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CURRENT THERAPEUTIC STRATEGIES AND CHALLENGES IN NSCLC TREATMENT: A COMPREHENSIVE REVIEW

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Non-small cell lung cancer (NSCLC) is one of the most lethal malignancies accountings for nearly 80% of all lung cancer cases diagnosed and causing over one million deaths annually worldwide. The discovery of molecular alterations including driver mutations and gene fusions has led to innovation of numerous targeted therapies, which certainly provided an edge over the classical chemotherapeutic treatment regimens and improved survival of the patients. Despite all the breakthrough innovations, the five-year survival statistics has not improved the way it was expected, pointing the challenges and limitations of currently approved diagnostic methods and therapies. This review summarizes various innovative therapies, treatment regimens developed over the last two decades for NSCLC treatment and the current challenges and limitations in the NSCLC treatment landscape.

***Key Words*: NSCLC, treatment, targeted therapies, therapeutic mAbs, chemoresistance.**

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Non-small cell lung cancer (NSCLC) is a subtype of lung cancer representing one of the leading causes of cancer-related deaths worldwide. It accounts for nearly 80% of all lung cancer cases detected and has one of the lowest five-year survival rates of around 24%. NSCLC is majorly sub-categorized into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma represents nearly half of the total NSCLC cases followed by squamous cell carcinoma, which arises from the tracheobronchial tree's origin. Numerous clinical and preclinical reports have suggested that NSCLC tumors develop through progressive pathological changes and harbor few unique molecular signatures of genomic alterations that have enabled the development of a few tailor-made inhibitors. These alterations mostly arise in the cells lining airways, predominantly exposed to harmful chemicals, including carcinogens in tobacco smoke, environmental pollutants such as asbestos, nickel, arsenic, etc. The precancerous cell then proceeds to various tumorigenesis stages, including hyperplasia, squamous metaplasia, squamous dysplasia, and finally, carcinoma *in situ* [1]. Dysplasia lesions themselves are further characterized as mild, moderate, and severe based on histological and cytological changes.

Franz Herman Muller, in 1939, published the first study comparing 86 lung cancer patients and a similar number of controls and concluded that lung cancer patients were far more likely to smoke than their non-cancer controls [2]. Following their conclusions, numerous research studies were also carried out in the UK and the USA verifying the link between tobacco and lung cancer [3]. The first pathological evidence of the adverse effects of tobacco smoke in lung airways cells came from the research of Anderson Hiding, who confirmed that tobacco smoking causes ciliostasis, deadening of the hair-like structures lining the upper respiratory tract which function to remove the contamination from airways; and the location of ciliostasis were precisely matching with the areas where tumors were most likely to develop (preneoplastic lesions) in lung cancer patients with a heavy smoking history [4]. The earlier lung cancer cases arising from smoking were more inclined towards squamous cell carcinoma; however, this changed in the 1960s with massive use of filters in cigarettes, and from that time, higher cases of adenocarcinoma started appearing in lung cancer patients compared to squamous cell carcinoma [5, 6]. Radiation therapy for the treatment of other cancers such as breast cancer, Hodgkin's lymphoma can also cause lung cancer [7, 8]. Other factors such as pulmonary fibrosis and HIV infection are also elevated risk factors for the development of lung cancer [9, 10].

CURRENT TREATMENT AND THERAPEUTIC PERSPECTIVES FOR NSCLC

Cytotoxic chemotherapeutic drugs such as cisplatin, cyclophosphamide, doxorubicin, and microtubule stabilizing drugs such as paclitaxel docetaxel were standard therapies used for NSCLC treatment [11]. Platinum-based chemotherapy (CT), pemetrexed, and docetaxel were used as the first-line therapy and provided significant advantages over the basic supportive care (NMAC Group, 2008). Docetaxel was also found useful in patients with relapsed NSCLC who had received the platinum-based first line of therapy and demonstrated a one-year survival rate of 37% *vs* 11%

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Abbreviations used: ALK – anaplastic lymphoma kinase; CT – chemotherapy; HDAC – histone deacetylase; ICI – immune checkpoint inhibitor; EGFR – epidermal growth factor receptor; LCSS – lung cancer symptom scale; mAbs – monoclonal antibodies; NSCLC – non-small cell lung cancer; ORR – overall response rate; OS – overall survival; PARP – poly ADP ribose polymerase; PD-1 – programmed cell death protein-1; PFS – progression-free survival; TKI – tyrosine kinase inhibitor; VEGF – vascular endothelial growth factor.

