Cutting-Edge Therapies for Lung Cancer

Subjects: Oncology

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Lung cancer remains a formidable global health challenge that necessitates inventive strategies to improve its therapeutic outcomes. The conventional treatments, including surgery, chemotherapy, and radiation, have demonstrated limitations in achieving sustained responses. Therefore, exploring novel approaches encompasses a range of interventions that show promise in enhancing the outcomes for patients with advanced or refractory cases of lung cancer. These groundbreaking interventions can potentially overcome cancer resistance and offer personalized solutions.

lung cancer conventional treatment innovative therapeutic modalities

1. Introduction

Lung cancer remains a significant cause of cancer-related deaths worldwide despite the progress made in cancer diagnosis and emerging treatment methods [1]. The 5-year overall survival rate for lung cancer patients is 19% across all stages of the disease. However, as the disease progresses from the early to advanced stages, there is a significant decline in the 5-year survival rate [2]. This is also observed in lung cancer patients with stage 1 tumors, where the 5-year recurrence-free survival only slightly exceeds 80% following curative surgical resection [1]. This implies that approximately 20% of individuals with lung cancer undergo disease recurrence within five years, underscoring the lack of a conclusive cure. Furthermore, a significant portion of lung cancer patients, constituting 57%, are diagnosed with metastasis, and their survival rate is as low as 5% [3].

Innovative approaches are continually shaping the landscape of lung cancer treatment, offering improved outcomes and novel options for patients. Advancements in this field encompass immunotherapy, targeted therapy, cryoablation, and the utilization of nanoparticle-based drug delivery systems, along with the evolving realm of gene therapy. However, ongoing research holds the promise of additional breakthroughs, contributing significantly to successful clinical outcomes that may revolutionize the care of lung cancer patients [4][5][6]. Combinatorial therapeutic approaches represent a significant spectrum of innovative strategies. The ESMO Congress 2023 notably highlights the efficacy of combining targeted drugs and immunotherapy, especially for lung cancer patients with EGFR mutations and rare tumor alterations.

2. Targeted Therapies

2.1. Epidermal Growth Factor Receptor (EGFR) Inhibitors

Epidermal growth factor receptor (EGFR)-activating mutations are prevalent in non-small cell lung carcinoma (NSCLC), which is the predominant type of lung cancer. Around 4–10% of NSCLC patients with EGFR mutations exhibit EGFR exon 20 insertion (ex20ins) mutations, whereas 46% have EGFR exon 19 deletion (ex19del) mutations and 38% harbor the EGFR L858R point mutation [7]. The discovery of tyrosine kinase inhibitors (TKIs) designed to target EGFR mutations in lung cancer patients marked the inception of the precision medicine era in lung cancer. EGFR TKIs have been designed to target these mutations effectively by inhibiting the activation of the tyrosine kinase domain and disrupting various EGFR-dependent/independent downstream signaling pathways in the lungs [8]. Currently, there are three generations of clinically available EGFR TKIs, namely the first generation of reversible inhibitors (gefitinib, erlotinib, and icotinib), the second generation of irreversible inhibitors (afatinib, dacomitinib), and the third generation of irreversible inhibitors (osimertinib, almonertinib, and lazertinib) [8].

Monoclonal antibodies offer an alternative strategy for inhibiting EGFR activation and signaling. These antibodies not only form complexes with the receptor, which are internalized and eliminated, but can also entirely block ligands from attaching to the extracellular domain. The available monoclonal antibodies targeting EGFR include cetuximab, necitumumab, panitumumab, and matuzumab. In two phase III trials, FLEX and BMS099, a combination of cetuximab and platinum doublet chemotherapy was employed to treat advanced NSCLC [9][10].

EGFR TKIs significantly enhance the objective response rate, progression-free survival, and quality of life when compared to conventional chemotherapeutic approaches, all while presenting minimal toxicity [11][12]. The adoption of EGFR TKIs marks a significant leap forward in the treatment of NSCLC, ushering in an era of targeted therapy and precision medication.

