparison with free drug[133] He et al. designed a nanocarrier based polymers polyethyleneglycol-polylactic acid (PEG-PLA) and Pluronic P105 for PTX encapsulation to synthesize a PEG-PLA/P105/PTX micelle. In this study, Ambroxol (AX) was used to stimulate the pulmonary system for secretion of surfactant and subsequent creation of a suitable environment for lung cancer drug delivery. According to their results, PEG-P-LA/P105/PTX micelle in the presence of AX exhibited excellent efficacy in the invitro and invivo study. This demonstrates that modulating the microenvironment could be a good strategy for better delivering cargoes in lung cancer. [134]

Dendrimers:

Dendrimers are synthetic globular branched structures that have a pivotal role in pharmaceutical science. The striking function of these polymers could be attributed to their extraordinary architectural backbone, branches and three-dimensional structures, which contributes to their bioavailability and water-solubility properties. Two synthetic methodologies are comprising of divergent and convergent approaches for the synthesis of dendrimers [135, 136]. Multiple types of dendrimers, including polyamidoamine (PAMAM), poly (propylene imine) (PPI), poly(glycerol-co-succinic acid), poly-l-lysine (PLL), melamine, triazine, poly(glycerol), poly[2,2-

bis(hydroxymethyl)propionic acid], poly(ethylene glycol) (PEG), and carbohydrate-based and citric acid-based ones, have been synthesized and investigated in various drug delivery studies[137, 138]. These nano-devices evolved dramatically in recent years. Their immense popularity is due to their numerous peripheral functional groups, which provide the possibility for covalently binding to chemotherapeutic agents, ligands and antibodies for accumulation in a specific tissue, creating a setting for tumor cell-specific delivery. Subsequently, hydrophobic drugs encapsulated into polycationic dendrimers through physical electrostatic interactions and hydrogen bonding, or hydrophobic interaction can be acquired[139, 140].
In a study by Liu et al., lung cancer-targeting peptide was conjugated to an acetylated polyamidoamine (PAMAM) dendrimer of generation 4 (G4) to form a PAMAM-Ac-FITC labeled-LCTP conjugate (PAMAM–Ac–FITC–LCTP) for targeting NSCLC and was tested in vivo [141]. Kaminskas et al. studied the efficiency of PEGylated polylysine dendrimers grafted to doxorubicin (DOX) to support the controlled and prolonged exposure of lung cancers to cytotoxic drugs. Their data demonstrated that PEGylated dendrimers have a capability as an inhalable drug delivery strategy to promote the longevity of lung cancers exposure to chemotherapeutic agents as well as to enhance anti-cancer activity[142].
Likewise, conjugates of DOX bind to PEGylated G4-polylysine dendrimer were explored by Leong et al. to study cathepsin B-cleavable peptide linker for drug conjugation in drug delivery kinetics, intravenous, and pulmonary pharmacokinetics in rats. The extracellular and lysosomal overexpression of this enzyme was confirmed by cancer cells, and the presence of linker in drug binding affect the drug liberation profile[143]. In another study, Zhang et al. prepared peptide-dendrimer-paclitaxel conjugates and tested on stage 1 NSCLC in 293T and L132 cell lines. Their data demonstrated acceptable results for both cell lines in terms of cancer cells target optimization and drug release profile to boost the therapeutic efficacy[144]. A novel strategy of chemotherapeutic combination for lung cancer was developed based on a folic acid (FA) conjugated polyamidoamine dendrimer. The study demonstrated that folic acid-binded dendrimers induce extensively notable cell death and DNA damage compared to nanoparticles without FA moiety[145].

The active role of dendrimers for the reduction and compensate of the adenovirus gene delivery was reported in 2016. In this study PEGylated PAMAM (PP) dendrimers and with an epidermal growth factor receptor (EGFR)-specific therapeutic antibody (ErbB) was prepared. Conjugated PEGylated PAMAM (PPE) dendrimer complexed with Ad showed More selective ErbB-mediated cellular internalization than naked Ad and P-complexed in EGFR-positiveA549 cell. The result of invivo studies in the orthotopic lung tumor model through systemic administration revealed the longevity in blood circulation as well as intra-tumoral accumulation of oncolytic Ad upon transfer with PPE-complex[146].

Table 2 lists some of the typical cases of using nanomedicine-based carriers for drug delivery of lung cancer.

Table2. Examples of nanomedicine carrier studies for lung anticancer drug delivery

Nanomedicine	***Therapeutic drug***	***Name***	***Invitro/invivo model***	***ref***
Octa-arginine (R8)-modified PEGylated liposomal doxorubicin	Doxorubicin	R8-PLD	A549 cell line	[108]
liposomal honokiol	Honokiol	LHK	HCC827, H1975 cancer cell lines	[101]
Baicalin-loaded nanoliposomes	Baicalin	-	Nude mice bearing orthotopic human lung cancer	[100]
GE11-modified liposomes	Doxorubicin	GE11-LP/DOX	A549 tumor-bearing nude mice	[109]
Liposomal curcumin dry powder inhaler	Curcumin	LCD	Rat model	[110]