for patients receiving basic supportive care only [12]. Pemetrexed also showed a similar efficacy profile compared to docetaxel as the second line of therapy in another phase III clinical study [13]. However, these therapeutics often had a wide range of toxicity and provided a limited increase in survival time for the treated patients ranging from 6–18 months [14]. The 5-year survival rate for NSCLC before 2004 was as low as 9% if the disease was diagnosed in advanced stages III and IV. NSCLC treatment landscape took a dramatic turn with the discovery of epidermal growth factor receptor (EGFR) mutations and selective tyrosine kinase inhibitors (TKI) erlotinib and gefitinib, which increased the progression-free survival (PFS) from 6 months to 12 months in particular subsets of NSCLC patients harboring EGFR mutations [15], and thus the advent of the first generation of targeted TKI therapies began which displayed superior overall response rate (ORR) and PFS compared to CT.

TKIs FOR NSCLC TREATMENT

Following the discovery of EGFR mutations in NSCLC patients and the benefits of first-generation TKIs, numerous other alterations such as fusion of anaplastic lymphoma kinase (*ALK*) with *EML4* gene were discovered in a smaller group of NSCLC patients [16]. The earlier first-generation TKIs, including erlotinib and gefitinib, were approved for NSCLC treatment [17] and did give promising results in increasing the overall survival (OS) compared to CT in NSCLC patients with mutated *EGFR* gene [18, 19]. However, they were found to have limited effect in wild-type *EGFR* patients being inferior compared to CT [20]. Second-generation TKIs were designed for better efficacy and lesser toxicity due to off-target binding as seen in first-generation TKIs, which were ATP binding competitors. Sorafenib, a small molecule inhibitor of c-Raf and b-Raf, vascular endothelial growth factor (VEGF) receptors 1/2/3 and PDGF receptors, FLT3 and c-KIT initially approved for the treatment of renal cell carcinoma, have also been found effective in selected subsets of NSCLC patients. Single-agent sorafenib in phase I and II trials showed significant anti-tumor activity in NSCLC patients with an ORR of 17% and median OS of 8.8 months [21]. Sorafenib also appeared to improve the OS of patients with recurrent NSCLC or those who previously received CT or first-generation TKIs treatment [22, 23]. PF-299, a second-generation irreversible EGFR inhibitor has demonstrated better efficiency than first-generation TKIs in T790M EGFR mutant tumor profiles in phase II randomized trial with 188 NSCLC patients who had received one or two prior chemotherapeutic treatment cycles and having mutational status of *K-Ras* — 81% and *EGFR* — 77%. 45 mg daily dose of PF-299 given to the test group *vs* a standard 150 mg dose of erlotinib [24]. Their results demonstrated a significantly higher ORR and improved PFS in PF-299 treated patients in the overall population under the study trial. They also found an impressive 30–40% better response across all subgroups (*EGFR* wild type or mutant, *K-Ras* wild type or mutant). Dabrafenib, another second-generation TKI targeting BRAF protein with potential antineoplastic activity, has been clinically effective against V600E BRAF mutant in NSCLC patients at the metastatic advance stages of cancer in multicenter phase II clinical trials [25, 26]. Their results showed robust antitumor activity against advanced metastatic NSCLC, combination with another TKI trametinib, and manageable safety profiles. Dabrafenib, along with trametinib, has been approved for clinical treatment for NSCLC patients harboring *BRAF* mutations. Crizotinib, a small molecule inhibitor of ALK, has been clinically studied for treating NSCLC patients carrying oncogenic *EML4-ALK* fusion gene. Oncogenic EML4-ALK fusion protein has N-terminal derived from EML4 and C-terminal derived from ALK, which contains ALK's tyrosine kinase domain. The evidence for the clinical efficacy of crizotinib came out from a non-randomized phase I study which demonstrated one-year and two-year survival rates of patients treated with crizotinib standing at 74% and 54% respectively, in contrast, the cohort of patients who did not receive crizotinib showed one-year and two-year survival rates of 44 and 12% [27]. Other Phase II/III trials showed rapid and dramatic response rates among patients who were treated with crizotinib. PFS was found to be ten months, similar to EGFR mutant NSCLC patient treatment with EGFR inhibitors [28]. Randomized phase III trials of crizotinib *vs* standard CT (cisplatin/carboplatin) (NCT01639001), docetaxel/pemetrexed demonstrated superior efficacy of crizotinib in ALK-positive patients compared to the latter [29, 30].