2.2. Kirsten Rat Sarcoma Viral Oncogene Homologue (KRAS) Inhibitors

Kirsten rat sarcoma viral oncogene homologue (KRAS) is a well-known oncogene encoding the Ras family of small GTPases, controlling crucial proliferation and survival pathways. Among three members of the Ras family, KRAS is the most frequently mutated in cancers (85%), followed by NRAS (11%) and HRAS (4%). The most frequent KRAS-activating mutations occur at the amino acid positions G12, G13, and Q61 [13]. The Ras oncogenes play a crucial role in oncogenesis and have been naturally considered potent targets for cancer therapy. However, several efforts to target Ras proteins have faced considerable challenges due to molecular features such as a highly dynamic structure and high intrinsic flexibility precluding stable binding of the inhibitors, thus deeming them “undruggable” [14]. However, new technologies and insights into the KRAS signaling pathways have renewed efforts to develop therapies for KRAS-driven cancers. These include direct KRAS targeting or indirect targeting by blocking the upstream factors activating KRAS [15].

A direct approach to targeting KRAS in lung cancer involves using sotorasib (AMG510) and adagrasib (MRTX849). Sotorasib is a covalent inhibitor designed for KRAS G12C and marked a milestone as the first KRAS inhibitor to receive US Food and Drug Administration (FDA) approval on 28 May 2021 [16]. This drug covalently binds to the mutant cysteine 12 in the switch II region, prompting KRAS to stay inactive in its GDP-bound form. Consequently, it inhibits KRAS signaling and suppresses the MAPK pathway. In a phase II clinical trial encompassing 126 patients

with advanced NSCLC, sotorasib demonstrated a 37.1% response rate, a progression-free survival of 6.8 months, and a median overall survival of 12.5 months [17]. Adagrasib is another FDA-approved small molecule directly targeting KRAS G12C by covalently binding to the mutant cysteine 12, effectively inhibiting KRAS-dependent signaling, such as the MAPK pathway [13].

Another chemotherapeutic approach is to target KRAS indirectly by inhibiting its upstream regulators. Currently, a phase I clinical trial (NCT04111458) is evaluating the efficacy of BI1701963, an inhibitor of SOS1, which serves as a guanine nucleotide exchange factor, turning KRAS into its GTP-bound active form. This study investigates the effectiveness of BI1701963 both as a monotherapy and in combination with the MEK inhibitor trametinib [18].

2.3. Anaplastic Lymphoma Kinase (ALK) Inhibitors

The anaplastic lymphoma kinase (ALK) receptor tyrosine kinase plays a pivotal role in cellular development, and alterations in the ALK gene may occur in cancers such as anaplastic large cell lymphoma, neuroblastoma, and NSCLC. When the ALK gene is activated in cancer, it can lead to cell development and rapid growth. This activation of ALK signaling in the tumor cells is brought about by mechanisms such as gene fusions, chromosomal translocations, gene amplification or deregulation, and activating point mutations [19][20]. In treating NSCLC patients with ALK alterations, targeted inhibitors such as crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib offer significant benefits [21]. Crizotinib is a potent small-molecule drug that effectively targets the tyrosine kinases ALK and c-MET [22]. Phase I/II clinical studies have demonstrated that crizotinib enhances progression-free survival in combination with bevacizumab, an angiogenesis-inhibiting antibody [23]. On the other hand, ceritinib, a second-generation ALK inhibitor, has been utilized to treat advanced or metastatic ALK-positive NSCLC, even in patients resistant to crizotinib [24][25].

2.4. ROS Proto-Oncogene 1, Receptor Tyrosine Kinase (ROS1) Inhibitors

ROS proto-oncogene 1, receptor tyrosine kinase (ROS1) is a paralog of ALK belonging to the insulin receptor family that functions as a growth or differentiation factor receptor. The incidence of ROS1 rearrangements is observed in 1% to 2% of NSCLC cases. Although some ROS1 inhibitors, specifically crizotinib (first generation), entrectinib (second generation) and lorlatinib (third generation), have received FDA approval for treating ROS1-positive NSCLC, the majority of patients still encounter challenges with treatment resistance and disease progression [12][26].

