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Mechanistic insights into molecular targeted therapy and immunotherapy for lung cancer

Teresa Vincent [a], Kunnathur Murugesan Sakthivel [b], C.M. Reena Josephine [c], Roopa Prasad [c], Kathirvelan Chinnadurai [d], Pavithra Kumar [b], Mythili Saravanan [e,1,*], Rajan Radha Rasmi [f,**,1]

[a] Apex Research and Scientific Writing Academy, NC, 27707, United States of America
[b] Department of Biochemistry, PSG College of Arts and Science, Civil Aerodrome Post, Coimbatore, 641 014, Tamil Nadu, India
[c] Department of Life Sciences, Kristu Jayanti College (Autonomous), Bengaluru, 560 077, Karnataka, India
[d] Department of Animal Nutrition, Veterinary College and Research Institute, TANUVAS, Udumalpet, 642 205, Tamil Nadu, India
[e] Department of Pharmaceutical Sciences, Biomanufacturing Research Institute and Technology Enterprise, North Carolina Central University, NC, 27707, United States of America
[f] Department of Biotechnology, PSG College of Arts and Science, Civil Aerodrome Post, Coimbatore, 641 014, Tamil Nadu, India

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ABSTRACT

Lung cancer is a serious public health concern and a leading cause of cancer related deaths worldwide. The major drawback of conventional therapies such as chemotherapy, radiotherapy, and surgery is their limited efficacy and lack of tumor specificity. Of these treatment options, targeted therapy and immunotherapy are of best interest due to their potential to selectively target cancer cells and enhance immune responses. Targeted therapy can bind to molecular targets and inhibit pathways involved in cell growth, proliferation, and survival. In the case of lung cancer, targeting expressions of EGFR, KRAS, and BRAF are important as their overexpression makes up a significant portion of cancer cases. Targets in the MAPK, PI3K, and MYC pathway are also inhibited as each of these pathways promote cell proliferation and growth. Immunotherapy directly kills off cancerous cells by amplifying the behavior of immune cells. Immunotherapeutic targets include NK-cells, T-cells, and immune checkpoints. NK cells and T cells are involved in the elimination of cancer cells, while immune checkpoints regulate the immune system but may be exploited by cancerous cells. The advent of molecular targeted therapy and immunotherapy has significantly transformed lung cancer treatment, offering precision and efficacy in combating tumor resistance. Their integration in combination strategies holds great promise for improved clinical outcomes and represents a pivotal direction for future therapeutic advancements.

1. Introduction

Lung cancer has the highest mortality rate and one of the leading diagnoses of cancer [1]. In 2022, lung cancer was the most diagnosed (2.5 million cases; 12.4 %) and deadliest (1.8 million deaths; 18.7 %) cancer globally. Over the past five years, it has consistently topped global incidence and mortality trends, highlighting an urgent need for intensified prevention and treatment efforts [2]. Despite additional Food and Drug Administration (FDA) therapy approvals and multidisciplinary treatments, the mortality rate is still rampant so the development of therapeutic agents for this fatal disease is significant in lowering the mortality rate. Lung cancer can be differentiated into two types: non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). NSCLC makes up around 85 % of lung cancer cases, leading to SCLC taking the smaller percentage of 15 % [3]. While smoking remains a major risk factor for lung cancer, particularly in developed countries, an increasing proportion of cases especially among non-smoking Asian females are associated with driver mutations such as EGFR, ALK, ROS1, and KRAS. These mutations have shifted the understanding of lung cancer pathogenesis beyond traditional risk factors. Other contributing elements include air pollution, genetic predisposition, and increased use of e-cigarettes, marijuana, and exposure to COVID-19 [4,5]. While lung

* Corresponding author. Department of Pharmaceutical Sciences, Biomanufacturing Research Institute and Technology Enterprise, North Carolina Central University, NC, 27707, United States of America.
** Corresponding author. Department of Biotechnology, PSG College of Arts and Science, Coimbatore, 641014, India.
E-mail addresses: mythisaran@gmail.com (M. Saravanan), rashmiffrajan@gmail.com (R.R. Rasmi).
[1] Authors Share Equal Correspondence.

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cancer mortality is plateauing in developed countries due to declining tobacco use, it is rising in developing nations amid growing tobacco consumption [6]. Urgency is needed for lung cancer as many patients will only receive a diagnosis in a late stage, which leads to death [7]. In order to combat this problem, a variety of therapeutics have been introduced to target different oncogenes and systems in the body. TKIs focus on targeting enzymes involved in signaling cascades that regulate cell growth, proliferation, and survival. The classical TKI signaling pathway begins with ligand binding to receptor tyrosine kinases (RTKs), such as EGFR, leading to receptor dimerization and autophosphorylation. This activates downstream signaling pathways, including the MAPK and PI3K/AKT/mTOR pathways, which promote oncogenic processes. Inhibiting these pathways using TKIs disrupts abnormal signaling, thereby limiting cancer progression. These mechanisms are particularly relevant in NSCLC, where EGFR and other RTKs are frequently mutated or overexpressed [8]. Lung cancer cases who have a mutation of a particular receptor or oncogene would find benefit in these inhibitors. There are multiple proteins who all have a task in the signaling cascade, so targeting these individual proteins have been researched as well. Immunotherapy is another emerging field of therapeutics that relies on the manipulation of the immune system. By targeting immune cell checkpoints or enhancing the ability of immune cells, immunotherapy can kill off cancerous cells. Studying and researching therapeutics for lung cancer is an ongoing challenge but yields significant results [9]. The human body is dynamic, but tumors also share this trait, which is why resistances keep pushing the study of lung cancer therapeutics.

1.1. Therapeutic targets

For NSCLC cases, platinum-based chemotherapy paired with supportive care raised the median overall survival from 4-5 months to 8–12 months. However, the benefits of chemotherapy have not shown an increase over time and instead has plateaued. Research instead shows further benefits, in the case of NSCLC, when chemotherapy is paired with bevacizumab, a tumor-blocking drug [10]. Other popular treatment options include surgery and radiotherapy, but immunotherapy and targeted therapy show incredible potential [11]. Immunotherapy has been proven useful like pembrolizumab and nivolumab, which are antitumor drugs that prevent cancer cells from inhibiting the immune system from working by binding to the programmed death 1 (PD-1) protein on T cells [1]. Chemotherapy is no longer the best treatment for every type of lung cancer. In the case of EGFR (epidermal growth factor receptor) overexpression, patients best benefit through targeted therapies rather than chemotherapy [12]. In the case of NSCLC, focusing on molecular pathways has proven to be more effective than chemotherapy. Targeting certain genetic mutations or over-expressions, like rat sarcoma (RAS), rapidly accelerated fibrosarcoma (RAF), or epidermal growth factor receptor (EGFR), provides a more personalized treatment [13]. By discovering a variety of types of therapeutics, it can be understood what works best in different types of cancer; certain therapeutics will work towards its maximum efficiency when paired with the right type of cancer [14] (Fig. 1).