MONOCLONAL ANTIBODY THERAPIES FOR NSCLC TREATMENT

Monoclonal antibodies (mAbs) bind to specific targets with excellent efficiency and are selectively specific against their targets across a wide variety of proteins that possess a higher degree of similarities with their targets. Therapeutic mAbs possess more significant advantages than chemical inhibitors in pharmacodynamics and pharmacokinetics and have very limited toxicity compared to their chemical inhibitor counterparts. Therapeutic mAbs also have the advantage of enhancing their effectiveness against cancer cells through their Fc domains, which can interact with target Fc receptors leading to recruitment of natural killer and other immune cells and initiating antibody-mediated cytotoxicity [31]. They may also mediate the complement system's activation through their Fc domains and trigger complement-dependent cytotoxicity [32].

Anti-EGFR therapeutic mAbs. Anti-EGFR antibodies bind to the extracellular domain of the EGF receptor and inhibit the binding of EGF ligand to the target receptor, thus inhibiting receptor dimerization followed by autophosphorylation and downstream signaling. Cetuximab, a chimeric mouse-human IgG_1, is one of the most studied therapeutic mAbs targeting

the EGFR. Cetuximab treatment has shown significant improvement in PFS and OS of NSCLC patients in numerous phase II/III clinical studies. Phase II clinical investigations showed significant antitumor activity of cetuximab in combination with erlotinib and bevacizumab. Dose-limiting toxicities were not observed at a dosage up to 375 mg/m^2 [33, 34]. Another clinical phase III study in lung cancer patients (FLEX) in which cetuximab was added to a platinum-based chemotherapeutic (cisplatin or vinorelbine), showed OS improvement of 1.2 months in patients with EGFR-positive tumors [35]. Necitumumab, a second-generation humanized mAb targeting EGFR, has been proven efficient in combination with standard CT for improving OS of squamous and non-squamous cell NSCLC patients in phase III trials SQUIRE [36, 37]. Both phase III studies demonstrated a significant OS improvement in the necitumumab arm (median 11.5 months *vs* 9.9 months in the gemcitabine-cisplatin alone group). The results showed a favorable trend to the addition of necitumumab in EGFR-positive patients with a median OS of 12.6 months in 111 EGFR positive patients *vs* 9.2 months in 97 patients.

Anti-VEGF/R therapeutic mAbs. Overproduction of VEGF has been directly associated with tumor progression, enhanced metastatic spread, and poor prognosis in NSCLC patients [38]. A meta-analysis of VEGF expression in NSCLC assessed by immunohistochemistry showed that VEGF overexpression is associated with poor prognosis with an associated hazard ratio of 1.46 [39]. Bevacizumab, a humanized murine mAb directed against VEGF selectively inhibiting its binding to the VEGFR1/2/3 receptors, was innovated by Genentech. Bevacizumab was the first FDA approved for the treatment of metastatic refractory colon cancer in 2004. Bevacizumab has been proven clinically effective for NSCLC treatment through numerous phase II and III clinical trials. Two phase III trials reported a median OS improvement of 2 months when using bevacizumab in combination with CT (12.3 months), compared to CT alone (10.3 months) in squamous and non-squamous NSCLC [40]. Another phase III clinical study demonstrated the improvement of pemetrexed mediated maintenance therapy by the addition of bevacizumab [41]. A further meta-analysis of twenty-nine clinical trials of bevacizumab with or without CT or TKIs concluded a significant improvement in PFS and OS when bevacizumab was added to CT or TKIs compared to CT or TKIs alone as the first line of treatment for NSCLC [42].

Ramucirumab, a fully human mAb targeting the extracellular domain of VEGF receptor-2 has been found significantly effective in numerous phase I/II and III clinical studies to treat advanced-stage NSCLC. A randomized phase III trial "REVEL" comprising of more than 1,250 NSCLC stage IV patients who were randomized into docetaxel plus ramucirumab and docetaxel plus placebo showed improvement in PFS and OS in patients who received ramucirumab plus docetaxel (4.5 months PFS and 10.5 months OS) *vs* docetaxel plus placebo (3.0 months PFS and 9.1 months OS) [43]. Further evaluation of the quality of life via assessment through lung cancer symptom scale (LCSS), revealed that the addition of ramucirumab (mean LCSS score 32.0) did not impair the quality of life of the patients compared to those receiving placebo with docetaxel (mean LCSS score 32.5). Another randomized phase II clinical study of ramucirumab plus docetaxel *vs* docetaxel plus placebo conducted in Japan comprising of stage IV NSCLC patients who had earlier received platinum-based CT as first-line treatment has demonstrated similar significantly longer median PFS and OS in patients treated with ramucirumab plus docetaxel *vs* the docetaxel plus placebo group [44]. Ramucirumab has been approved for treating both squamous and non-squamous NSCLC patients with advanced-stage disease second line of treatment (Figure).