2.5. BRAF V600E Mutation Inhibitors

BRAF mutations are rare mutations in NSCLC, with a higher prevalence observed in never-smokers, women, and aggressive histological types, particularly the micropapillary subtype [27]. Cancer cells harboring the V600E BRAF mutation rely predominantly on the activity of this oncogene for their growth and survival [28]. Some BRAF V600E mutation inhibitors are vemurafenib, dabrafenib, and sorafenib. Clinical investigation has demonstrated that vemurafenib, a potent inhibitor of the BRAF V600E mutation, exhibits an antitumor effect in NSCLC [29]. Furthermore, dabrafenib demonstrated enhanced efficacy in treating advanced NSCLC characterized by the BRAF

V600E mutation [30]. Combination therapy strategies have enhanced the treatment efficacy in lung cancer patients harboring the BRAF V600E mutation.

2.6. Human Epidermal Growth Factor Receptor (HER2 or ERBB2) Mutation Inhibitors

In lung cancer, approximately 90% of HER2 mutations consist of in-frame non-frameshift insertions located in exon 20 of the tyrosine kinase domain (ex20ins) [31]. The discovery of HER2 provides hope for lung cancer patients with HER2 abnormalities [32]. Monoclonal antibodies play a vital role in anti-HER2 therapy, with trastuzumab deruxtecan (T-DXd, DS-8201) standing out as a notable example that has shown encouraging antitumor effects in HER2-mutant lung cancer patients.

3. Immunotherapy

3.1. Adoptive Cell Transfer

Adoptive cell transfer (ACT) for lung cancer involves extracting T cells from the patient's bloodstream [33]. An example of adoptive cell transfer is CAR-T cell therapy, which involves the genetic modification of T lymphocytes from lung cancer patients to make them express chimeric antigen receptors (CARs) [34]. Such CAR-T cells are introduced back into the body, and the CARs recognize the antigens expressed by cancer cells, which trigger their destruction [35]. Currently, the research on CAR-T cell therapy for lung cancer is in its initial exploration phase. Despite numerous clinical trials, there are several challenges to address, such as on-target/off-tumor toxicity, tumor antigen variability, the immunosuppressive tumor microenvironment, neurological toxicity, and cytokine release syndrome. Addressing these challenges represents the forefront of the research in CAR-T cell therapy for lung cancer [36].

3.2. Immune Checkpoint Inhibitors

Checkpoint proteins such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) constitute a restraining mechanism of the immunity system that prevents it from autoimmune reactions but, at the same time, is related to immune escape by cancer cells. Dysregulation in these pathways is associated with immune escape and increased cancer progression [37]. Immune checkpoint inhibitors have demonstrated impressive clinical effectiveness and safety in the treatment of lung cancer, leading to their incorporation across all stages of managing NSCLC using both adjunctive (e.g., atezolizumab) and pre-adjunctive (such as nivolumab) therapies [38].

3.3. Cancer Vaccines

DNA and mRNA vaccines for cancer have become a promising strategy for both prevention and treatment. This method includes the introduction of DNA or RNA sequences that encode tumor-associated antigens (TAAs) or neoantigens, resulting in specific targeting of cancer cells [39]. Despite being in the early stages of development

and clinical testing, cancer therapeutic vaccines, particularly those designed for lung cancer, show potential in treating patients resistant to the standard-of-care treatment [40].

3.4. Oncolytic Viruses (OVs)

In lung cancer treatment, oncolytic viruses (OVs) operate by selectively identifying, infecting, and eliminating cancer cells while minimizing the harm to healthy cells [41]. The main mechanism of OVs involves inducing specific antitumor immune responses and selective cell death, resulting in tumor cell lysis and a reduction in tumor progression [42]. Currently, clinical trials are ongoing to evaluate the effectiveness of the following OVs in treating lung cancer: RT-10 (NCT05205421), ADV/HSV-tk (NCT03004183), MEM-288 (NCT05076760), and YSCH-01 (NCT05180851) [43].

3.5. Targeting Immune Checkpoint Receptors (ICRs)

Targeting immune checkpoint receptors (ICRs) such as lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin and mucin-domain-containing-3 (TIM-3), and T cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif (ITIM) domain (TIGIT) represent a promising immunotherapy for lung cancer treatment. Clinical trials are ongoing to investigate the efficacy of targeting LAG3, TIM-3, and TIGIT in lung cancer. For instance, a clinical trial (NCT02964013; MK-7684-001) evaluating the anti-TIGIT (T cell immunoglobulin and ITIM domain) antibody vibostolimab in combination with pembrolizumab revealed significant anti-tumor activity compared to vibostolimab monotherapy in advanced NSCLC [44].