1.2. Tyrosine kinase inhibitors therapeutics

In the recent decade, small molecular tyrosine kinase inhibitors - anticancer treatment that blocks growth signal enzymes - have been approved for treatment. Tyrosine kinases regulate the growth processes of cellular life, essential in proliferation and metabolism. If these kinases lose connection with ligands, the process of proliferation is no longer properly regulated, causing excessive growth [15]. Membrane receptors are differentiated based on the ligand they match with, their overall function, and structure. Receptor tyrosine kinases (RTK) are a class of membrane receptors and are responsible for phosphorylation [16]. RTKs are activated in connection to ligands through dimerization. Ligands are bound through the RTKs extracellular area and are known as signaling molecules. The bind signals the cell to dimerize with another RTK and perform autophosphorylation [17]. ATP contains three phosphate groups, one being the γ-phosphate group, which RTK transfers to their or each other's tyrosine residues [18]. Tyrosine kinase inhibitors (TKIs) are able to reduce proliferation in cancer cells through slowing down the process of phosphorylation. The epidermal growth factor receptor (EGFR) resides on the cell surface and promotes survival of the cell

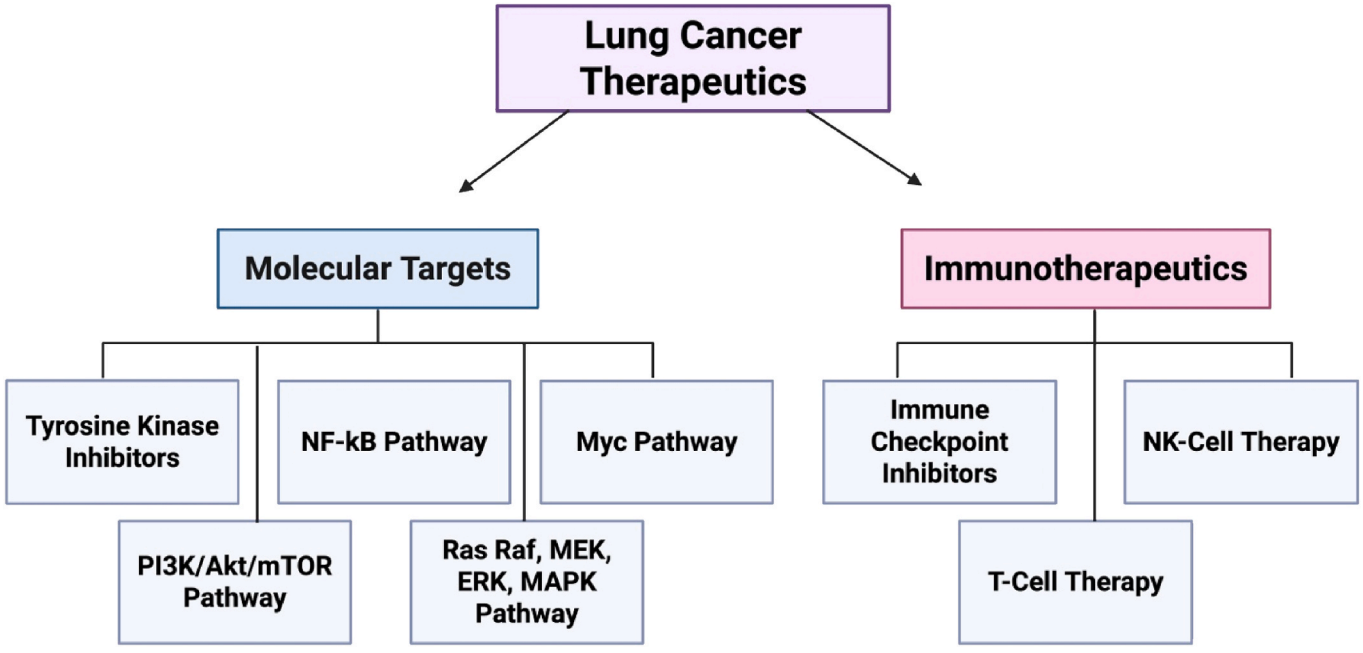

Fig. 1. Overview of lung cancer therapeutics. Various lung cancer therapeutics are shown, highlighting different signaling mechanism mediators. The connections between the therapeutics are shown under different categories. In molecular target therapeutics, molecular pathways and the mediators within those pathways are targeted, such as RAS, MAPK, MYC, and TKIs. In immunotherapeutics, therapies relating to the enhancement of immune cells are provided, such as immune checkpoint inhibitors, NK-cell therapy, and T-cell therapy (Schematic was generated using BioRender.com with an academic license).

(Fig. 2).

An overexpression of this gene may cause mutational growth (Jiao et al., 2018). Gefitinib and Erlotinib are FDA approved TKIs that challenge EGFR that compete with ATP to prevent phosphorylation [19]. They would be part of the first generation of TKIs, along with crizotinib, which targets another kinase: ALK. Anaplastic lymphoma kinase (ALK) would be another targeted gene of lung cancer, with 3–7 % of NSCLC patients conditioned with an ALK rearrangement [20]. The generation proved a 70 % success rate but resistance was inevitable, bringing in further research to find drugs that will break resistance (Ray et al., 2010). A second generation of inhibitors were designed to work against the acquired resistance that the T790 M mutation brought onto the EGFR gene. The second generation shares characteristics shown in afatinib and dacomitinib including a covalent bond to EGFR, leading to prolonged inhibition. Afatinib was able to irreversibly block the ErbB family receptors [1] ray. Second generation inhibitors focused on attacking the broader family members of HER. Afatinib was made with the hope of treating patients with acquired resistance to first generation inhibitors, but now it is a first-line therapy option [21]. With more than 60 % of patients experiencing acquired resistance to first and second generation TKIs, another generation had started its development. Third generation TKIs were developed with the purpose to overcome the T790 M mutation, as the second generation attempted, but without failing this time. TKIs like Osimertinib proved efficacy against mutations like exon19del and L858R as well [22]. As a result of third generation progress, the prescriptions of first generation TKIs have decreased for NSCLC, while second and third generation TKIs have shown an increasing pattern with the third generation showing the greatest increase due to decreased side effects and better efficacy compared to the other generations [23]. Fourth generation TKIs are currently under clinical trials since resistance against Osimertinib has started to appear. The C797S mutation prevents a covalent bond between the EGFR and Osimertinib, provoking more research [24]. Osimertinib still has its disadvantages as well, including decrease in white blood cells, invoking bacterial infections [25]. Fourth generation inhibitors are known as allosteric kinase inhibitors as they bind differently but may be used in complement with ATP-competitive TKIs. The first fourth generation TKI for EGFR is EAI-045. EAI-045 can prevent phosphorylation in EGFR Y1173 in highly potent cancer cells, blocking their growth [26]. However, it showed limited activity without the use of cetuximab, which is