IMMUNE CHECKPOINT INHIBITORS FOR NSCLC TREATMENT

A plethora of evidence for immune surveillance evasion by growing and circulating tumor cells led to the characterization of this specific ability enacted by tumor cells as one of the emerging cancer hallmarks [45]. Immune evasion, especially by NSCLC cells, could be broadly categorized into two categories identified by their cellular and molecular characteristics and inflamed T-cell phenotype characterized by CD8$^+$ T-cell tumor infiltration suppression of immune response and a non-inflamed phenotype leading to immune evasion [46]. These co-inhibitory signals referred to as immune checkpoints, designed for the avoidance of self-destruction, are majorly exploited by the tumor cells. Many novel therapeutic mAbs have been designed to target these checkpoints by blocking the activation of checkpoint receptors leading to enhanced immune cell activation, which eventually could eliminate the tumor.

CTLA4 inhibitors. CTLA4 inhibition has been shown to increase immune activity mostly by depressing T_{regs} and expanding tumor infiltration CD4$^+$ T-cells [47, 48]. One of the first therapeutic mAbs designed for targeting immune checkpoint activation is ipilimumab, a fully-humanized IgG against the epitope of the CTLA4 receptor. Clinical efficacy of ipilimumab was demonstrated through a randomized phase II clinical trial which showed improved immune-related PFS when ipilimumab was given as a single agent in a phased manner (5.7 months PFS); however, it did not show any improvement in combination with CT in comparison to CT alone (4.6 months) [49]. Further, a randomized phase III trial of ipilimumab or placebo in combination with CT conducted by Govindan *et al*. [50] demonstrated a median OS of 13.4 months in CT plus ipilimumab arm compared to 12.4 months in the CT plus placebo arm. Both groups involved in the study showed a median PFS of 5.6 months, concluding very limited to no benefit of the addition of ipilimumab with a CT treatment regimen. Another