4. Radiation Therapy

4.1. Intensity-Modulated Radiation Therapy (IMRT) and Volumetric-Modulated Arc Therapy (VMAT)

Intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) represent advanced radiotherapeutic modalities that have improved dosimetric outcomes in lung cancer treatment [45]. This technique directs high-dose radiation to targeted disease sites by effectively minimizing the exposure to the neighboring organs at risk [46]. Clinical studies have been carried to investigate the efficacy of either IMRT or VMAT and IMRT/VMAT in lung cancer. For instance, a hybrid technique incorporating two partial arcs of VMAT along with a five-field IMRT approach was developed for 15 NSCLC patients. This hybrid IMRT/VMAT method notably enhanced both the target dose conformity and homogeneity, demonstrating superior efficiency compared to standalone IMRT and VMAT techniques [47].

4.2. Boron Neutron Capture Therapy (BNCT)

Boron neutron capture therapy (BNCT) is a radiation therapy method that selectively targets and eliminates cancer cells while sparing normal cells [48]. This method is based on the preferential accumulation of compounds containing the boron isotope ^{10}B in cancer cells. Upon exposure to a beam of low-energy neutrons, ^{10}B is

converted into unstable ^{11}B, which decays into α particles (4He) and 7Li recoil particles. The high-energy particles generated as a result of the boron–neutron interaction exhibit a limited impact range, primarily affecting the cells in which boron is concentrated. This leads to localized damage to the cancer cells, sparing the surrounding healthy tissues [48].

BNCT is a pivotal treatment option, offering selectivity and reduced toxicity for lung cancer and metastatic lung disease [49]. Previous studies have shown that BNCT exhibited minimal toxicity and effectively suppressed lung metastases within a short treatment period in a BDIX rat model with lung metastases of colon carcinoma [50][51]. BNCT mediated by 10B-carrier L-para-boronophenylalanine-10B (BPA) treatment was also monitored in normal lungs of Fischer 344 rats by assessing the established relative biological effectiveness (RBE) and compound biological effectiveness (CBE) factors [52]. This method was employed in patients with recurrent lung cancer who had previously undergone chest wall irradiation with two fractions of BNCT. The tumor exhibited regression within seven months, with minimal or delayed adverse effects [53].

The integration of BNCT with additional therapeutic modalities has been explored in mouse model studies. Specifically, the combination of BPA-mediated BNCT with mild temperature hyperthermia and the hypoxic cytotoxin tirapazamine (TPZ), targeting the quiescent tumor cell population, significantly reduced lung metastases [54] (**Figure 1**).