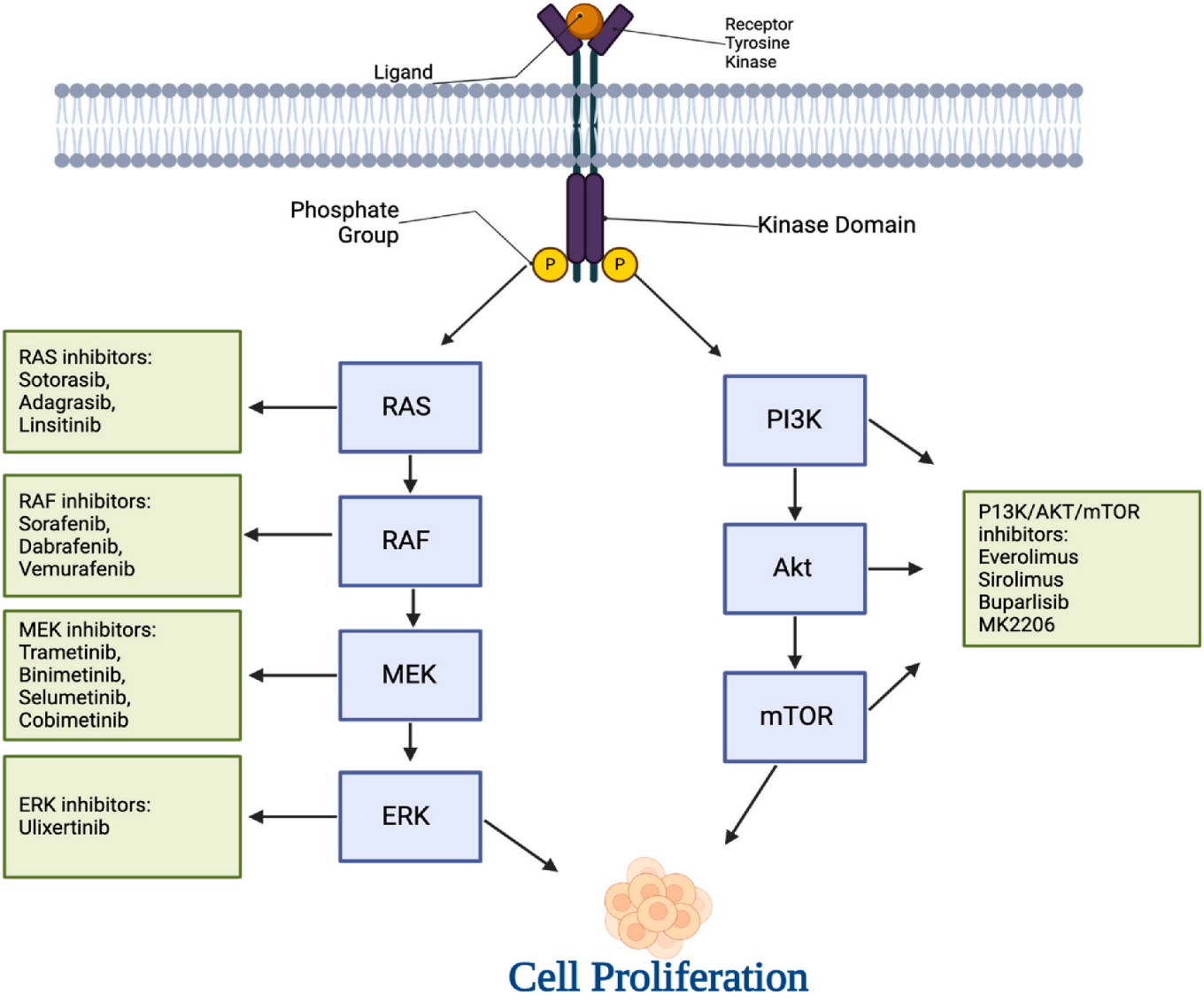

Fig. 2. Function of EGFR signaling pathway. The receptor tyrosine kinase binds with a ligand, which would include growth factors like EGF. The binding prompts dimerization to activate the TK and their residues are autophosphorylated. Different pathways are activated through the binding to result in cell proliferation and survival (Schematic was generated using BioRender.com with an academic license).

an antibody that disrupts EGFR function by blocking dimerization [27]. BBT-176 is one TKI under research designed against the C797S, T790 M, and L858R mutations without forming a covalent bond (Table 1) [24].

Combination strategies are also in development where TKIs are supplemented with an additional targeted therapy that targets the mutation [27]. The MET receptor is theorized to be the cause of acquired resistance specific to the first-generation drugs, where the Hepatocyte growth factor (HGF) ligands signals for phosphorylation of this receptor. Combining Osimertinib and MET inhibitors are currently in research but show valid potential [28]. If MET overexpression is targeted, resistance can be prevented, which is why the EGFR-MET TKI combination therapy has shown promise so far [29]. Chemotherapy in combination with EGFR TKIs is still in research and hasn't shown significant results as of yet [30]. Chemotherapies and some targeted therapies focus on cell death and destruction of DNA, which has been theorized to have led to the Warburg effect, metabolizing energy in a different way. Scientists have suggested using enzymes as targets of therapy to inhibit cell metabolism in cancer cells, acting as another option for research [31].

1.3. MAPK pathway therapeutics

The Mitogen activated protein kinase (MAPK) pathway is a signaling pathway involved in cellular survival and proliferation. Signals are transmitted from extraneous factors (hormones, cellular molecules) and play a major role in cell proliferating processes. The RAS oncogene is involved with MAPK since they can bind with it to trigger cell processes [32]. The correlative relationship can be explored further. When growth factor receptors bind with their respective growth factor, downstream signaling transduction is activated. To activate phosphorylation, the RAS family is the first in line. RAF depends on the activation of RAS (RAS-GTP) to perform their downstream effector role. RAF contributes to their role in the signaling pathway by continuing the cascade to MEK (MAP2K) [33]. The MAPK pathway consists of RAS/RAF/MEK/ERK. 2–4 % of NSCLC patients experience mutations in BRAF, but throughout different cancers this mutation is prominent. 2 % of NSCLC patients relate towards mutations in MEK, but still contribute towards cell proliferation, so targeted therapies against MEK has shown antitumor properties [34]. The MAPK family is categorized into 5 main families: RSK, MSK, MNK, MK2/3, and MK5. Each of these subgroups consists of different functions. In the case of MK5, they moderate tumor suppression and show expression in the lung. For RSK1-4 they mediate cell growth, proliferation, and survival. Recent evidence suggests that MK5 is involved in cell senescence [35]. Mutations of MAPK are common in NSCLC and less common in SCLC but contribute to the aggressive nature of SCLC. However in SCLC-A, a subtype characterized with an overexpression of ASCL-1, the MAPK pathway may reduce cancerous cells by attacking the G2/M phase of the cell cycle and prevents division [36]. EGFR, which is commonly mutated in NSCLC patients, leads to the overactivation of the pathway and leads to uncontrolled cell growth through downstream signaling. Targeting the MAPK pathway would halt any uncontrolled cell growth that is activated by lung cancer prominent RTKs like EGFR [37]. General MAPK inhibitors target certain proteins within the pathway like Dabrafenib, which is approved for BRAF V600 NSCLC patients by inhibiting the BRAF gene. Emerging MAPK inhibitors include p38 MAPK inhibitor SB203580 for NSCLC, which is undergoing trials with combination therapies as well as it inhibits certain isoforms of p38 MAPK by binding to the p38 MAPK ATP binding pocket to inhibit phosphorylation within the pathway [38].

Table 1
Different EGFR-TKI generations of inhibitors.

Generation	Drugs	Mechanism
1	Gefitinib, erlotinib	● ATP-competitive TKIs to block phosphorylation to inhibit EGFR
2	Afatinib, dacomitinib	● Added benefits of covalent bond with EGFR ● Targeted HER family ● Focused on overcoming T790 M mutation
3	Osimertinib	● Overcame resistance in T790 M, exon19del and L858R mutations
4	EAI-045, BBT-176	● Allosteric kinase inhibitors ● Overcomes resistance in T790 M, exon19del, L858R, and C797S mutations ● Able to bond differently to counteract against C797S mutations

1.4. RAS pathway therapeutics

Another emerging therapeutic approach would include targeting the Kirsten rat sarcoma viral oncogene homolog (KRAS). KRAS, along with EGFR, is one of the most altered genes in NSCLC. The RAS family shares a similar purpose as EGFR including cell growth and survival but functions differently [39]. RAS proteins act as a switch, signifying "on" when attached to GTP, and otherwise "off" when attached to GDP. Once attached to GTP (Ras-GTP), it can attach to effectors and provide downstream signaling. However, if the protein transmits faulty signals, then signs of cancer start to appear. Ras pathway inhibition has been proven to be difficult, as drugs couldn't bind and inhibiting their downstream signals is still in research [40].

