Key Strategies in Precision medicine for Overcoming resistance in Lung cancer.

ABSTRACT

The burden of lung cancer in Nigeria represents a significant clinical problem due to the high mortality rate. Added to this is the lack of a comprehensive cancer treatment strategy in Nigeria, resulting in underdiagnosis and poor access to treatment. Furthermore, the challenges of chemoresistance represent a major obstacle to lung cancer therapy in Nigeria. These challenges highlight the need for precision medicine that targets specific genetic mutations and can potentially overcome resistance. The aim of this review article was to provide a comprehensive compilation of studies on the resistance mechanisms in the different types of therapy and current key strategies for overcoming resistance in lung cancer. Herein, we selected significant studies from the Web of Science and PubMed databases by conducting a systematic search for articles published between 2018 and 2024 with the keywords "Precision Medicine", "Targeted Therapy", "Overcoming Resistance", " Lung cancer", "Treatment"and any analogies and combinations of the keywords. In summary, resistance mechanisms in lung cancer therapy, such as genetic mutations and changes in the tumor microenvironment, were examined and promising strategies to overcome them were discussed.

Keywords: Precision medicine, Targeted therapy , Overcoming resistance, Lung cancer, treatment.

Introduction

About 1 in 8 million people worldwide lose their lives to lung cancer each year, making it a serious global health concern [1]. It encompasses two subtypes, such as small cell lung cancer [SCLC] and non-small cell lung cancer [NSCLC], each of which poses particular difficulties in terms of diagnosis and treatment choices [2]. It is more prevalent in developing nations with high smoking rates [1]. Lung cancer poses a substantial clinical challenge in Nigeria due to its high mortality rate and insufficient treatment approaches [3]. The issue is made worse by underdiagnosis and restricted access to care; a more focused strategy to enhance patient outcomes is the answer [3]. Lung cancer's molecular heterogeneity emphasizes how crucial accurate subtyping is to choosing the right course of treatment [4], [5]. Targeting specific genetic mutations and signaling pathways implicated in tumor progression through precision medicine presents promising avenues to address issues like chemoresistance [6]. Important driver genes that are involved in the pathophysiology of NSCLC and SCLC include EGFR, TP53, KRAS, and others. Comprehending the genetic terrain facilitates the implementation of customized treatment strategies, such as immune checkpoint inhibitors [ICIs] and tyrosine kinase inhibitors [TKIs], which enhance clinical results [7]. Despite the availability of multiple treatment modalities such as immunotherapy, chemotherapy, surgery, and targeted therapy, issues like treatment-related toxicity and drug resistance persist [8], [9]. Resolving drug resistance is still a major clinical challenge, especially in relation to immunotherapy and chemotherapy [10]. The investigation of alternative tactics, such as combination therapies and selective drug delivery systems, has resulted from attempts to address these issues [11].

Furthermore, current investigations into the mechanisms underlying resistance to immunotherapy and targeted therapies seek to discover novel targets for therapeutic intervention and enhance the efficacy of treatment [11, 12]. In summary, diagnosing, treating, and overcoming resistance to lung cancer presents a variety of challenges. This review article's main goal was to provide a thorough synthesis of the literature on resistance mechanisms in different therapeutic modalities and the most cutting-edge strategies currently used to treat resistance in lung cancer patients.

Method

A systematic and advanced search of PubMed and Web of Science databases was carried out to select significant articles, clinical trials and abstracts published in the English language, between 2018 and 2024. The keywords used for the search were "Precision Medicine", "Targeted Therapy", "Overcoming Resistance", "lung cancer", "treatment". " and any analogies and combinations of the keywords.

Results

Resistance mechanisms in lung cancer therapy

Resistance to targeted therapy

Resistance to pharmacological inhibitors such as tyrosine kinase inhibitors [TKIs] is a common challenge in the treatment of non-small cell lung cancer [NSCLC][13]. Resistance to targeted therapies is generally categorized as primary [intrinsic] or secondary [acquired][14]. Primary resistance refers to an initial lack of response to treatment, while acquired resistance manifests itself as progression after an initial positive response [15]. Of note, acquired resistance in NSCLC often involves secondary mutations in EGFR and ALK,resulting in resistance to tyrosine kinase inhibitors [TKIs][16],[17],[18].