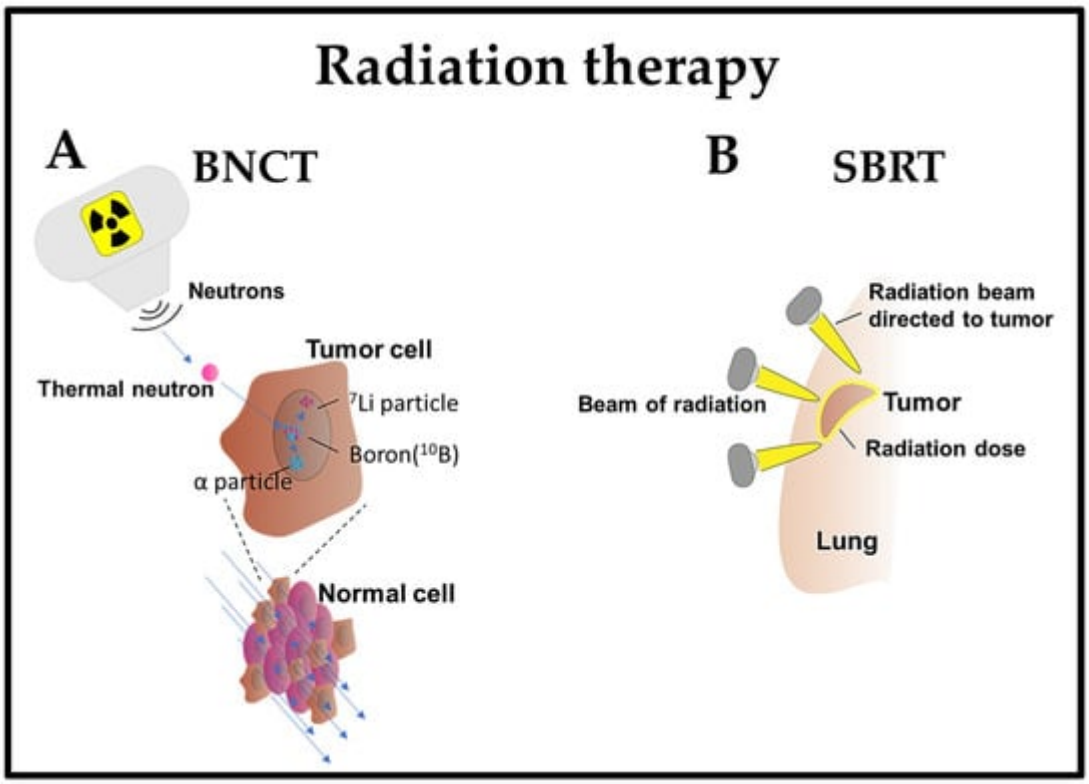

Figure 1. Emerging radiotherapy strategies. (**A**) BNCT: After the administration of a non-radioactive compound containing the inert isotope ^{10}B, which is specifically homed in cancer cells, the patient is exposed to a low-energy neutron beam. This beam initiates the fission of the ^{10}B isotope within the tumor cells, leading to the emission of a high-energy α-particle. This particle selectively kills cancer cells containing the ^{10}B isotope compound; (**B**) SBRT: A

four-dimensional CT scan is employed to observe the movement of lung cancer during inhalation and exhalation. High-dose radiation beams from various angles are then precisely directed at the tumor.

4.3. Stereotactic Body Radiation Therapy (SBRT)

Stereotactic body radiation therapy (SBRT) is an efficient and potentially effective option for treating inoperable early-stage NSCLC patients [55] or any stage of lung cancer [56]. It is a non-invasive treatment that delivers high doses of radiation with precision in a few treatments, achieving superior local control and survival rates compared to conventional radiation therapy [57]. SBRT utilizes sophisticated imaging and localization techniques to enhance the precision of radiotherapy targeting. This optimization enables the administration of hypofractionated and ablative doses of radiation [58]. The effectiveness of SBRT lies in its ability to deliver therapeutic radiation doses with a relatively high probability of tumor control while minimizing the exposure of normal tissue to these doses [59].

SBRT is gaining prominence in intricate cases, including patients with tumors situated close to vital organs, those with a history of previous radiation exposure, individuals with interstitial lung disease (ILD), or patients with metastatic disease. In instances of ultracentral tumors (those close to the trachea or proximal bronchial tree), SBRT poses an increased risk of severe toxicity, encompassing pulmonary hemorrhage or airway necrosis [57]. SBRT remains a viable treatment choice for medically inoperable and operable patients diagnosed with early-stage NSCLC, providing excellent local and regional control, accompanied by lower toxicity rates [60] (**Figure 1**).

5. Cryoablation

Cryoablation is a therapeutic approach that destroys tumors using extreme cold [61]. This process involves connecting cryoprobes to pressurized argon, which rapidly cools the probe upon its expansion to temperatures as low as −160 °C. Consequently, this results in the formation of an ice ball at the tip of the cryoprobe. The freezing and thawing process disrupts the cell membrane and initiates microvascular injury, subsequently inducing hypotonic stress and leading to cell necrosis [62]. In lung tumors, cryoablation is typically conducted with the guidance of CT scans, accompanied by sedation and local anesthesia [61]. The procedure can be performed via endobronchial, direct intrathoracic, or percutaneous routes, depending on the location and size of the tumor [63].

Typically, patients with lung metastases frequently struggle to attain curative results despite undergoing chemotherapy, radiotherapy, or surgery [62]. However, studies indicate that cryoablation can potentially treat lung metastasis effectively [64]. A promising strategy involves combining cryoablation with immunotherapy; however, cryosurgery alone cannot elicit a robust immunotherapeutic response to cancer [62]. The administration methods for combining cryoablation with immunotherapy include percutaneous and bronchoscopic approaches [63].

6. Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) is a non-invasive lung cancer treatment that utilizes photosensitive compounds and light activation to selectively destroy cancer cells [27]. PDT has demonstrated efficacy in enhancing the survival rate

of patients with incurable malignancies by using three fundamental factors: photosensitizer drugs, light, and oxygen [65]. Photosensitizers exert their photodynamic activity through photo-oxidative mechanisms, triggering diverse biochemical and morphological reactions that lead to cytotoxic effects in tumors [66].

Several PDT clinical trials have been undertaken; the most recent significant study was centered on the combination of Laserphyrin®-based PDT and chemotherapy for advanced NSCLC cases in which curative surgical interventions were not feasible. The aim was to address bronchial stenosis and obstruction in the central and peripheral (lobar or segmental bronchi) lung areas, and PDT resulted in improved symptoms and quality of life [67]. Additionally, second-generation Radachlorin®-based PDT was employed for advanced NSCLC, resulting in a one-year post-treatment survival rate of 70%, with improved treatment effectiveness and safety [68].

7. Hyperthermia Therapy

Hyperthermia therapy (HT), or thermal therapy, is a cancer treatment involving artificial elevation of the body tissue temperature. This is accomplished by administering heat from external sources such as microwaves, radio waves, lasers, ultrasound, etc., to locally elevate the temperature to 42–45 °C. This process aims to eliminate cancer cells or inhibit their growth without causing harm to normal tissues [69]. HT induces direct cytotoxic effects in lung cancer cells [70], as well as enhancing tumor perfusion, thus increasing the drug delivery capability [71].

HT combined with chemotherapy [71] or radiotherapy [72] has the potential to enhance the outcomes of lung cancer. HT serves as a supplementary or adjunctive therapy when used in conjunction with radiation and chemotherapy, particularly in the case of inoperable lung cancer [61]. For example, the combination of HT with radiation suppressed lung cancer progression in A549 cells and in vivo xenograft models [72].

8. Nanoparticles as a Tool for Targeted Therapy

8.1. Hafnium Oxide Nanoparticles (HfO_2 NPs)

Hafnium oxide nanoparticles (HfO_2 NPs) are utilized as both radiosensitizers and X-ray contrast agents due to their chemical inertness, high dielectric constant, elevated melting point, density, refractive index, and transparency to visible light, combined with minimal reactivity in biological systems [73]. HfO_2 NPs are applicable in X-ray-induced photodynamic therapy (X-PDT) because they generate high-energy electrons and free radicals upon absorbing high-energy X-ray radiation [74]. NBTXR3, a type of HfO_2 NP, was reported to help in treating metastatic lung cancer patients, irrespective of their sensitivity or resistance to immunotherapy [75].

8.2. Magnetic Nanoparticles (MNPs)

Magnetic nanoparticles (MNPs) are made from materials with intrinsic magnetic properties, such as iron oxides, cobalt, and nickel. These MNPs can be employed in targeted drug delivery systems for lung cancer, offering significant drug-loading capabilities and effective tumor penetration [76]. Previous reports have shown that loading

MNPs with cisplatin reduced the concentration of lung-resistance-related proteins, thereby enhancing cisplatin's cytotoxicity in a cisplatin-resistant A549 cancer cell xenograft model [77]. Superparamagnetic iron oxide nanoparticles (SPIONs) could act as T2 contrast agents. When coated with oleic acid and carboxymethyl dextran and then conjugated with an anti-CD44v6 monoclonal antibody, they exhibit specific detection capabilities for metastatic lung cancer cells [78].

8.3. Lipid Nanoparticles (LNPs)

Lipid nanoparticles (LNPs) are composed of biocompatible lipids that encapsulate therapeutic compounds with diverse physicochemical properties that facilitate their absorption into cells and tissues. Subsequently, they optimize drug delivery to specific target areas in lung cancer, concurrently minimizing exposure to healthy tissues, thereby increasing the treatment efficacy and decreasing side effects [79].

8.4. Polymeric Nanoparticles (PNPs)

Polymeric nanoparticles (PNPs) comprise synthetic and natural polymers for targeted drug delivery in lung cancer [80]. PNPs have shown enhanced drug release, biocompatibility, and increased anticancer effects due to their composition of polylactic acid (PLA), polyethylene glycol (PEG), poly(lactic-co-glycolic acid) (PLGA), chitosan-loaded lomustine, and gelatin conjugated with biotinylated epidermal growth factor (EGF) [81]. In lung cancer, nitroimidazole- and hyaluronic-acid-based PNPs and lipid nanoparticles (PNP-LNP hybrids) are utilized for the targeted delivery of cisplatin to lung cancer cells and xenografts, resulting in a potent anti-tumor response while minimizing toxicity [82].