CPP33 dual-ligand modified triptolide-loaded liposomes	Triptolide	dl-TPL-lip	Orthotopic lung cancer model	116
Arginine-glycine-aspartate (RGD) DOX loaded liposome	Doxorubicin	RGD-modified, DOX-loaded liposomes	Tumor-bearing mice	112
Liposome	Paclitaxel / Carboplatin / Gemcitabine	-	Stage III NSCLC patients	64
OCT-modified (epirubicin/ Honokiol) liposomes	Honokiol and epirubicin	DSPE-PEG2000-OCT (epirubicin/ Honokiol) liposomes	Tumor-bearing mice	115
ATRA-cationic liposome)/IL-12 plasmid DNA (pDNA)	IL-12/ATRA	ATRA-cationic liposome/IL-12 pDNA	CDF1 tumor bearing mice	120
ATRA liposomal formulation	ATRA	lipo-ATRA	Cancer bearing mice	121
Liposome	Cisplatin	Lipoplatin	histologically or cytologically confirmed NSCLC patients	113, 114
Polymeric micelles	Paclitaxel	Genexol-PM	Advanced NSCLC patients	124
Multifunctional PLA polymeric micelle	SPIONs/ Doxorubicin	LCP-encoded MFM	H2009 lung cancer cells	125
poly(ethylene glycol)-b-poly(d,l-lactide) loaded paclitaxel and itra-conazole	Paclitaxel / itraconazole	PTX/ITA PEG-PLA micelle	Orthotropic A549 NSCLC mouse model	126
Chitosan-cholesterol micellar form	Curcumin / siRNA	(C-CCM/siRNA)	A549 cell line	127
Polymer micelles	Cisplatin	NC-6004	Patients with Solid Tumors	128
CendR peptide ligand(Cys-Arg-Gly-Asp-Ly) modified micelles	Doxorubicin	DSPE-PEG2000with CRGDK peptides	Tumore bearing mice	129
Folat conjugated dactolisib -poly(ethylene glycol)-b-poly(acrylic acid) (PEG-b-PAA) polymeric micelles	Dactolisib (DLB)	FA_DLB - PEG-b-PAA	A549 cells Tumore bearing mice	130
Paclitaxel loaded aminoglucose (AG)-conjugated, polyethylene glycol - polylactic acid polymeric micelles	Paclitaxel (PTX)	AG-PEG-SS-PLA/PTX	A549 Nude mice bearing A549/ADR xenograft tumors	131
Paclitaxel loaded tocopheryl succinate-polyethylene glycol 1000 and 5000 Da polymeric micelles	Paclitaxel (PTX)	TPGS1K-TPX TPGS5K-TPX	A549 cell line	133
Polyethyleneglycol-polylactic acid (PEG-PLA) and Pluronic P105 polymeric micelles encapsulate PTX	Paclitaxel (PTX)	PEG-PLA/P105-PTX	A549 cell line Tumore bearing mice	134
Peptide dendrimer conjugates (PAMAM–Ac–FITC–LCTP)	Non-small cell lung cancer-targeting peptide (LCTP)	PAMAM–Ac–FITC–LCTP	Athymic mice with lung cancer xenografts	141
PEGylated polylysine dendrimer	Doxorubicin	-	Tumor bearing male Sprague Dawley rats	142

GE11-Peptide-dendrimer-conjugates	Paclitaxel	GE11-PAMAM-PTX)	293T and L132 cell lines	[144]
DOX -PEGylated G4-polylysine dendrimer	Doxorubicin		Rat model	[143]
folic acid (FA)-conjugated polyamidoamine dendrimer (Den)-based nanoparticle (NP)) system	HuR mRNA (HuR siRNA), cis-diamine platinum (CDDP)	-	H1299 lung cancer cells	[145]
Epidermal growth factor receptor (EGFR)-specific therapeutic antibody (ErbB)-conjugated and PEGylated poly(amidoamine) (PAMAM) dendrimer (PPE)	Oncolytic adenovirus(Ad)	-	A549 cell line, A549 orthotopic tumor was established, tumor-bearing mice	[146]

However, the role of nanotechnology in cancer therapy is not confined to drug delivery research and development. This evergrowing field can be exploited in other areas such as gene therapy, hyperthermia and RNAi technology for cancer cell inhibition (48).
Since curbing the expression of the target gene in cancer cells is highly dependent on the efficient transition of oligonucleotides, micro RNA (miRNA), small interfering RNA (siRNA) and short hairpin RNA (shRNA), RNAi technology is coming into the spotlight of cancer therapy research. [79, 147]. Some of the studies based on the delivery of nucleic acid-based therapeutics via nanotechnology systems are listed in table3.

Table 3. Nanotechnology application in RNAi/Gene delivery to lung cancer cells

Vehicle	***RNAi/Gene type***	***Target***	***Invitro/invivo test***	***Ref***
Cationic Lipoplexes	miR-133b	prosurvival gene MCL	A549 "non-small cell lung cancer" (NSCLC) cells.	[148]
Aptamer conjugated cationic lipoplexes	shRNA	Bcl-Xl	A549 NSCLC cells	[149]
Cationic Lipoplexes	miR-29b	"cyclin-dependent protein kinase 6" (CDK6)	xenograft murine model using A549 cells	[148, 150]
Aptamer conjugated PAMAM Lipoplexes	shRNA	Bcl-Xl	A549 NSCLC cells	[150, 151]
Liposomal nanoparticle	p53 and FHIT genes		xenograft mouse model (H1299 and A549)	[152, 153]
Liposomal nanoparticle	Survivin shRNA	knockdown survivin	nude mice bearing H292 xenograft tumors	[154, 155]
Liposomal nanoparticle	let-7a	receptor EphA2	CRL-2081 and CRL-5830 cells (MPM cell lines) and A549 cells (NSCLC cell line)	[155, 156]

Liposomal nanoparticle	miR-200c	regulating the oxidative response genes PRDX2, SESN1, and GAPB/Nrf2	xenograft mouse model	[153, 157]
Lipid/calcium/phosphate (LCP) nanoparticle	MDM2, c-myc, and VEGF siRNA	silencing of the respective oncogenes in metastatic nodules	C57BL/6 mice bearing B16F10 cells xenograft tumors	[158, 159]
Lipid/calcium/phosphate (LCP) nanoparticle	Luciferase siRNA	examine the siRNA delivery activity of NP	nude mice bearing H460 xenograft tumors	[157, 158]
Lipid/calcium/phosphate (LCP) nanoparticle	(VEGF) siRNA and gemcitabine monophosphate (GMP)	VEGFs	xenograft mouse models of NSCLC	[156]
RGD gold nanoparticles	C-myc siRNA	tumor growth blocking via c-myc oncogene inhibition	lung cancer syngeneic orthotopic murine model	[154, 159]
DOTAP: cholesterol nanoparticle	TUSC2/FUS1 (TUSC2) gene	Tumor suppressor	Patients with recurrent or metastatic lung cancer	[152, 160]

Therapeutic Nanomedicine for lung cancer in Clinical Trials

Even though nanomedicine-based therapeutic settings have rendered new opportunities for cancer treatment and diagnosis, there are many challenges for advancing nanomaterials in clinical practices. In the present section, a list of the approved formulation under Clinical trial for lung cancer therapy is represented in Table4.

Conclusion and future perspective

Despite various advances in lung cancer management, it is still accounted for as one of the deadliest types of cancer worldwide. Compared to other types of malignancies, early diagnosis and adoption of appropriate therapeutic approaches have a significant role in managing patients with lung cancer. Due to the drawbacks and limitations of traditional modalities of cancer treatment, systematic toxicity and the damage resulting in healthy cells along with tumor cells, nanomedicine as a state of the art technology opens up new windows in diagnostic and therapeutic strategies. Lately, nanomedicine's strength includes liposomes, polymeric nanoparticles, polymeric conjugates, polymeric micelles, dendrimer and so forth to transfer the therapeutic agent, including drugs, genes, and oligonucleotide,s have been investigated. Therefore, these innovative integrated modalities can target tumor cells genetically and chemically.