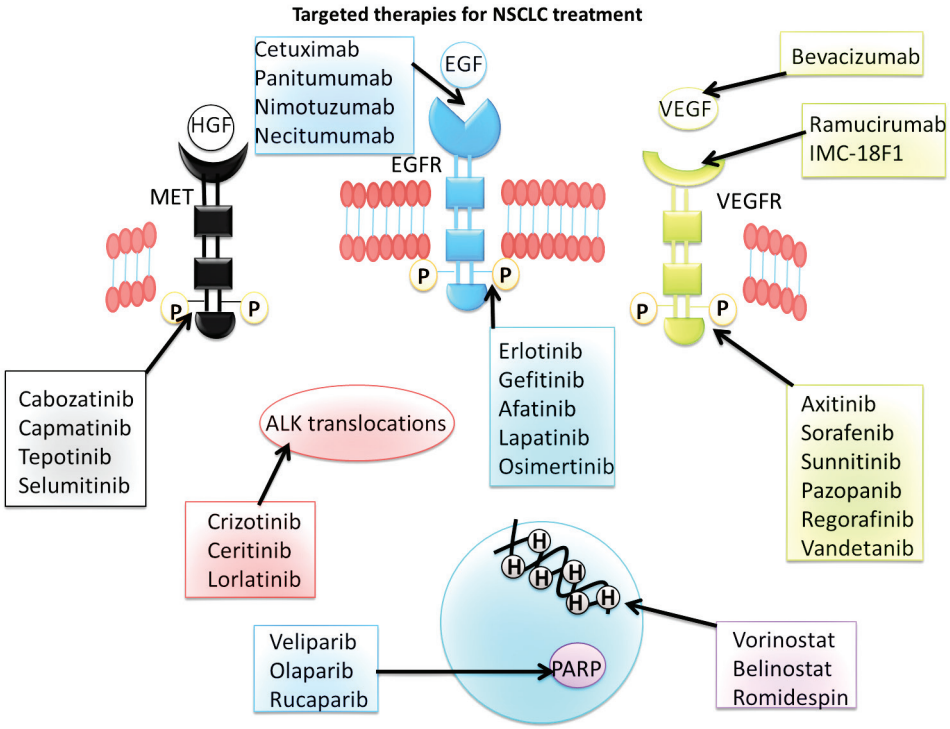

Figure. Graphical art summarizes various targeted therapies developed for the treatment of NSCLC. Multiple promising candidate proteins, which have been known to play a crucial role in the process of oncogenesis such as receptor tyrosine kinases (EGFR, VEGFR) and other genes regulating cell proliferation and DNA repair have been explored for therapeutic development. Various therapeutic candidates interfering with the activation and functionality of these oncoproteins have shown remarkable results and have prolonged the overall survival and progression free survival of NSCLC patients

phase III trial of the same CT plus ipilimumab or placebo conducted in stage III/IV SCLC patients showed similar nil significant improvement of both PFS and OS [51]. Both the phase III studies reported elevated immune-related toxicities and higher death counts during treatment in CT plus ipilimumab arm compared to CT plus placebo. However, the results of a recent phase III trial (CheckMate 9LA) assessing the immune checkpoint inhibitor (ICI) ipilimumab in combination with another ICI nivolumab has shown that ipilimumab plus nivolumab along with two cycles of CT significantly increased the OS (14.1 months) compared to CT alone (10.7 months) [52]. Few other phase III trials of ipilimumab plus CT and EGFR inhibitors are currently ongoing (NCT04026412, NCT03001882, NCT02477826, and NCT04026412).

PD-1/PD-L1 inhibitors. The surface receptor programmed cell death protein-1 (PD-1) belongs to the B7-CD28 superfamily and is another critical pathway involved in self-tolerance that is hijacked by cancer cells to evade immune detection and destruction. The binding of ligand PD-L1 to PD-1 receptor inhibits T-cell response and induces apoptosis in tumor-specific T-cells. NSCLC and various other tumors have been reported to express elevated levels of PD-L1 [53]. Nivolumab, a fully human IgG4 antibody directed against the PD-1 receptor, has been shown effective through various phase I/II and III trials. A randomized phase II trial in patients with advanced refractory NSCLC showed an ORR of 14.5% and stable disease (SD) in 26% of the patients [54]. Another phase I trial comprising of 129 heavily pretreated NSCLC patients showed a median OS of 9.9 months across all doses with a median response duration of 17 months.

Similarly, survival results were seen in both squamous and non-squamous NSCLC patients [55]. Another randomized phase III trial evaluating nivolumab *vs* docetaxel demonstrated a significant increase in the median OS in the nivolumab arm *vs* the docetaxel arm (9.2 months for nivolumab *vs* six months for docetaxel) [56]. Nivolumab has been clinically approved for treating metastatic squamous and non-squamous NSCLC patients who have stopped responding to CT. Pembrolizumab, another high-affinity human IgG antibody targeting PD-1 protein, has shown significant results in phase I/II clinical studies. A randomized phase II/III multinational clinical study (KEYNOTE-010) compared pembrolizumab versus docetaxel efficacy in heavily pretreated NSCLC patients. The median OS was found to be 10.4 months in the 2 mg/kg pembrolizumab arm, 12.7 months in the 10 mg/kg pembrolizumab group, and 8.5 months in the docetaxel group. Adverse effects of grade 3/4 were seen in a lesser percentage of patients receiving a 2 mg/kg dose of pembrolizumab [57]. After its clinical efficacy was established, pembrolizumab has been approved for treating pretreated squamous and non-squamous NSCLC patients as the second line of therapy.

Durvalumab, a high affinity human IgG1 antibody targeting PD-L1 ligand and blocking its interaction with PD-1 receptor, was designed and rigorously studied in clinical settings for its efficacy against advanced

NSCLC. A phase I/II trial of durvalumab in PD-L1 positive patients bearing stage III/IV NSCLC demonstrated a remarkable ORR of 25% and a disease control rate of 56% [58]. Numerous randomized phase III trials have assessed the efficacy of durvalumab in combination with chemo- and radiotherapies for treating stage III NSCLC patients. PACIFIC trial (NCT02125461) conducted in patients after concurrent chemoradiotherapy showed the PFS improvement in the durvalumab arm (16.8 months) compared to placebo (5.6 months). A significant improvement in four years OS was in the durvalumab arm compared to placebo (49.6% in the durvalumab arm *vs* 36.3% in the placebo group). 35.3% of the live patients randomized to durvalumab were reported to have the progression-free disease compared to 19.6% in the placebo arm [59]. Durvalumab has been approved for treating stage III NSCLC patients having unresectable tumors and without disease progression after chemoradiotherapy. Numerous other phase III trials are currently ongoing including PACIFIC 5 and 6 (NCT03706690, NCT02453282 and NCT03693300) for the evaluation of durvalumab as monotherapy as well as consolidation therapy.