Though once seemed impossible, as new therapeutics have arrived, new approaches to target KRAS have emerged. Direct inhibition of KRAS has been made possible in various clinical trials as of recently by providing a solution to how KRAS has preferability towards GTP attachment [41]. Small molecule inhibitor Sotorasib was the first to enter clinical trials as an inhibitor of KRAS G12C. Sotorasib covalently and irreversibly binds to the KRAS' "off" GDP state, rendering it inactive. Eventually Sotorasib was approved by the FDA in May 2021 for NSCLC patients with KRAS G12C tumor mutations after trying one other systemic therapy [42]. Adagrasib was another FDA approved drug in December 2022 for patients under similar circumstances as Sotorasib patients. [43]. Adagrasib also combats KRAS G12C through a covalent bond with cysteine 12 in the KRAS G12C protein to create inactivity, which cancels cell proliferation. Though these drugs are able to target KRAS, resistance has already been activated. Intratumor heterogeneity, diversity of cells within the tumor, do not all have the same response to treatment. Some cells may synthesize new KRAS G12C proteins, and with the signals from EGFR and AURKA, are able to maintain their GTP-bound activate state, avoiding the inhibitor treatment [44]. To overcome this resistance, combination therapy is one suggested approach. Afatinib can be used with Sotorasib in a trial since afatinib inhibits EGFR, which would theoretically disrupt resistance. One trial executed the combination of these drugs, leading to an overall response rate of 34.8 %. Adverse effects like diarrhea were consequently involved [45]. Another combination proposed includes a KRAS inhibitor with a Src homology phosphatase 2 inhibitor (SHP2). KRAS mutant cells are hypothesized to depend on SHP2 and thrive upon it, which is further backed by studies. When combining a KRAS inhibitor with a SHP2 inhibitor, preclinical studies have shown greater efficacy than monotherapy of either inhibitor [46]. Attempts to combine a MEK inhibitor with KRAS have also been suggested since it would target the signaling pathways downstream. One KRAS inhibitor, ARS-1620, was combined with linsitinib and everolimus, a three-drug combination, and showed significantly slowed cell growth. Compared to when ARS-1620 was only used with either linsitinib or everolimus, thorough inhibition was only shown with the three-drug combination instead of only two drugs [47]. KRAS has only started to show promise in the recent decade, so additional research will expand new discoveries and understandings to overcome resistance and create new drugs. 20–30 % of all NSCLC cases have shown a mutation in the KRAS gene, which proves its significance in lung cancer cell growth. Targeting this gene would help NSCLC cases since it is an emerging key biomarker in lung cancer [48]. New therapeutics developed to target KRAS include K20, which declined ERK phosphorylation levels and GTP active form, as well as inducing cancer cell apoptosis [49].

1.5. RAF pathway therapeutics

As discussed before, RAF is part of the MAPK pathway involving RAS/RAF/MEK/ERK. Just how RAS can be individually targeted for certain subtypes of cancer, the RAF kinases can be inhibited to disrupt signaling. Although inhibiting RAS has not been proven effective for small cell lung cancer, activating the MAPK pathway may lead to cell cycle arrest by triggering anti-growth pathways, thus fighting against SCLC [50]. Sorafenib is a drug that is able to inhibit BRAF/CRAF and other growth factor receptors like VEGFR. Using this inhibitor is proven to be effective against NSCLC. [51]. Dabrafenib also inhibits BRAF, specifically the BRAF V600 mutation. The drug acts as an ATP competitive inhibitor, similarly to first generation TKIs like gefitinib [52]. Vemurafenib also acts against BRAF V600. These drugs are part of BRAFi therapy, where sorafenib falls under as well. BRAF mutations often occur in adenocarcinoma cases [53]. CRAF is also part of the RAF family and research shows how CRAF is deeply involved in the growth and survival of KRAS, which impacts a hefty percentage of lung cancer. Overexpression of CRAF is an early sign of cancer development, which is more common than a RAF1 mutation [54]. The Raf kinase inhibitory protein (RKIP) is being studied for its tumor-suppressive properties. It is found in the cytoplasm, plasma membrane, and/or nucleus in various tissues. Functions of RKIP include cell growth, mobility, and invasion but also has control over the MAPK pathway where it can control activation. RKIP also acts as a biomarker for lung cancer [55]. RAF mutations don't make up a lot of cancer cases, but inhibiting certain families

Table 2
Some of the FDA approved drugs for lung cancer.

Cancer Type	Drug	Type	Clinical Effect	Reference
NSCLC	Chemotherapy + bevacizumab	Recombinant humanized monoclonal antibody (Tumor blocking drug)	Bevacizumab plus chemotherapy significantly improved OS (HR 0.89), PFS (HR 0.73), and response rates (OR 2.34) compared to chemotherapy alone.	[3,66]
	Pembrolizumab	Inhibits PD1 protein to promote immune response	Pembrolizumab-based therapy significantly improved OS (HR 0.66) and PFS (HR 0.60) compared to chemotherapy.	[3,67]
	Gefitinib and Erlotinib	EGFR TKI	Analysis of 28 studies, including three on afatinib, showed similar efficacy (ORR, PFS, OS) between erlotinib and gefitinib, with afatinib causing more diarrhea, rash, and paronychia. All three TKIs had higher ORRs in first-line treatment of EGFR-mutant tumors.	[19,68]
	Afatinib and Dacomitinib	EGFR TKI	In a study of 101 patients (70 afatinib, 31 dacomitinib), partial response rates were 85.7 % and 80.6 %, respectively ($p = 0.522$). Median PFS (18.9 vs. 16.3 months, $p = 0.975$) and TTF (22.7 vs. 15.9 months, $p = 0.324$) were comparable between the two treatments.	[69,70]
	Osimertinib	EGFR TKI	In the study, osimertinib monotherapy showed a progression-free survival (PFS) rate of 41 % at 24 months, with an objective response rate of 76 % and a median response duration of 15.3 months. It had a lower incidence of grade ≥3 adverse events compared to the combination therapy, indicating a more favorable safety profile.	[24,71]
	Atezolizumab	PD-L1 Checkpoint Inhibitor	In the atezolizumab arm, ORR was 16 % and median PFS was 4.2 months (iRECIST) vs. 2.8 months (RECIST v1.1). Post-progression OS was 12.7 months with treatment beyond progression (TBP), 8.8 months with nonprotocol therapy, and 2.2 months with no further therapy. Among TBP patients, 7 % showed post-progression response and 49 % had stable disease, with no added safety risks.	[72,73]
	Ipilimumab	CTLA4 Checkpoint Inhibitor	ipilimumab combined with chemotherapy improved immune-related PFS (5.68 months phased, 5.52 months concurrent) vs. 4.63 months with chemotherapy alone. Immune-related adverse events were manageable with glucocorticoids and may correlate with response.	[74,75]
	Sorafenib	BRAF Inhibitor Therapy	Sorafenib improved PFS (2.8 vs. 1.4 months) and time to progression (2.9 vs. 1.4 months) versus placebo, but OS was similar overall (8.2 vs. 8.3 months). In EGFR-mutant patients, both OS (13.9 vs. 6.5 months) and PFS (2.7 vs. 1.4 months) were significantly better with sorafenib. PFS benefit was seen regardless of KRAS status, and common adverse events included rash, diarrhea, and fatigue.	[51,76]
	Dabrafenib + Trametinib	BRAF Inhibitor Therapy	Dabrafenib monotherapy in 78 previously treated patients showed a lower ORR of 27 %, indicating that trametinib is essential to enhance treatment efficacy. Common adverse effects (≥20 %) included pyrexia, fatigue, nausea, vomiting, diarrhea, rash, dry skin, and cough.	[52,62,77]
	Vemurafenib	BRAF Inhibitor Therapy	Vemurafenib demonstrated promising efficacy in NSCLC patients with BRAFV600 mutations, showing prolonged progression-free survival in untreated patients. Median overall survival was not reached due to ongoing responses. Its safety profile was consistent with melanoma studies, supporting BRAF inhibition as a treatment option in BRAF-mutant NSCLC.	[53,78]
SCLC/ NSCLC	Nivolumab	PD1 Inhibitor	In patients with PD-L1 ≥5 %, median PFS was 4.2 months with nivolumab vs. 5.9 months with chemotherapy (HR 1.15, $P = 0.25$), and median OS was 14.4 vs. 13.2 months (HR 1.02). Sixty percent of chemotherapy patients later received nivolumab. Any-grade treatment-related adverse events occurred in 71 % with nivolumab and 92 % with chemotherapy; grade 3–4 events occurred in 18 % vs. 51 %, respectively.	[3,79]
	Crizotinib	ALK TKI	Among 82 ALK-positive patients treated with crizotinib, median overall survival was not reached, with 1- and 2-year survival rates of 74 % and 54 %. Survival was similar across age, sex, smoking status, and ethnicity. In second- or third-line treatment, crizotinib significantly improved survival compared to other therapies (median OS not reached vs. 6 months; HR 0.36, $p = 0.004$). Crizotinib-treated ALK-positive patients had similar survival to EGFR-positive patients on EGFR TKIs, while crizotinib-naive ALK-positive patients had survival comparable to wild-type controls.	[20,80]
KRAS G-12C NSCLC	Sotorasib	KRAS inhibitor	Based on the CodeBreaK 100 trial, sotorasib showed a 36 % overall response rate and a median response duration of 10 months. Common side effects included diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough. This is the first targeted therapy approved for KRAS G12C-mutated NSCLC, with a dose comparison study ongoing as a post-marketing requirement.	[42,81]