Nevertheless, lack of knowledge of the fate of nanostructures in terms of their toxicity and in vivo behavior, only a few nano-formulations are available to manage lung cancers. Further investigation is required to provide evidence for changing nanomedicine's paradigm from the laboratory into the clinic. The advancement in nanoparticle-based diagnostics and therapeutics holds promise for improving the outcome for patients with lung cancer.

Funding: None to mention.

Consent for publication

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgements

Declared none.

Table 4. Nanoparticle cancer therapeutics undergoing clinical studies

Trial ID	***Year***	***Stage/Disease***	***Formulation/Drug***	***Delivery system***	***Status***	***Phase***	***Country***
NCT02016209	2013	IIB/IIIA NSCLC	nanoparticle albumin-bound paclitaxel (nab-paclitaxel)	Nanoparticle	Unknown	II	China
NCT02283320	2014	advanced or metastatic NSCLC	BIND-014 (Docetaxel Nanoparticles for Injectable Suspension)	Nanoparticles	Completed	II	United States
NCT01872403	2012	IIB /IIIA NSCLC	nanoparticle albumin-bound paclitaxel/carboplatin (paclitaxel /carboplatin)	Nanoparticles	Unknown	II	China
NCT00748163	2008	IV NSCLC	paclitaxel albumin-stabilized nanoparticle formulatio n and sunitinib malate	Nanoparticles	Withdrawn	II	-----
NCT01455389	2011	IV NSCLC	TUSC2-nanoparticles	Nanoparticles	Active, not recruiting	I	United States
NCT01380769	2011	Advanced NSCLC	CRLX101 (a Nanoparticle Formulation of Camptothecin)	Nanoparticle	Completed	II	Russian
NCT04486833	2020	IV NSCLC	GPX-001 (encapsulate by non-viral lipid nanoparticles)/ osimertinib	lipid nanoparticl es	Not yet recruiting	I/II	-------
NCT04505267	2020	I-III NSCLC	Hafnium Oxide-containing Nanoparticles NBTXR 3	Nanoparticles	Not yet recruiting	I	United States
NCT04727853	2021	SCLC	irinotecan liposome injection	Liposome	Not yet recruiting	II	-------
NCT00104754	2005	SCLC	liposomal SN-38	Liposome	Withdrawn	II	-------
NCT03088813	2017	SCLC	Irinotecan Liposome Injection (ONIVYDE®)	Liposome	Active, not recruiting	II	United States
NCT01872416	2013	SCLC	Liposomal Doxorubicin Combined With ifosfamide	Liposome	Unknown	II	China
NCT04381910	2020	SCLC	LY01610(Irinotecan hydrochloride liposome injection)	Liposome	Recruiting	II	China
NCT02996214	2016	Advanced NSCLC	Paclitaxel Liposome	Liposome	Active, not recruiting	IV	-------
NCT01051362	2006	NSCLC	PEGylated Liposomal Doxorubici n (PLD) and Carboplatin	Liposome	Unknown	II	China

NCT00059605	2003	IIIB/IV NSCLC	DOTAP:Cholesterol-fus1 Liposome Complex (DOTAP:Chol-fus1)	Liposome	Completed	I	United States
NCT00828009	2009	IIIA /IIIB NSCLC	BLP25 liposome vaccine together with bevacizumab	Liposome	Completed	II	United States
NCT00960115	2009	III NSCLC	Tecemotide (L-BLP25) Liposome Vaccine	Liposome	Completed	I/II	Germany
NCT00277082	2006	Metastatic or Recurrent NSCLC	Aerosolized Liposomal 9-Nitro-20 (S)- Camptothecin (L9NC)	Liposome	Completed	------	United States
NCT00157209	2005	NSCLC	Tecemotide (L-BLP25) Liposome Vaccine	Liposome	Completed	II	Germany
NCT01023347	2009	IIIB /IV NSCLC	Paclitaxel loaded polymeric micelle (Genexol-PM®)and Cisplatin	Polymeric micelle	Completed	II	Korea
NCT01770795	2013	IIIB /IV NSCLC	Genexol-PM(CrEL-free polymeric micelle formulated paclitaxel) and gemcitabine	Polymeric micelle	Completed	II	Korea
NCT01023347	2009	IIIB /IV NSCLC	Paclitaxel loaded polymeric micelle (Genexol-PM®)	micelle	Completed	II	Korea
NCT02667743	2016	IIIB /IV NSCLC	Paclitaxel Micelles	micelle	Active, not recruiting	III	China

References

1. Ostrowski M, Marjański T and Rzyman W. Low-dose computed tomography screening reduces lung cancer mortality. *Advances in Medical Sciences*. 2018; 63: 230-6.
2. Sung JH, Sim CS, Ock M, Oh I, Jeong KS and Yoo C. Comparison of a 10-year cumulative age-standardized incidence rate of lung cancer among metropolitan cities in korea (During the 2000–2009 period): Review of occupational and environmental hazards associated with lung cancer. *International Journal of Environmental Research and Public Health*. 2018; 15.
3. Zhang J, Zhao T, Xu C, Huang J and Yu H. Genetic susceptibility of lung cancer in Chinese population: An overview of systematic reviews and meta-analyses. *Journal of Evidence-Based Medicine*. 2017; 10: 207-11.
4. Kanwal M, Ding XJ and Cao Y. Familial risk for lung cancer. *Oncol Lett*. 2017; 13: 535-42.
5. Smolle E and Pichler M. Non-Smoking-Associated Lung Cancer: A distinct Entity in Terms of Tumor Biology, Patient Characteristics and Impact of Hereditary Cancer Predisposition. *Cancers (Basel)*. 2019; 11: 204.
6. Sanguedolce F, Loizzi D, Sollitto F, et al. Bladder Metastases from Lung Cancer: Clinical and Pathological Implications: A Systematic Review. *Oncology (Switzerland)*. 2017; 92: 125-34.
7. Malhotra J, Malvezzi M, Negri E, La Vecchia C and Boffetta P. Risk factors for lung cancer worldwide. *European Respiratory Journal*. 2016; 48: 889-902.
8. Warren GW and Cummings KM. Tobacco and lung cancer: risks, trends, and outcomes in patients with cancer. *American Society of Clinical Oncology educational book / ASCO American Society of Clinical Oncology Meeting*. 2013: 359-64.
9. Arghir OC, Halichidis S, Cambrea SC, Ruta MV, Ciobotaru C and Man MA. Environmental risk factors for lung cancer in never-smokers. *Journal of Environmental Protection and Ecology*. 2014; 15: 348-52.
10. Ruano-Ravina A, Lorenzo-González M, Provencio M, et al. P2.10-05 Indoor Radon and Lung Cancer Risk. A Pooling Study on the Second Risk Factor for Lung Cancer. *Journal of Thoracic Oncology*. 2019; 14: S786.
11. Azhari, Ivhatry, Bremmy, Winni and Suhardjo. Effects of Radon Gas Exposure on Lung Cell Immunity at Low Doses and High Doses : A Review. 2019.
12. Mani D, Haigentz Jr M and Aboulafia DM. Lung cancer in HIV infection. *Clinical Lung Cancer*. 2012; 13: 6-13.
13. Kumar S and Ranjit S. Recent advances in cancer outcomes in HIV-positive smokers [version 1; referees: 2 approved]. *F1000Research*. 2018; 7.
14. Wang YH and Shen XD. Human immunodeficiency virus infection and mortality risk among lung cancer patients. *Medicine (United States)*. 2018; 97.
15. Jia Y, Li F, Liu YF, Zhao JP, Leng MM and Chen L. Depression and cancer risk: a systematic review and meta-analysis. *Public Health*. 2017; 149: 138-48.
16. Wang Y-H, Li J-Q, Shi J-F, et al. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. *Molecular Psychiatry*. 2020; 25: 1487-99.
17. Wang TH, Hsia SM, Shih YH and Shieh TM. Association of smoking, alcohol use, and betel quid chewing with epigenetic aberrations in cancers. *Int J Mol Sci*. 2017; 18.
18. Takahashi K, Porcel JM, Lee P and Leung CC. Year in review 2014: Lung cancer, pleural diseases, respiratory infections and tuberculosis, bronchoscopic intervention and imaging. *Respirology*. 2015; 20: 674-83.
19. El-Telbany A and Ma PC. Cancer genes in lung cancer: racial disparities: are there any? *Genes & cancer*. 2012; 3: 467-80.
20. Lazarus DR and Ost DE. How and when to use genetic markers for nonsmall cell lung cancer. *Curr Opin Pulm Med*. 2013; 19: 331-9.
21. Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the