OTHER NOVEL THERAPIES APPROVED OR UNDER CLINICAL INVESTIGATION FOR NSCLC TREATMENT

Poly ADP ribose polymerase (PARP) inhibitors. PARP inhibitors block the transfer of ADP ribose from nicotinamide dinucleotide to the Glu/Asp residues of its substrate protein, which includes DNA damage repair proteins which are pivotal for the mutation-induced damage repair of the genome. Numerous inhibitors targeting PARP have been developed, and few of them have shown promising results in early-stage clinical trials and are currently under investigation. Veliparib and olaparib are two orally bioavailable promising potent inhibitors of PARP presently under clinical trials to assess their efficacy as either monotherapy or in combination with standard CT or targeted therapies. A phase II trial conducted in small cell lung cancer patients for evaluating the safety of veliparib in combination with cisplatin and etoposide concluded reasonable tolerance of 60 mg/kg dose, and the median PFS for CE plus veliparib arm was 6.1 months versus 5.5 months in CE plus placebo arm. In another phase III randomized trial, interim PFS in the veliparib arm was reported to be 24.1 months [60, 61]. A randomized phase II trial of olaparib *vs* placebo in chemosensitive advanced NSCLC cancer patients demonstrated significant median PFS improvement compared to placebo (16.6 weeks *vs* 12 weeks) [62]. It is further assessed in randomized, double-blind phase III trials for various cancers including lung and ovarian cancer [63].

Histone deacetylase inhibitors. Acetylation of DNA packaging histone proteins is one of the novel ways of controlling gene expression through increased accessibility to the promoter regions of the genes by the transcription factors and other promoter binding elements. Histone deacetylases (HDACs) are the class of enzymes that reverses this process leading to repression of gene expression phenomena through chromatin condensation. HDAC inhibitors are an entirely new class of inhibitors that have shown impressive anti-neoplastic activity by inhibiting deacetylation, leading to growth arrest and apoptosis in cancer xenograft models. Vorinostat (SAHA), a hydroxamic acid-based HDAC inhibitor, has been clinically studied for its efficacy in phase I/II clinical studies in NSCLC patients. A phase I study of two doses (400 mg/kg once for two weeks or 300 mg/kg twice for one week) combined with carboplatin or docetaxel was conducted in twenty-six patients, ten out of which had advanced stages of NSCLC. The study reported a partial response in 11 of the 26 patients, and none of the patients exhibited any dose-limiting toxicities [64]. Another randomized double-blind phase I/Ib clinical study designed for evaluating the efficacy of vorinostat in combination with ICI pembrolizumab was conducted in advanced stage NSCLC patients. They reported a partial response in four out of six ICI naïve and in ICI pretreated cohort, three patients showed partial response and other ten had shown SD with vorinostat. A marginal improvement of PFS (6.0 months *vs* 4.1 months) and OS (13.0 months *vs* 9.7 months) was observed in the vorinostat arm [65]. Randomized phase III trials of vorinostat combined with CT and EGFR-TKIs are currently ongoing for a detailed evaluation of its efficacy in treating advanced stage NSCLC (NCT00473889). Few other HDAC inhibitors, including pivanex, N-acetyldinaline (CI-994), and entinostat, are currently under phase II/III clinical studies to assess their efficacy in treating advanced stage NSCLC [66].