of RAF may show benefits for other mutations, like in the case of KRAS [56]. Encorafenib and binimetinib are treatments for BRAF V600 mutations. In a phase II trial, the combination of both these drugs had proven to show effects in both previously treated and untreated NSCLC [57]. Novel therapeutics targeting RAF include lifirafenib and LXH254. Lifirafenib targets BRAF mutant tumors and KRAS NSCLC without intense side effects. LXH254 is still currently under clinical trials, but one trial has shown their potential against BRAF and KRAS [58]. The RAF pathway is significant in lung cancer especially since it plays a role in the MAPK pathway, and mutations in BRAF exist in NSCLC cases.

1.6. MEK pathway therapeutics

MEK is part of the MAPK pathway. When dealing with BRAF mutations, targeting the MAPK pathway is useful as treatment. MEK inhibitors are used as an agent alongside other treatments like TKIs or chemotherapy to enhance efficacy. MEK is a protein that processes extracellular mitogen signals to the nucleus. A few MEK inhibitors have been approved by the FDA including trametinib, binimetinib, selumetinib, and cobimetinib, which all prevent downstream activity of ERK by blocking MEK1/2 proteins (Table 2) [59]. MEK doesn't serve as a target for mutations, but instead it is used to block other mutations related to RAS,RAF,etc. MEK follows the functions of MAPK including cell proliferation and apoptosis, so blocking MEK in the signaling cascade may influence RAS mutations [60]. In V600E/non V600E BRAF, MEK inhibition showed greater effects compared to MEK inhibition in EGFR or KRAS overexpression. Although BRAF mutations make up a small percentage of NSCLC cases, they are to be treated differently than EGFR mutations due to different characteristics. BRAF is still the most common kinase domain tumor mutation [61]. MEK Inhibitor monotherapy isn't very effective on its own, but combination therapies have shown greater use of MEK inhibitors. Dabrafenib, a BRAF inhibitor, used in combination with trametinib showed great survival results. The combination is FDA approved in both first line and second line therapy. [62]. By blocking MEK, the signal transduction is disrupted so RAF signals won't pass through [63]. There are a couple of downsides to MEK therapeutics, including the chance of toxicity and limited antitumor activity with the use of inhibitors. MEK and PI3K inhibitor combination causes increased toxicity as well [64]. MEK is involved in multiple cellular pathways, proving their significance in upstream mutations including BRAF and KRAS which are prominent in NSCLC cases [65].

1.7. ERK therapeutics

Excessive signaling of ERK (extracellular signal-regulated kinase) is a known cause of mutations in RAS and RAF [61]. ERK therapeutics are in consideration for whether they are better than MEK therapeutics. ERK proteins can activate targets in the cytoplasm and nucleus, which is why their inhibitors may be more significant than MEK inhibitors. ERK inhibitors are also able to prevent drug resistance markers like bypass and feedback activation [64]. ERK is involved in numerous cellular tasks, so directly inhibiting it may show greater results [63]. The ERK MAPK pathway activation shows a lack of apoptosis, the process of programmed cell death, which factors into cancerous cell transformations. When the ERK signaling pathway continues to be set in motion, tumor development starts to activate as well. The inhibition of this pathway would therefore slow tumor development [82]. Combination therapies with ERK therapeutics are an ongoing study, such as in the case of MEK with ERK and BRAF with ERK. However, resistance has started to form in the allosteric drug-binding pocket, which is where substrate binding occurs [83]. ERK still shows potential through its anti-metastatic properties. Due to the ERK pathway's role in cell motility and the expression of matrix metalloproteinase (mmp)-9 gene. MMP9 is related to metastatic properties in tumors, and inhibiting this would decrease metastatic potential in cancerous cells [84]. ERK still contains characteristics that make it unique as a target. ERK acts as the only substrate for MEK, and MEK is one of few effectors for RAF. ERK can also act as a negative inhibitor of RAF. By targeting ERK 1/2, deformities caused by MAPK pathway activation can be avoided in the case of some mutations, like RAS [85]. ERK inhibitors are mostly still in development, but Ulixertinib is an inhibitor that is FDA-approved for BRAF V600 cancer [86]. Current ERK inhibitors in phase 1/2 clinical trials include GDC0994 and VRT752271, which have shown activity against tumors. These inhibitors were used in clinical testing where the inhibition of ERK effectively overcame resistance acquired by Osimertinib [87]. ERK therapeutics can work with MEK inhibitors to create a complete blockage of the MAPK pathway to prevent mutational RTKs (EGFR) from initiating growth, especially for upstream mutations like KRAS and BRAF [64]. These properties show that research into ERK therapeutics may provide great benefits.

1.8. PI3K/AKT/mTOR pathway therapeutics

The pathway is first started with the binding of a ligand with an RTK. Phosphatidylinositol-3-kinase (PI3K) is a lipid kinase involved in producing signaling mechanisms. PI3K creates phosphatidylinositol-3,4,5-trisphosphate (PI-3,4,5-P3), which plays a role in transporting Akt, which is a serine/threonine kinase. Akt is phosphorylated in the plasma membrane and activated by two enzymes, allowing Akt to play its role in cellular proliferation and survival. Akt activation also triggers the downstream pathway mammalian target of rapamycin (mTOR), a protein kinase. mTORC1 is activated through the phosphorylation of the tuberous sclerosis complex 2 gene (TSC2) which leads to the activation of Rheb (Ras homolog enriched in the brain), a GTP binding protein. Eventually these signaling mechanisms trigger the eIF4 (eukaryotic initiation factor 4) complex, which is involved in cell cycle, tumorigenesis, and apoptosis inhibition [88]. The PI3K pathway is involved in 50–70 % of all NSCLC cases, and mutations in this pathway, as well as parallel pathways, leads to increased cell survival and growth. Specific proteins in this pathway can be targeted to combat mutated RTKs. First generation EGFR TKIs may not be effective, but if paired with a PI3K inhibitor, can show improvements [89]. Various PI3K pathway drugs are currently undergoing clinical trials. Buparlisib is a PI3K inhibitor under trial, along with Akt inhibitor MK2206, and mTOR inhibitor sirolimus. The PI3K pathway has also been theorized to be involved in angiogenesis, which provides nutrients and oxygen to tumor cells to aid in their growth. The connection is explained by how hypoxia-inducible factor-1α (HIF-1α) is involved in tumor blood vessel growth, and this transcription factor is also regulated by the PI3K pathway [90]. The combination of taselisib, a PI3K inhibitor, with trametinib (MEK inhibitor) had shown to overcome EGFR resistance. However, taselisib is not FDA approved due to its serious side effects, but this case still proves that PI3K shows potential in combination therapy to overcome RTK resistances [91]. As of now there aren't any FDA approved PI3K/Akt/mTOR drugs that are specifically meant for lung cancer, but several options are being studied for further approval. In the case of PI3K, inhibitors would show the best effectivity under combination therapy since monotherapy options show that cancer cells continue to grow even after the drug is administered [92]. The Akt/mTOR pathway is also involved in contributing to radio/chemotherapy resistance due to their cell growth properties that interrupt treatment, so inhibitors are useful against this problem. Current inhibitors being tested for mTOR inhibitors include everolimus and sirolimus, which are FDA approved for other types of cancer [15]. New PI3K pathway inhibitors include pictilisib, which is being tested for its anti-tumor properties against lung cancer [93]. Another potential inhibitor is LY294002 as it helps regulate tumor growth [94]. As PIK3CA mutations are still present in NSCLC, targeting this pathway would help target this mutation [88].