College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *The Journal of molecular diagnostics : JMD*. 2018; 20: 129-59.
22. Kim EY, Lee SH, Kim A, Kim T and Chang YS. Tumor clonal status predicts clinical outcomes of lung adenocarcinoma with EGFR-TKI sensitizing mutation. *Journal of Cancer*. 2019; 10: 5549-56.
23. Garrido P, Conde E, de Castro J, et al. Updated guidelines for predictive biomarker testing in advanced non-small-cell lung cancer: a National Consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*. 2020; 22: 989-1003.
24. Ooi AT and Gomperts BN. Molecular Pathways: Targeting Cellular Energy Metabolism in Cancer via Inhibition of SLC2A1 and LDHA. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2015; 21: 2440-4.
25. Hirano H, Maeda H, Yamaguchi T, Yokota S, Mori M and Sakoda S. Survivin expression in lung cancer: Association with smoking, histological types and pathological stages. *Oncol Lett*. 2015; 10: 1456-62.
26. Choy B, LaLonde A, Que J, Wu T and Zhou Z. MCM4 and MCM7, potential novel proliferation markers, significantly correlated with Ki-67, Bmi1, and cyclin E expression in esophageal adenocarcinoma, squamous cell carcinoma, and precancerous lesions. *Hum Pathol*. 2016; 57: 126-35.
27. Khalil AA, Sivakumar S, Lucas FAS, et al. TBX2 subfamily suppression in lung cancer pathogenesis: a high-potential marker for early detection. *Oncotarget*. 2017; 8: 68230-41.
28. Wang L, Zhang J, Wan L, Zhou X, Wang Z and Wei W. Targeting Cdc20 as a novel cancer therapeutic strategy. *Pharmacology & therapeutics*. 2015; 151: 141-51.
29. Alevizakos M, Kaltsas S and Syrigos KN. The VEGF pathway in lung cancer. *Cancer Chemother Pharmacol*. 2013; 72: 1169-81.
30. Xu Y, Gao P, Lv X, Zhang L and Zhang J. The role of the ataxia telangiectasia mutated gene in lung cancer: Recent advances in research. *Therapeutic Advances in Respiratory Disease*. 2017; 11: 375-80.
31. Wu G, Jiang B, Liu X, Shen Y and Yang S. Association of GSTs gene polymorphisms with treatment outcome of advanced non-small cell lung cancer patients with cisplatin-based chemotherapy. *International journal of clinical and experimental pathology*. 2015; 8: 13346-52.
32. Jamsai D, Watkins DN, O'Connor AE, et al. In vivo evidence that RBM5 is a tumour suppressor in the lung. *Scientific Reports*. 2017; 7: 16323.
33. Sanchez-Cespedes M. The role of LKB1 in lung cancer. *Familial Cancer*. 2011; 10: 447-53.
34. Westcott PMK and To MD. The genetics and biology of KRAS in lung cancer. *Chinese journal of cancer*. 2013; 32: 63-70.
35. Tan Z, Yang C, Zhang X, Zheng P and Shen W. Expression of glucose transporter 1 and prognosis in non-small cell lung cancer: a pooled analysis of 1665 patients. *Oncotarget*. 2017; 8: 60954-61.
36. Bronte G, Ulivi P, Verlicchi A, Cravero P, Delmonte A and Crinò L. Targeting RET-rearranged non-small-cell lung cancer: future prospects. *Lung Cancer (Auckland, NZ)*. 2019; 10: 27-36.
37. Planchard D, Kim TM, Mazieres J, et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016; 17: 642-50.
38. Lawrence RE and Salgia R. MET molecular mechanisms and therapies in lung cancer. *Cell adhesion & migration*. 2010; 4: 146-52.
39. Yu YX, Wang Y and Liu H. Overexpression of PTEN suppresses non-small-cell lung carcinoma metastasis through inhibition of integrin αVβ6 signaling. *Am J Transl Res*. 2017; 9: 3304-14.
40. Liang H and Wang M. MET Oncogene in Non-Small Cell Lung Cancer: Mechanism of MET Dysregulation and Agents Targeting the HGF/c-Met Axis. *Onco Targets Ther*. 2020; 13: 2491-510.
41. Rosell R, Chaib I and Santarpia M. Targeting MET amplification in EGFR-mutant non-small-cell lung cancer. *The Lancet Respiratory Medicine*. 2020; 8: 1068-70.