CHALLENGES AND OBSTACLES IN NSCLC TREATMENT LANDSCAPE

Despite all the advances in diagnosis and treatment, NSCLC remains a formidable foe taking over 1.5 million lives every year worldwide. Early-stage detection, resistance to therapeutics, and failure to control metastatic spread and relapse of tumors are a few of the critical challenges limiting long-term and disease-free survival. Lung cancers, especially NSCLC, are known not to show any prominent symptoms in the early development stages. Chest and back pain, trouble in breathing, chronic headaches, blood in cough, etc., are the symptoms that arrive in later tumor development stages. Diagnostic imaging is one of the primary tools for detecting growing tumors. Low dose computed tomography, contrast-enhanced computed tomography, and positron emission tomography are the most utilized radio diagnostic tools for screening purposes [67]. Until 2004, only clinical diagnosis of SCLC or NSCLC was performed, and therapeutic strategies were designed accordingly. The discovery of EGFR and other gene mutations and further sub-categorization in NSCLC

has made the molecular diagnostic approach a complicated process [68]. Typical diagnosis of lung cancer requires identification and complete classification of the malignancies, immunohistochemistry-based profiling for prediction of likely subtype squamous or non-squamous NSCLC (markers such as TTF-1, p63 for adenocarcinoma or cytokeratin 5/6 for squamous cell carcinoma), and further molecular testing for extended diagnosis [69, 70].

A vast majority of over 50% of the diagnosed cases have unknown driver mutations. In most cases, those patients are found non-suitable for targeted therapies (Clinical Practice Guidelines in Oncology). There is a need for better and more accurate predictive marker panels that can cover multiple phenotypes and genotypes of each sub-category of NSCLC [71]. Innovative molecular diagnostic approaches such as whole-exome sequencing, complete genome SNP profiling, deliver remarkable results in identifying signature aberrations in the patient-specific cancer genome. However, they are not always the ideal strategy because of numerous factors such as limited samples from biopsy, tissue type, cost incurred, etc. Circulating tumor cells and circulating DNA are new promising techniques for detecting NSCLC. Currently, they are inefficient, mostly due to a lack of better and more sensitive detection tools. Studies have shown that roughly 1–10 circulating tumor cells are present in around 10 ml of blood obtained from advanced stage NSCLC patients, which are very difficult to detect [72].

There's a plethora of clinical evidence that suggests diminishing effects of CT with progressive number of treatment cycles given to the patients. NSCLC, amongst all other types, is much more prone to acquire resistance despite the variety and combination of drugs being used. Almost all patients who receive treatment acquire resistance after cycles of treatment [73, 74]. Targeted therapies also do face multiple challenges in the real-world treatment landscape. The first major challenge for targeted therapies, they benefit only a smaller subset of patients who harbor those specific driver mutations such as EGFR gene amplification, EML4-ALK fusion gene; therefore, a vast majority of NSCLC patients still have to rely on CT as their first line of treatment. Secondly, NSCLC tumors have shown in numerous clinical studies to acquire resistance to specific targeted inhibitors either by incorporating other mutations that dramatically reduce the effects of TKIs or through activating parallel pathways of signal transduction, which substitutes for the signaling mechanism of the drug targets [75]. NSCLC tumors have become resistant to first and second-generation EGFR TKIs after multiple cycles of treatment through the incorporation of T790M mutation, amplification of the *c-MET* gene, *BRAF* mutations, etc. in numerous clinical studies [76, 77]. Third-generation TKIs such as osimertinib, sunitinib, unfortunately also have been seen to develop resistance after a median PFS of 9.6 months in clinical studies [78]. *K-Ras* mutations account for nearly 30% of the NSCLC tumors. They are used as exclusion criteria for identifying druggable targets as this specific mutation is shown to neutralize the efficacy of TKIs in clinical studies [79, 80]. Direct inhibition approaches for K-Ras through targeted inhibitors such as salisarib have been attempted, but unfortunately, have been unsuccessful in clinical trials [81].