1.9. NF-kB

Nuclear Factor Kappa B (NF-kB) is a transcription factor involved in

regulating oncogenesis by tipping the balance between apoptosis and cell proliferation. NF-kB has anti-apoptotic properties, which means that it promotes the inhibition of apoptosis, leading to further cell proliferation. If NF-kB activation is inhibited, then the balance between proliferation and apoptosis would be restored, which is why research is invested with the goal of preventing malignant tumors [95]. NF-kB is able to activate hundreds of genes related to a cell's life and death. They are also able to activate cell cycle regulators (cyclin A, cyclin D1) and the traits of prolonged cell life are expressed through NF-kB expression [96]. To understand NF-kB, following its role in the canonical pathway is crucial. The canonical pathway is triggered through various signals that activate the IkB kinase (IKK) complex and phosphorylates IkB. IkB then undergoes ubiquitination and is sent to the proteasome to be broken down. The sequence triggers the NF-kB complex to control gene expression in the nucleus if a binding site is present for NF-kB. Inhibiting NF-kB would inhibit proteasomes as they are interconnected in the same pathway, which disrupts the cell cycle. NF-kB inhibition would also help switch the function of macrophages from M2 to M1, essentially transforming them from tumor-assisting to tumor-killing [97]. NF-kB would be best used in combination therapy, as they are able to enhance the treatment of other therapeutic options and help against drug resistance. Side effects may still arise such as decreased function of the immune system against other pathogens [98]. IKK inhibitors and proteasome inhibitors are both in relation to inhibiting NF-kB since they work in the same pathway. Bortezomib is an FDA approved proteasome inhibitor that blocks NF-kB activity. Blocking NF-kB is effective for lung cancer as resistance to apoptosis and tumor growth are prevented [99]. Emerging therapeutics including Corylin, which inhibits NF-kB, specifically their downstream signaling genes. Lung cancer cell growth is stalled under the treatment of Corylin [95]. NLOC-015A is a small-molecule inhibitor of NF-kB that inhibits EGFR/AKT/mTOR as well. Clinical trial data shows that NLOC-015A is proven to be effective with Osimertinib [100].

1.10. MYC pathway therapeutics

The MYC oncogene family contains three main genes: C-Myc, N-Myc, and L-Myc. The family is involved in cell proliferation and growth of tumors. The gene has been identified in multiple tumor samples, with most cases coming from SCLC cells [101]. MYC genes are transcription factors and the different family members all perform similar functions as each other. MYC has the power to trigger cellular cascades since it is a transcription factor, also involved in the replication of DNA. If there was an overexpression of MYC, the cell growth rate would increase since MYC transcription factors are involved in the cell proliferation process. Targeting MYC has shown challenges, but its value is well known as MYC abnormalities occur often in various cancer cases [102]. MYC plays a role in NSCLC as an overexpression of MYC is found in 41 % of NSCLC cases. Research even proves a positive correlation with PD-L1 and MYC in NSCLC, indicating a relationship with the immune system. MYC may play a role in protecting tumor cells since it induces PD-L1, explaining relations with the immune system [103]. Similar to RAS, MYC has also been traditionally thought of as incapable as a target for drugs, but recent progress has proven otherwise for inhibitors. Omomyc is an inhibitor of MYC undergoing clinical trials, and is able to block cancer-driven interactions. Omomyc is able to block MYC's role in DNA transcription to prevent the activation of cancer genes. Its anticancer effects have been demonstrated in a variety of animal tumor models. BGA002 is another MYC inhibitor which specifically targets N-Myc. By working against DNA, BGA002 works at the roots to inhibit MYC and is proven to be highly efficient in preclinical trials [104]. Prodrug MI3-PD is delivered through nanotherapy and has shown inhibition against C-Myc (Weber & Hartl, 2023). MYC inhibitors are still emerging as research is recent, so time is still needed before an inhibitor reaches FDA approval. MYC inhibitors are significant in lung cancer because of their role in being overexpressed in SCLC [105].

2. Immunotherapy

2.1. Cell cycle based therapeutics

Immunotherapy has shown increasing promise over the years. The immune system is responsible for the role of surveillance and protection. The role of killing off cancer cells is enhanced through the use of immunotherapy [106]. Immune checkpoints help the body preserve its cell and recognize itself to prevent self-destruction. However, tumor cells are able to benefit from this and prevent the immune system from destroying them. With the help of immune checkpoint inhibitors (ICI), cancer cell proliferation would decrease and instead would be killed off [107]. Tumor cells are able to escape cell activation by emitting inhibitory cytokines and triggering T-cell inhibitory signaling pathways [108]. These inhibitors function by enhancing autoimmune functions themselves rather than attacking the proliferation [109]. Cytotoxic T-lymphocyte associated antigen 4 (CTLA4) and programmed death ligand-1 (PD-L1) are main targets in immunotherapy for checkpoint inhibitors [110]. CTLA-4 is expressed on B lymphocytes, fibroblasts, and other immune cells but usually expressed on T cells. Anti CTLA4 inhibitors operate by decreasing regulatory T-cells in the tumor microenvironment (TME), which police cell activation, and making sure CTLA-4 doesn't bind with its respective ligands. For context, CTLA-4 and CD28 compete to bind with B7-1 and B7-2 ligands on antigen-presenting cell surfaces to either mitigate or increase cell activation [108]. The TME is able to determine how the immune system reacts to the checkpoint inhibitors, but analysis may be disrupted due to other treatments that affect ICI response rate [111]. CTLA4 and PD-L1 are both inhibitors to immune cell activation, along with Programmed death 1 (PD-1) [112]. Nivolumab and pembrolizumab are both drugs to inhibit PD-1, while atezolizumab inhibits PD-L1. These drugs are all approved as second-line therapy for metastatic NSCLC [72]. When used as monotherapy, a small percentage of patients show a response rate and there is still a variety of adverse effects related to ICI intake (hepatitis, pneumonitis, etc.). Combination therapies with ICIs have been studied and tried for efficacy. Pembrolizumab + chemotherapy has been FDA approved as it reduced mortality rate. Combining CTLA4 inhibitors with PD-1/PD-L1 is still under investigation, such as in the case of nivolumab and ipilimumab (CTLA4). In a phase III clinical trial, results showed that the combination therapy approach showed greater efficacy in patients with high tumor mutation burden (TMB) compared to chemotherapy [74]. If ICI therapy doesn't help, it may be due to low anti-tumor T-cell count, or impaired memory/function of the T-cells themselves. Impaired function would be the result of the TME. Resistance of ICIs have also started to form [113]. Errors in antigen presentation or depletion of immunogenic neoantigens, which induce the immune response, contribute to tumor related reasons on why acquired resistance has occurred. Inflammatory cytokines also help cancer cells escape immune response and develop resistance. The gut microbiome may also play a part in resistance, and controlling it may help prevent it. Resistance may be reversed with the help of combination therapy as discussed before since monotherapy is less effective [94].