42. Zhang M, Li G, Wang Y, et al. PD-L1 expression in lung cancer and its correlation with driver mutations: a meta-analysis. *Scientific reports*. 2017; 7: 10255-.
43. Lin PY, Yu SL and Yang PC. MicroRNA in lung cancer. *British journal of cancer*. 2010; 103: 1144-8.
44. Ali Syeda Z, Langden SSS, Munkhzul C, Lee M and Song SJ. Regulatory Mechanism of MicroRNA Expression in Cancer. *Int J Mol Sci*. 2020; 21: 1723.
45. Yang X, Zhang Q, Zhang M, et al. Serum microRNA Signature Is Capable of Early Diagnosis for Non-Small Cell Lung Cancer. *Int J Biol Sci*. 2019; 15: 1712-22.
46. Aiso T, Ohtsuka K, Ueda M, et al. Serum levels of candidate microRNA diagnostic markers differ among the stages of non-small-cell lung cancer. *Oncol Lett*. 2018; 16: 6643-51.
47. Wang J, Chen J and Sen S. MicroRNA as Biomarkers and Diagnostics. *J Cell Physiol*. 2016; 231: 25-30.
48. Takamizawa J, Konishi H, Yanagisawa K, et al. Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. *Cancer Res*. 2004; 64: 3753-6.
49. Inamura K and Ishikawa Y. MicroRNA In Lung Cancer: Novel Biomarkers and Potential Tools for Treatment. *Journal of clinical medicine*. 2016; 5: 36.
50. Zhang H, Mao F, Shen T, et al. Plasma miR-145, miR-20a, miR-21 and miR-223 as novel biomarkers for screening early-stage non-small cell lung cancer. *Oncol Lett*. 2017; 13: 669-76.
51. Kim YH, Lee WK, Lee EB, Son JW, Kim DS and Park JY. Combined Effect of Metastasis-Related MicroRNA, miR-34 and miR-124 Family, Methylation on Prognosis of Non–Small-Cell Lung Cancer. *Clinical Lung Cancer*. 2017; 18: e13-e20.
52. Yuwen DL, Sheng BB, Liu J, Wenyu W and Shu YQ. MiR-146a-5p level in serum exosomes predicts therapeutic effect of cisplatin in non-small cell lung cancer. *European review for medical and pharmacological sciences*. 2017; 21: 2650-8.
53. Di Leva G, Garofalo M and Croce CM. MicroRNAs in cancer. *Annual review of pathology*. 2014; 9: 287-314.
54. Gao ZJ, Yuan WD, Yuan JQ, Yuan K and Wang Y. miR-486-5p functions as an oncogene by targeting PTEN in non-small cell lung cancer. *Pathology Research and Practice*. 2018; 214: 700-5.
55. Yang W, Bai J, Liu D, et al. MiR-93-5p up-regulation is involved in non-small cell lung cancer cells proliferation and migration and poor prognosis. *Gene*. 2018; 647: 13-20.
56. Gao X, Zhao H, Diao C, et al. miR-455-3p serves as prognostic factor and regulates the proliferation and migration of non-small cell lung cancer through targeting HOXB5. *Biochemical and Biophysical Research Communications*. 2018; 495: 1074-80.
57. Sun B, Liu HF, Ding Y and Li Z. Evaluating the diagnostic and prognostic value of Serum miR-770 in non-small cell lung cancer. *European Review for Medical and Pharmacological Sciences*. 2018; 22: 3061-6.
58. Ma Z, Cai H, Zhang Y, Chang L and Cui Y. MiR-129-5p inhibits non-small cell lung cancer cell stemness and chemoresistance through targeting DLK1. *Biochemical and Biophysical Research Communications*. 2017; 490: 309-16.
59. Xu J, Wu W, Jun W, et al. MiR-367 promotes the proliferation and invasion of non-small cell lung cancer via targeting FBXW7. *Oncology Reports*. 2017; 37: 1052-8.
60. Parashar B, Arora S and Wernicke AG. Radiation therapy for early stage lung cancer. *Seminars in interventional radiology*. 2013; 30: 185-90.
61. Lackey A and Donington JS. Surgical management of lung cancer. *Seminars in interventional radiology*. 2013; 30: 133-40.
62. Liu Y, Shan L, Shen J, et al. Choice of surgical procedure - lobectomy, segmentectomy, or wedge resection - for patients with stage T1-2N0M0 small cell lung cancer: A population-based study. *Thorac Cancer*. 2019; 10: 593-600.
63. Lemjabbar-Alaoui H, Hassan OU, Yang YW and Buchanan P. Lung cancer: Biology and treatment options. *Biochim Biophys Acta*. 2015; 1856: 189-210.

64. Lu B, Sun L, Yan X, Ai Z and Xu J. Intratumoral chemotherapy with paclitaxel liposome combined with systemic chemotherapy: a new method of neoadjuvant chemotherapy for stage III unresectable non-small cell lung cancer. *Medical Oncology*. 2014; 32: 345.
65. Bharali DJ and Mousa SA. Emerging nanomedicines for early cancer detection and improved treatment: current perspective and future promise. *Pharmacol Ther*. 2010; 128: 324-35.
66. Sivarajakumar R, Mallukaraj D, Kadavakollu M, et al. Nanoparticles for the Treatment of Lung Cancers. *Journal of Young Pharmacists*. 2018; 10.
67. Naddafi F. Monoclonal antibodies in non-small-cell lung cancer: Light at the end of the tunnel. *Trends in Medicine*. 2019; 19.
68. Lee SH. Chemotherapy for Lung Cancer in the Era of Personalized Medicine. *Tuberculosis and respiratory diseases*. 2019; 82: 179-89.
69. Socinski MA, Evans T, Gettinger S, et al. Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013; 143: e341S-e68S.
70. Chan BA and Hughes BGM. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. *Translational lung cancer research*. 2015; 4: 36-54.
71. Lee H-Y, Mohammed KA and Nasreen N. Nanoparticle-based targeted gene therapy for lung cancer. *American journal of cancer research*. 2016; 6: 1118-34.
72. Pirker R and Filipits M. Monoclonal antibodies against EGFR in non-small cell lung cancer. *Crit Rev Oncol Hematol*. 2011; 80: 1-9.
73. Hicklin DJ and Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*. 2005; 23: 1011-27.
74. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *The Lancet*. 2014; 383: 31-9.
75. Garon EB, Ciuleanu T-E, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *The Lancet*. 2014; 384: 665-73.
76. Topalian SL, Weiner GJ and Pardoll DM. Cancer immunotherapy comes of age. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011; 29: 4828-36.
77. Ruiz R, Hunis B and Raez LE. Immunotherapeutic Agents in Non-small-cell Lung Cancer Finally Coming to the Front Lines. *Current Oncology Reports*. 2014; 16: 400.
78. Lara-Guerra H and Roth JA. Gene Therapy for Lung Cancer. *Critical reviews in oncogenesis*. 2016; 21: 115-24.
79. Amreddy N, Babu A, Muralidharan R, Munshi A and Ramesh R. Polymeric Nanoparticle-Mediated Gene Delivery for Lung Cancer Treatment. *Top Curr Chem (Cham)*. 2017; 375: 35.
80. Salvioni L, Rizzuto MA, Bertolini JA, Pandolfi L, Colombo M and Prosperi D. Thirty Years of Cancer Nanomedicine: Success, Frustration, and Hope. *Cancers (Basel)*. 2019; 11: 1855.
81. Pugazhendhi A, Edison T, Karuppusamy I and Kathirvel B. Inorganic nanoparticles: A potential cancer therapy for human welfare. *International journal of pharmaceutics*. 2018; 539: 104-11.
82. Sukumar UK, Bhushan B, Dubey P, Matai I, Sachdev A and Packirisamy G. Emerging applications of nanoparticles for lung cancer diagnosis and therapy. *International Nano Letters*. 2013; 3: 45.
83. Wang Y, Yang P, Zhao X, et al. Multifunctional Cargo-Free Nanomedicine for Cancer Therapy. *Int J Mol Sci*. 2018; 19: 2963.
84. Dai W, Wang X, Song G, et al. Combination antitumor therapy with targeted dual-nanomedicines. *Advanced drug delivery reviews*. 2017; 115: 23-45.
85. Arranja AG, Pathak V, Lammers T and Shi Y. Tumor-targeted nanomedicines for cancer theranostics. *Pharmacol Res*. 2017; 115: 87-95.