CONCLUSION AND FUTURE PERSPECTIVES OF NSCLC TREATMENT

NSCLC treatment landscape has been drastically changed in the past two decades and gradually has shifted its focus from classical cytotoxic CT to new age targeted therapeutics. Owing to the discovery of various oncogenic markers and subsequent development of multiple therapeutics targeting those cancer-driving proteins, the long-term survival outcomes of patients have dramatically improved as well to 25% in 2020 from 8% in 2008. Specific small molecule inhibitors such as gefitinib, sorafenib that prevent the activation of the receptor tyrosine kinases such as EGFR, VEGFR, hepatocyte growth factor receptor, fibroblast growth factor receptors have shown lesser side effects and much better tumor regression and disease control compared to their chemotherapeutic counterparts. Small molecules targeting oncogenic fusion proteins such as ALK inhibitors crizotinib and brigatinib also have been largely effective in controlling cancer in the patients harboring those genomic alterations. Moreover, the discovery and deployment of mAbs targeting specific cellular receptors specifically EGFR and VEGFR have also widened the horizon of treatment as these biomolecules work not only by preventing the binding of ligands to their target receptors, also through immune response including antibody dependent cellular toxicity and activating the complement systems. The most remarkable breakthrough achieved in NSCLC treatment has been the development of immunotherapy, which achieves controlling and elimination of the disease through enhancing the immune activity of the patient. Over the past two decades, therapies targeting multiple candidate immune checkpoint receptors, specifically CTLA4, PD-1 and PD-L1 have been developed and clinically approved for NSCLC treatment. These therapeutics including ipilimumab, nivolumab and durvalumab have greatly benefitted patients suffering from NSCLC and have increased their overall and progression free survival by more than a year.

These new age therapeutics did have increased the survival outcomes but currently are not sufficient for eliminating the disease due to multiple complications of the disease itself as well as in the prolonged usage of these therapeutics. The early-stage diagnosis of NSCLC, controlling metastatic spread and preventing resistance of therapy are the major challenges

faced for controlling and eliminating the disease. Metastatic spread and developing escaping mechanisms from therapies after few cycles of treatment are particularly of concern as they drastically reduce and limit the effectiveness of therapeutics in controlling and eliminating the disease no matter how advanced or novel therapy being used for the treatment.

Despite these challenges, the futuristic aspects of NSCLC treatment landscape indeed looks bright with multiple promising new therapeutics targeting new marker proteins and being less prone to acquiring resistance being developed and many of them even under stages of clinical investigation. New innovative therapies targeting other immune checkpoint receptors such as Toll-like receptors TLR 7 and 8 (MEDI 9197/3M-052), various neoadjuvant therapies, antibody drug conjugates including ABBV-399 (Telisotuzumab vedotin) and BAY94-9343 (Anetumab ravtansine) have showing remarkable results in preclinical studies and currently are under clinical stages of investigation. New small molecules targeting RTKs rearranged during transfection with potential antineoplastic activity such as selpercatinib and praseltinib, next generation c-MET inhibitors capmatinib and tepotinib have been recently approved for NSCLC treatment which are expected to further improve long term survival of NSCLC patients. Multiple other innovative small molecule inhibitors such as entrectinib, belizatinib, reprocitinib targeting both ALK translocations as well as acting as pan-TKIs, avitinib and olmutinib targeting EGFR with T790M/L858R mutations, second generation FLT3 inhibitor crenolanib with inhibitory activity against FLT3-ITD and FLT3-D835 mutations, have shown promising results in phase I clinical trials are currently are being studied in advanced phase II and phase III clinical trials. All these new therapeutics have shown remarkable activity against resistance acquiring mutations in their target genes and hopefully will further improve the long-term survival and life quality of NSCLC patients.

DATA AVAILABILITY

The systemic PubMed search data and extracted information are with authors and can be made available on request.

AUTHOR CONTRIBUTION

MK and AS contributed to the planning and data collection of the review article. MK wrote the original manuscript.

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CONFLICT OF INTEREST

All authors declare no competing or conflict of interest.

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СУЧАСНІ СТРАТЕГІЇ ТЕРАПІЇ ТА ВИКЛИКИ В ЛІКУВАННІ ПАЦІЄНТІВ З НЕДРІБНОКЛІТИННИМ РАКОМ ЛЕГЕНІ: КОМПЛЕКСНИЙ ОГЛЯД

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Недрібноклітинний рак легені (НДРЛ), на який припадає близько 80% усіх випадків раку легені, спричиняє щорічно понад мільйон смертей по всьому світу. Виявлення молекулярних змін, включаючи драйверні мутації та злиті гени, дозволило розробити новітні методи таргетної терапії. Але незважаючи на це, статистика п'ятирічної виживаності не покращилася настільки, як цього очікували. Усе це вказує на недостатність наявних методів діагностики та лікування хворих на НДРЛ. В огляді розглянуто різноманітні інноваційні підходи до терапії та схеми лікування, розроблені впродовж останніх двох десятиріч. Увагу зосереджено на питаннях, які ще потребують свого вирішення стосовно підходів до лікування хворих на НДРЛ.

Ключові слова: недрібноклітинний рак легені, таргетна терапія, терапевтичні моноклональні антитіла, хіміорезистентність.