2.2. T-cell based therapeutics

Immunotherapy is rising as a new substantial procedure to cancer treatment, and T-cell therapy is an immunotherapeutic approach. There are a couple of properties that make T-cells an ideal approach for therapy [114]. T-cells, along with NK-cells, are able to knock down cancerous cells. Tumors are a different case for them, as they provide obstacles in order for T-cells to eradicate them [115]. Besides that, T cells are still able to differentiate between malignant vs normal cells and exhibit a strong defense mechanism against T-cells. They are also able to display memory, as they'll remember the specific antigen and continue treatment years later [114]. Exchanging T-cells to a cancer patient has been effective for viral infections and has shown progress with cancer as

well. The transfusion of T-cells is known as adoptive therapy. By genetically modifying T-cells, they are able to efficiently attack tumors. T-cells are flexible to modification, allowing research and trials to continue [116]. Genetic modifications include the solution to overcoming tumors and increase survival rate and efficacy. Chimeric antigen receptor T-cells (CAR T-cells) are genetically modified T cells that are able to recognize cancer antigens so immune evasion is prevented since cancer cells would be identified. Other genetic modifications that could occur would be additional cytokines to assist in sustaining T-cells [117]. T-cells are unique since chimeric receptors are able to act like original T-cell receptors. When the receptor is bound to a target antigen on a cancer cell, a signal is triggered to the cell, which is known as cell activation. The drugs that are currently under clinical trials are listed in Table 3. The activation allows effector T-cells to fulfill their function [118]. CAR T-cells have gone through generations of development, with the first not surviving long. Soon it had advanced through the addition of costimulatory molecules to persist through survival problems and cytokines were added to survive the TME. Currently, CAR T-cells are in early clinical trial phases with EGFR, HER2, and PD-L1, which are all receptors that affect survival and growth of lung cancer cells [10]. The TME poses a challenge for T-cells. Hematological malignancies have shown vast success and compatibility with CAR T-cell therapy, but they lack the TME, which poses a problem for other types of cancer. Though solutions have arrived, they are still under trial for efficacy. CAR T-cells have shown great advancements when facing different problems. When faced with antigenic heterogeneity, as tumors contain a variety of cells, CAR T-cells have been engineered with multiple chimeric antigen receptors targeting different antigens [119]. CAR T-cell therapy comes with a risk of non-specificity of an antigen target, as solid tumors have a diversity of cells within them and this diversity comes with similar antigens as normal cells. It is important to target the right antigen otherwise healthy cells will be affected and killed off. An exceptional risk comes up when an overexpression of a specific antigen is shown in cancer cells, leading to its elimination, but it may still exist in healthy cells at a lower expression, so healthy cells would be eliminated as well. [120]. Neo-antigen identification must be researched in order to overcome these problems. Manipulating CAR structure with cytokines would aid like using IL-10. Inducing IL-10 promotes survival of T-cells in the TME by aiding in the generation of energy. Targeting physical barriers may help survival as well [121]. Tumor stroma provides a barrier in T-cell mobility. To avoid it, T-cells would be injected directly in the area of cancerous cells. Since the tumor cells would no longer be engaging with the bloodstream, the chances of harming healthy cells would decrease [122]. TCR T-cell therapy is another option for immunotherapy. TCR T-cell therapy may be seen as the better alternative for solid tumors since CAR T-cells show excellency in hematological malignancies, but there is still progress needed for solid tumors. The TCR (T-cell receptor) can be modified to identify overexpressed antigens in solid tumors. TCR T-cells can also be modified to overexpress molecules that promote cell activation. Cost of research and off-target toxicity are main concerns of TCR T-cell therapy. Although CAR T-cells are able to target more than just peptide antigens, TCR T-cells are able to target intracellular antigens, contrary to CAR T-cells who are only able to target cell surface antigens. The weakness of TCR T-cells is their limitation of recognition to MHC presented antigens, which could be interfered with by mutations in tumor MHC molecules [117]. Currently progress with adoptive CAR T-cell therapy has been extraordinary with hematological malignancies, but progress for solid tumors is still undergoing. Whether with TCR T-cell therapy or with advances in CAR T-cell therapy, both pathways have the possibility to break through the TME of solid tumors and any other immunosuppressives to act against them [123,124].

Table 3
Immunotherapy drugs under Clinical trials for Lung Cancer.

Target	Objective	Phase of Clinical trials	ID
CEA positive advanced NSCLC	CEA (CD66e, classic tumor marker) Targeting Chimeric Antigen Receptor T Lymphocytes (CAR-T)	Phase I	NCT06992583
CAR-T Targeting GPC3/ Mesothelin/ Claudin18.2/ GUCY2C/B7–H3/ PSCA/PSMA,/MUC1/ TGFβ/HER2/Lewis-Y/AXL/EGFR	To test the anti-cancer function of the these individual or combination of the CAR-T cells for immunotherapy of human cancer patients with GPC3, Mesothelin, Claudin18.2, GUCY2C, B7–H3, PSCA, PSMA, MUC1, TGFβ, HER2, Lewis-Y, AXL, or EGFR expressions.	Phase I	NCT03198052
GPC3/Mesothelin Targeted CAR-γδT for Immunotherapy of Solid Cancer	To test anti-cancer function of the CAR-γδT cells for immunotherapy of human cancer patients with GPC3 or Mesothelin expressions.	Phase I	NCT06196294
TCR-T Cells	TCR-T Cells Targeting Cancer Cells for Immunotherapy of Lung Cancer	Phase I	NCT03778814
TEIPP24 (LRPAP7-30V-SLP vaccine in Montanide ISA-51)	T-cell Epitopes Associated With Impaired Peptide Processing (TEIPP)-Targeting Immunotherapy in Patients With Relapsed Advanced Non Small Cell Lung Cancer (NSCLC)	Phase 1 Phase 2	NCT05898763
Domvanalimab Etrumadenant Zimberelimab	A Phase 2 Study to Evaluate the Safety and Efficacy of zimberelimab (AB122) Monotherapy, domvanalimab (AB154) in Combination With zimberelimab (AB122), and domvanalimab (AB154) in Combination With zimberelimab (AB122)and etrumadenant (AB928) in Front-Line, Non-Small Cell Lung Cancer	Phase 2	NCT04262856
SLC-391+ Pembrolizumab	An Open-Label, Phase 1b/2a Study of SLC-391, an AXL Inhibitor, in Combination with Pembrolizumab in Subjects with Advanced or Metastatic Non-Small. Cell Lung Cancer (NSCLC)	Phase 1 Phase 2	NCT05860296

2.3. NK cell-based therapeutics

One approach to therapeutics for lung cancer would include the use of Natural Killer (NK) cell-based therapeutics. NK cells are lymphocytes, along with B cells and T cells, though their purpose differs from the other classes. NK cells play a part in identifying foreign pathogens/abnormal cells and are able to attack these pathogens without prior sensitization to them, unlike T cells which require exposure to antigen presentation. As the first line of defense, research on incorporating NK cells into cancer immunotherapy has increased [125]. NK cells are the perfect candidate since they are able to identify the difference between abnormal and

normal with MHC Class I molecules. When a target cell is present with MHC-1 molecules, the NK cells are not obligated to attack it unless it is missing, in which they'll perform their response of killing the target cell. Abnormal cells show a lack of MHC-1 molecules, so NK cells are provoked to kill the infected cells. NK cells have shown potential for the field of adoptive immunotherapy [126]. NK cell activation occurs through the response of the activating receptors towards the ligands of the tumor cells, preventing any inhibitory receptors to prevent this killing [127]. Cancer patients show limited NK cell function due to the NK cell activating receptors not working to their full efficacy, leading to decreased immunity in these patients to fend off cancerous cells [128].