86. Jahan ST, Sadat SMA, Walliser M and Haddadi A. Targeted Therapeutic Nanoparticles: An Immense Promise to Fight against Cancer. *J Drug Deliv*. 2017; 2017: 9090325.
87. Zamani P, Momtazi-Borojeni AA, Nik ME, Oskuee RK and Sahebkar A. Nanoliposomes as the adjuvant delivery systems in cancer immunotherapy. *Journal of Cellular Physiology*. 2018; 233: 5189-99.
88. Muthu MS and Wilson B. Multifunctional radionanomedicine: a novel nanoplatform for cancer imaging and therapy. *Nanomedicine (Lond)*. 2010; 5: 169-71.
89. Jeon J. Review of Therapeutic Applications of Radiolabeled Functional Nanomaterials. *Int J Mol Sci*. 2019; 20: 2323.
90. Man F, Lammers T and T M de Rosales R. Imaging Nanomedicine-Based Drug Delivery: a Review of Clinical Studies. *Mol Imaging Biol*. 2018; 20: 683-95.
91. Gonda A, Zhao N, Shah JV, et al. Engineering tumor-targeting nanoparticles as vehicles for precision nanomedicine. *Med one*. 2019; 4.
92. Lamichhane N, Udayakumar T, D'Souza W, et al. Liposomes: Clinical Applications and Potential for Image-Guided Drug Delivery. *Molecules*. 2018; 23: 288.
93. Yu G, Ning Q, Mo Z and Tang S. Intelligent polymeric micelles for multidrug co-delivery and cancer therapy. *Artificial Cells, Nanomedicine, and Biotechnology*. 2019; 47: 1476-87.
94. Chis AA, Dobrea C, Morgovan C, et al. Applications and Limitations of Dendrimers in Biomedicine. *Molecules (Basel, Switzerland)*. 2020; 25: 3982.
95. Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK and Hua S. Advances and Challenges of Liposome Assisted Drug Delivery. *Front Pharmacol*. 2015; 6: 286.
96. Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK and Hua S. Advances and Challenges of Liposome Assisted Drug Delivery. *Frontiers in Pharmacology*. 2015; 6.
97. Zhou J, Zhao WY, Ma X, et al. The anticancer efficacy of paclitaxel liposomes modified with mitochondrial targeting conjugate in resistant lung cancer. *Biomaterials*. 2013; 34: 3626-38.
98. Zhou X, Tao H and Shi KH. Development of a nanoliposomal formulation of erlotinib for lung cancer and in vitro/in vivo antitumoral evaluation. *Drug design, development and therapy*. 2018; 12: 1-8.
99. Jinturkar KA, Anish C, Kumar MK, Bagchi T, Panda AK and Misra AR. Liposomal formulations of Etoposide and Docetaxel for p53 mediated enhanced cytotoxicity in lung cancer cell lines. *Biomaterials*. 2012; 33: 2492-507.
100. Wei Y, Liang J, Zheng X, et al. Lung-targeting drug delivery system of baicalin-loaded nanoliposomes: development, biodistribution in rabbits, and pharmacodynamics in nude mice bearing orthotopic human lung cancer. *International journal of nanomedicine*. 2016; 12: 251-61.
101. Yang J, Wu W, Wen J, et al. Liposomal honokiol induced lysosomal degradation of Hsp90 client proteins and protective autophagy in both gefitinib-sensitive and gefitinib-resistant NSCLC cells. *Biomaterials*. 2017; 141: 188-98.
102. Immordino ML, Dosio F and Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. *International journal of nanomedicine*. 2006; 1: 297.
103. Kraut EH, Fishman MN, Lorusso PM, et al. Final results of a phase I study of liposome encapsulated SN-38 (LE-SN38): safety, pharmacogenomics, pharmacokinetics, and tumor response. *Journal of Clinical Oncology*. 2005; 23: 2017-.
104. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. *Nature reviews Drug discovery*. 2005; 4: 145-60.
105. Whiteman K, Subr V, Ulbrich K and Torchilin V. Poly (HPMA)-coated liposomes demonstrate prolonged circulation in mice. *Journal of Liposome Research*. 2001; 11: 153-64.
106. Petersen GH, Alzghari SK, Chee W, Sankari SS and La-Beck NM. Meta-analysis of clinical and preclinical studies comparing the anticancer efficacy of liposomal versus conventional non-liposomal doxorubicin. *Journal of controlled release : official journal of the Controlled Release Society*. 2016; 232: 255-64.