9. Conclusions

In summary, the field of lung cancer treatment is experiencing a profound transformation, marked by the introduction of groundbreaking therapies (**Figure 2**). Advancements in personalized medicine, targeted therapies, and immunotherapy provide new hope for patients with this challenging disease. A combination approach to using these cutting-edge therapies could enhance lung cancer treatment by boosting the treatment effectiveness while minimizing toxicity effects. As scientific research delves deeper into the intricacies of the disease, continuous progress in emerging therapies for lung cancer has the potential to redefine the standard of care.

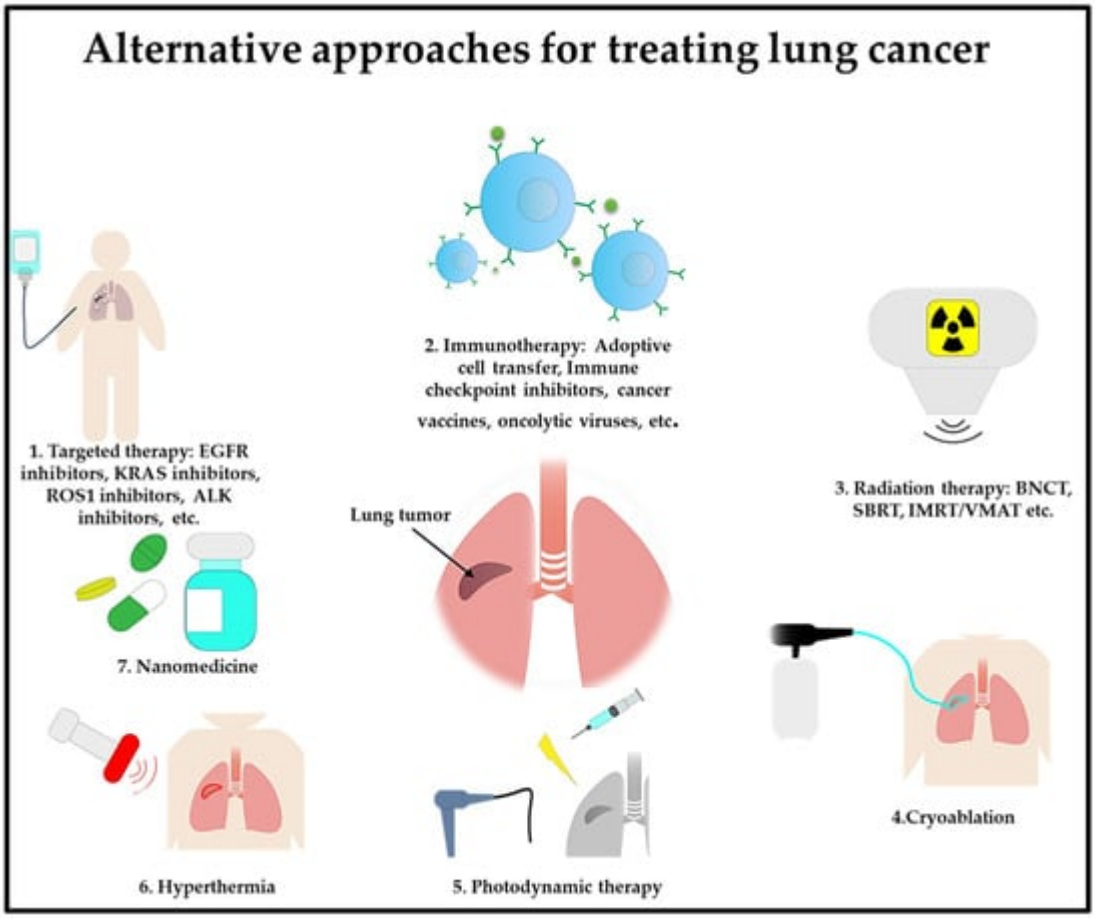

Figure 2. Emerging lung cancer treatments are targeted therapy, immunotherapy, radiation therapy, cryoablation, photodynamic therapy, hyperthermia, and nanomedicine.

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