Cytokines such as IL-2, IL-15 and IL-21 are significant to culturing NK cells, so it's been suggested to use these for effective immunotherapy treatment [129]. However, various clinical trials provide evidence against the use of IL-2 due to the adverse effects shown when tested on cancer patients including liver toxicity and vascular leak syndrome [130]. IL-2 treatment could not work by itself, but when in association with adoptive T-cell therapy, clinical response improved. Since IL-2 triggered the growth of regulatory T cells (Tregs), other cytokines like IL-12, IL-15, IL-18, and IL-21 are subjects of research for further treatments since they show similar potential as IL-2 did without the negative effect of Tregs growth [131]. Through the proliferation of Treg cells, the inhibition of NK cells from performing their duty to its full potential is possible so the research of other cytokines would avoid this problem from occurring [132]. Though these cytokines have shown potential, IL-18 and IL-12 don't show significant results alone and it is only in the cooperation of these two cytokines where results are prominent through higher results of CD25. The combination of IL-12/15/18 showed especially high results of CD25 when tested on both mice and human cells, which translates as a better option for treatment than IL-12 or IL-18 alone (Fig. 3) [133]. Monoclonal antibodies would help NK cells through the antibody dependent cell cytotoxicity (ADCC) function. Monoclonal antibody therapies include rituximab, cetuximab, trastuzumab or daratumumab [134]. ADCC essentially is the function that kills target cells through the identification of antibodies, thus utilizing monoclonal antibodies expands the potential of NK cells [135].

Although NK cells show promise for numerous benefits, they show limited action against solid tumors. Transferred NK cells don't show efficacy against solid tumors due to barriers including survival problems within the proximity of a tumor [136]. The environment of a tumor contains cytokine IL-10 and prostaglandin E2, which both slow down the movement and function of NK cells, debuffing their ability (Fig. 3). The cause of this trouble are the M2 macrophages, which take up a majority of the mass of a solid tumor [137]. M2 macrophages promote tumor growth and survival through angiogenesis, and release the molecules mentioned [138]. In order to infiltrate solid tumors, combatting the microenvironment is an important hurdle to overcome. Monoclonal antibodies would be one solution as ADCC is increased by them. Another solution, specific to NSCLC, provided the possibility of utilizing anti-KIRs, but showed limited promise unless used in combination with anti-PD-1 [139]. However, NK cells have been genetically engineered to protect themselves against immunosuppressives and are named CAR-NK cells. These cells would be able to survive TME as it serves as the biggest challenge against adoptive NK cell therapy [138].

3. Conclusion

Lung cancer continues to drive as the leading cause of cancer deaths with resistances forming as well. Resistance in lung cancer often arises through secondary mutations and pathway reactivation, limiting the long-term efficacy of targeted and immunotherapies. However, therapeutic research also continues to combat these resistances to adjust to the ever-adapting structure of genetic mechanisms. Mutations, dysregulations, and over-expressions claim to be the cause of these resistances, but various drugs under clinical trials are made to overcome these adversities. Overexpression of EGFR and RAS are prominent in NSCLC cases. Generations of TKIs have been manufactured against EGFR and more will continue due to its significance in lung cancer. RAS is a prominent target, and still runs as a common gene overexpression, so labeling it as "undruggable" has been disproven as research has produced FDA approved RAS inhibitors. Different targets in the MAPK pathway, including ERK, MEK, and RAF have also been targeted due to their role in cell proliferation and their involvement in the signaling cascade. PI3K/Akt/mTOR is another signaling pathway that has been targeted due to their similar role as MAPK, but their role in lung cancer isn't as significant. NF-kB inhibitors relate to the control of gene expression and preventing their anti-apoptotic properties from performing. Immunotherapy has also started to advance with the introduction of gene modification to several immune cells, including CAR-T cells and CAR-NK cells. Immunotherapy focuses on killing cancer cells rather than the prevention of it but still manages to fight resistances as well. The diversity in treatment options is all adjusted to deal with unique mutations and will continue to evolve against the rate of resistance. Despite these advances, challenges such as acquired resistance, limited efficacy in solid tumors, and immune evasion remain significant barriers. To address these issues, combination therapies, biomarker-driven treatment selection, and strategies to modulate the tumor microenvironment are under intensive investigation. Moving forward,

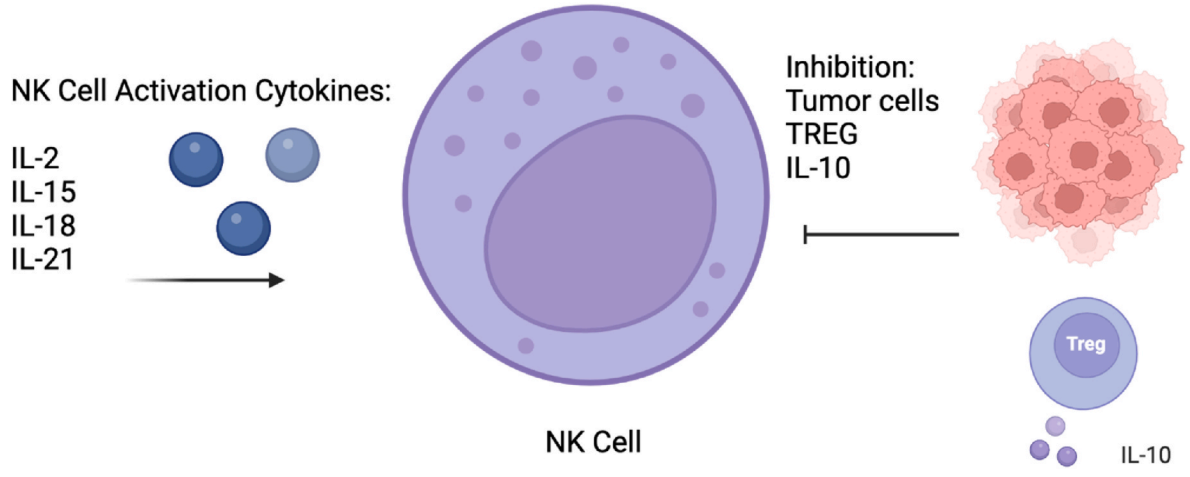

Fig. 3. NK Cell Cytokines. NK cells respond in activation when reacting to certain cytokines like IL-2, IL-15, IL-18 and IL-21. However, inhibitory responses are initiated by interactions with the tumor microenvironment and the cytokines that are excreted, such as IL-10 (Schematic was generated using BioRender.com with an academic license).

the future of lung cancer therapy lies in personalized medicine, adaptive trial designs, and next-generation therapeutics that target resistance mechanisms and enhance immunogenicity. Drugging the undruggable has already been accomplished, the future of lung cancer research only shows promise and results.

CRediT authorship contribution statement

Teresa Vincent: Writing – original draft, Conceptualization. **Kunnathur Murugesan Sakthivel:** Investigation, Conceptualization. **C.M. Reena Josephine:** Resources, Investigation. **Roopa Prasad:** Writing – review & editing, Validation. **Kathirvelan Chinnadurai:** Visualization. **Pavithra Kumar:** Formal analysis. **Mythili Saravanan:** Writing – review & editing. **Rajan Radha Rasmi:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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