107. Barenholz YC. Doxil®—the first FDA-approved nano-drug: lessons learned. *Journal of controlled release*. 2012; 160: 117-34.
108. Biswas S, Deshpande PP, Perche F, Dodwadkar NS, Sane SD and Torchilin VP. Octa-arginine-modified pegylated liposomal doxorubicin: an effective treatment strategy for non-small cell lung cancer. *Cancer Lett*. 2013; 335: 191-200.
109. Cheng L, Huang F-Z, Cheng L-F, et al. GE11-modified liposomes for non-small cell lung cancer targeting: preparation, ex vitro and in vivo evaluation. *International journal of nanomedicine*. 2014; 9: 921.
110. Zhang T, Chen Y, Ge Y, Hu Y, Li M and Jin Y. Inhalation treatment of primary lung cancer using liposomal curcumin dry powder inhalers. *Acta Pharmaceutica Sinica B*. 2018; 8: 440-8.
111. Lin C, Zhang X, Chen H, et al. Dual-ligand modified liposomes provide effective local targeted delivery of lung-cancer drug by antibody and tumor lineage-homing cell-penetrating peptide. *Drug Deliv*. 2018; 25: 256-66.
112. Fu S, Zhao Y, Sun J, et al. Integrin αvβ3-targeted liposomal drug delivery system for enhanced lung cancer therapy. *Colloids and Surfaces B: Biointerfaces*. 2021; 201: 111623.
113. Stathopoulos GP, Antoniou D, Dimitroulis J, Stathopoulos J, Marosis K and Michalopoulou P. Comparison of liposomal cisplatin versus cisplatin in non-squamous cell non-small-cell lung cancer. *Cancer Chemother Pharmacol*. 2011; 68: 945-50.
114. Stathopoulos GP, Stathopoulos J and Dimitroulis J. Two consecutive days of treatment with liposomal cisplatin in non-small cell lung cancer. *Oncol Lett*. 2012; 4: 1013-6.
115. Song X-l, Ju R-j, Xiao Y, et al. Application of multifunctional targeting epirubicin liposomes in the treatment of non-small-cell lung cancer. *International journal of nanomedicine*. 2017; 12: 7433.
116. Lin C, Wong BCK, Chen H, et al. Pulmonary delivery of triptolide-loaded liposomes decorated with anti-carbonic anhydrase IX antibody for lung cancer therapy. *Scientific Reports*. 2017; 7: 1097.
117. Costantini L, Molinari R, Farinon B and Merendino N. Retinoic Acids in the Treatment of Most Lethal Solid Cancers. *Journal of clinical medicine*. 2020; 9.
118. Suzuki S, Kawakami S, Chansri N, Yamashita F and Hashida M. Inhibition of pulmonary metastasis in mice by all-trans retinoic acid incorporated in cationic liposomes. *Journal of controlled release : official journal of the Controlled Release Society*. 2006; 116: 58-63.
119. Kawakami S, Suzuki S, Yamashita F and Hashida M. Induction of apoptosis in A549 human lung cancer cells by all-trans retinoic acid incorporated in DOTAP/cholesterol liposomes. *Journal of controlled release : official journal of the Controlled Release Society*. 2006; 110: 514-21.
120. Charoensit P, Kawakami S, Higuchi Y, Yamashita F and Hashida M. Enhanced growth inhibition of metastatic lung tumors by intravenous injection of ATRA-cationic liposome/IL-12 pDNA complexes in mice. *Cancer gene therapy*. 2010; 17: 512-22.
121. Berlin Grace VM and Viswanathan S. Pharmacokinetics and therapeutic efficiency of a novel cationic liposome nano-formulated all trans retinoic acid in lung cancer mice model. *Journal of Drug Delivery Science and Technology*. 2017; 39: 223-36.
122. Cho H, Lai TC, Tomoda K and Kwon GS. Polymeric micelles for multi-drug delivery in cancer. *AAPS PharmSciTech*. 2015; 16: 10-20.
123. Zhou Q, Zhang L, Yang T and Wu H. Stimuli-responsive polymeric micelles for drug delivery and cancer therapy. *International journal of nanomedicine*. 2018; 13: 2921-42.
124. Kim DW, Kim SY, Kim HK, et al. Multicenter phase II trial of Genexol-PM, a novel Cremophor-free, polymeric micelle formulation of paclitaxel, with cisplatin in patients with advanced non-small-cell lung cancer. *Ann Oncol*. 2007; 18: 2009-14.
125. Guthi JS, Yang SG, Huang G, et al. MRI-visible micellar nanomedicine for targeted drug delivery to lung cancer cells. *Molecular pharmaceutics*. 2010; 7: 32-40.
126. Zhang L, Liu Z, Kong C, et al. Improving Drug Delivery of Micellar Paclitaxel against Non-Small Cell Lung Cancer by Coloading Itraconazole as a Micelle Stabilizer and a Tumor Vascular Manipulator. *Small (Weinheim an der Bergstrasse, Germany)*. 2018; 14: e1802112.

127. Muddineti OS, Shah A, Rompicharla SVK, Ghosh B and Biswas S. Cholesterol-grafted chitosan micelles as a nanocarrier system for drug-siRNA co-delivery to the lung cancer cells. *International journal of biological macromolecules*. 2018; 118: 857-63.
128. Subbiah V, Grilley-Olson JE, Combest AJ, et al. Phase Ib/II Trial of NC-6004 (Nanoparticle Cisplatin) Plus Gemcitabine in Patients with Advanced Solid Tumors. *Clinical Cancer Research*. 2018; 24: 43-51.
129. Wei T, Liu J, Ma H, et al. Functionalized Nanoscale Micelles Improve Drug Delivery for Cancer Therapy in Vitro and in Vivo. *Nano Letters*. 2013; 13: 2528-34.
130. Shi H, van Steenbergen MJ, Lou B, Liu Y, Hennink WE and Kok RJ. Folate decorated polymeric micelles for targeted delivery of the kinase inhibitor dactolisib to cancer cells. *International journal of pharmaceutics*. 2020; 582: 119305.
131. Zhou Y, Wen H, Gu L, et al. Aminoglucose-functionalized, redox-responsive polymer nanomicelles for overcoming chemoresistance in lung cancer cells. *Journal of Nanobiotechnology*. 2017; 15: 87.
132. Abdelaziz HM, Gaber M, Abd-Elwakil MM, et al. Inhalable particulate drug delivery systems for lung cancer therapy: Nanoparticles, microparticles, nanocomposites and nanoaggregates. *Journal of controlled release : official journal of the Controlled Release Society*. 2018; 269: 374-92.
133. Rezazadeh M, Davatsaz Z, Emami J, Hasanzadeh F and Jahanian-Najafabadi A. Preparation and Characterization of Spray-Dried Inhalable Powders Containing Polymeric Micelles for Pulmonary Delivery of Paclitaxel in Lung Cancer. *Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques*. 2018; 21: 200s-14s.
134. He W, Xiao W, Zhang X, et al. Pulmonary-Affinity Paclitaxel Polymer Micelles in Response to Biological Functions of Ambroxol Enhance Therapeutic Effect on Lung Cancer. *International journal of nanomedicine*. 2020; 15: 779-93.
135. Cheng Y, Xu Z, Ma M and Xu T. Dendrimers as drug carriers: applications in different routes of drug administration. *Journal of pharmaceutical sciences*. 2008; 97: 123-43.
136. Palmerston Mendes L, Pan J and Torchilin VP. Dendrimers as Nanocarriers for Nucleic Acid and Drug Delivery in Cancer Therapy. *Molecules (Basel, Switzerland)*. 2017; 22: 1401.
137. Tomalia DA, Reyna LA and Svenson S. Dendrimers as multi-purpose nanodevices for oncology drug delivery and diagnostic imaging. *Biochemical Society transactions*. 2007; 35: 61-7.
138. Bhadra D, Bhadra S, Jain S and Jain NK. A PEGylated dendritic nanoparticulate carrier of fluorouracil. *International journal of pharmaceutics*. 2003; 257: 111-24.
139. Christensen JB. Dendrimers-Based Nanoparticles for Cancer Therapy and Bioimaging. In: Gonçalves G and Tobias G, (eds.). *Nanooncology: Engineering nanomaterials for cancer therapy and diagnosis*. Cham: Springer International Publishing, 2018, p. 281-304.
140. Franiak-Pietryga I, Ziemba B, Messmer B and Skowronska-Krawczyk D. Dendrimers as Drug Nanocarriers: The Future of Gene Therapy and Targeted Therapies in Cancer. 2018, p. 7-27.
141. Liu J, Liu J, Chu L, et al. Novel peptide-dendrimer conjugates as drug carriers for targeting nonsmall cell lung cancer. *International journal of nanomedicine*. 2010; 6: 59-69.
142. Kaminskas LM, McLeod VM, Ryan GM, et al. Pulmonary administration of a doxorubicin-conjugated dendrimer enhances drug exposure to lung metastases and improves cancer therapy. *Journal of controlled release : official journal of the Controlled Release Society*. 2014; 183: 18-26.
143. Leong NJ, Mehta D, McLeod VM, et al. Doxorubicin Conjugation and Drug Linker Chemistry Alter the Intravenous and Pulmonary Pharmacokinetics of a PEGylated Generation 4 Polylysine Dendrimer in Rats. *Journal of pharmaceutical sciences*. 2018; 107: 2509-13.
144. Zhang W-w, Wang Y-c, Kan X-m, Wang X-m and Geng D-m. Preparation and evaluation of peptide-dendrimer-paclitaxel conjugates for treatment of heterogeneous stage 1 nonsmall cell lung cancer in 293T and L132 cell lines. *Tropical Journal of Pharmaceutical Research*. 2017; 16: 737-42.

145. Amreddy N, Babu A, Panneerselvam J, et al. Chemo-biologic combinatorial drug delivery using folate receptor-targeted dendrimer nanoparticles for lung cancer treatment. *Nanomedicine : nanotechnology, biology, and medicine*. 2018; 14: 373-84.
146. Yoon AR, Kasala D, Li Y, et al. Antitumor effect and safety profile of systemically delivered oncolytic adenovirus complexed with EGFR-targeted PAMAM-based dendrimer in orthotopic lung tumor model. *Journal of controlled release : official journal of the Controlled Release Society*. 2016; 231: 2-16.
147. Babu A, Muralidharan R, Amreddy N, Mehta M, Munshi A and Ramesh R. Nanoparticles for siRNA-Based Gene Silencing in Tumor Therapy. *IEEE Trans Nanobioscience*. 2016; 15: 849-63.
148. Wu Y, Crawford M, Yu B, Mao Y, Nana-Sinkam SP and Lee LJ. MicroRNA delivery by cationic lipoplexes for lung cancer therapy. *Molecular pharmaceutics*. 2011; 8: 1381-9.
149. Askarian S, Abnous K, Taghavi S, Oskuee RK and Ramezani M. Cellular delivery of shRNA using aptamer-conjugated PLL-alkyl-PEI nanoparticles. *Colloids and Surfaces B: Biointerfaces*. 2015; 136: 355-64.
150. Wu Y, Crawford M, Mao Y, et al. Therapeutic Delivery of MicroRNA-29b by Cationic Lipoplexes for Lung Cancer. *Molecular therapy Nucleic acids*. 2013; 2: e84-e.
151. Ayatollahi S, Salmasi Z, Hashemi M, et al. Aptamer-targeted delivery of Bcl-xL shRNA using alkyl modified PAMAM dendrimers into lung cancer cells. *The International Journal of Biochemistry & Cell Biology*. 2017; 92: 210-7.
152. Ramesh R, Saeki T, Smyth Templeton N, et al. Successful Treatment of Primary and Disseminated Human Lung Cancers by Systemic Delivery of Tumor Suppressor Genes Using an Improved Liposome Vector. *Molecular Therapy*. 2001; 3: 337-50.
153. Cortez MA, Valdecanas D, Zhang X, et al. Therapeutic Delivery of miR-200c Enhances Radiosensitivity in Lung Cancer. *Molecular Therapy*. 2014; 22: 1494-503.
154. Tian H, Liu S, Zhang J, et al. Enhancement of cisplatin sensitivity in lung cancer xenografts by liposome-mediated delivery of the plasmid expressing small hairpin RNA targeting Survivin. *Journal of biomedical nanotechnology*. 2012; 8: 633-41.
155. Lee H-Y, Mohammed KA, Kaye F, et al. Targeted delivery of let-7a microRNA encapsulated ephrin-A1 conjugated liposomal nanoparticles inhibit tumor growth in lung cancer. *International journal of nanomedicine*. 2013; 8: 4481-94.
156. Zhang Y, Schwerbrock NMJ, Rogers AB, Kim WY and Huang L. Codelivery of VEGF siRNA and Gemcitabine Monophosphate in a Single Nanoparticle Formulation for Effective Treatment of NSCLC. *Molecular Therapy*. 2013; 21: 1559-69.
157. Li J, Yang Y and Huang L. Calcium phosphate nanoparticles with an asymmetric lipid bilayer coating for siRNA delivery to the tumor. *Journal of controlled release : official journal of the Controlled Release Society*. 2012; 158: 108-14.
158. Yang Y, Li J, Liu F and Huang L. Systemic delivery of siRNA via LCP nanoparticle efficiently inhibits lung metastasis. *Molecular therapy : the journal of the American Society of Gene Therapy*. 2012; 20: 609-15.
159. Conde J, Tian F, Hernández Y, et al. In vivo tumor targeting via nanoparticle-mediated therapeutic siRNA coupled to inflammatory response in lung cancer mouse models. *Biomaterials*. 2013; 34: 7744-53.
160. Lu C, Stewart DJ, Lee JJ, et al. Phase I clinical trial of systemically administered TUSC2(FUS1)-nanoparticles mediating functional gene transfer in humans. *PloS one*. 2012; 7: e34833-e.

÷