In the context of EGFR/ALK-mutant NSCLC, acquired resistance typically arises after an effective response or stable disease for more than six months under targeted therapy [19].

Resistance to targeted therapies such as EGFR inhibitors and ALK inhibitors is based on complex molecular mechanisms. EGFR mutations initially contribute to susceptibility, but resistance can arise through secondary mutations, oncogenic shifts, and EMT conversion[20].The T790-M mutation in EGFR represents a predominant mechanism of resistance to first- or second-generation EGFR tyrosine kinase inhibitors [TKIs], accounting for approximately 50% of resistance cases [21]. This mutation occurs at the hydrophobic pocket for the ATP binding cleft in the 790 residue of EGFR. It induces a conformational change that impairs the binding of EGFR-TKIs and restores receptor affinity for ATP [21]. In addition, various second point mutations, including D761Y, T854A or L747S, contribute to acquired EGFR-TKI resistance, although their specific mechanisms remain unclear [22]. Furthermore, researchers have proposed a novel mechanism implicating activation-induced cytosine deaminase [AICDA] in the T790-M mutation [23]. According to this proposal, AICDA induced by EGFR-TKIs mediates the deamination of 5-methylcytosine to thymidine, leading to the development of T790-M. Inhibition of AICDA or the NF-

κB signaling pathway that regulates AICDA is a promising potential strategy to delay or prevent T790-M-related resistance to TKIs [23].Therefore, evaluating the EGFR T790 M mutation is crucial for defining acquired resistance and guiding therapeutic decisions.

Resistance to immunotherapy

Resistance to immunotherapy can be categorized based on the timing of its development, the characteristics of the cancer cell, and the type of immune infiltrate [34]. Primary resistance occurs during first-line immune checkpoint inhibitor [ICI] treatment, while acquired resistance is defined as tumour progression after initial disease control [35]. In the case of non-small cell lung cancer [NSCLC], acquired resistance, according to a revised definition, excludes stable disease due to its heterogeneity [36]. The cancer cell itself can exhibit intrinsic resistance or extrinsic resistance [37]. Intrinsic resistance arises from genomic or proteomic characteristics of cancer cells. Immune checkpoints, such as PD-L1, play a crucial role in modulating inhibitory immune signaling pathways [37,39]. Expression of inhibitory signals [checkpoints] by the cancer cell is an essential mechanism of immune evasion and can include a number of inhibitory molecules such as PD-L1 [CD274], IDO, LAG3, TIM-3, VISTA and others [40]. Oncogene addiction, has been linked with primary resistance to immunotherapy [34]. Other pathways and genes implicated in NSCLC, such as STK11/LKB1, KEAP1, and TP53, also contribute to intrinsic resistance [41]. Extrinsic resistance is modulated by the tumor microenvironment [TME], including immune cells. The spatial distribution of immune cells within tumors can vary significantly [37].Extrinsic resistance involves factors like the antigen repertoire of T cell receptors [TCRs], T cell infiltration, and the immunosuppressive TME [34, 42, 43, 44,45]. The presence of CD8+ T cells correlates with better outcomes in NSCLC [43]. The TME produces immunosuppressive cytokines and growth factors like VEGF and TGF-β, contributing to resistance [34]. Tumor-induced neoangiogenesis affects immune cell infiltration due to abnormal vascular structure, hypoxia, and acidosis, while TGF-β promotes cancer cell invasion and an immunosuppressive environment [46–50]. Targeting molecules like VEGFR may help normalize the vasculature and enhance immune response [47]. Understanding the interplay between intrinsic and extrinsic resistance mechanisms is crucial for developing effective immunotherapies.

Resistance to immune checkpoint inhibitors [ICI's]

Factors contributing to ICI resistance include impaired T cell priming and infiltration. Dendritic cells [DCs], which are crucial for T cell priming, are influenced by cytokines in the tumor microenvironment [TME][34]. Reduced IFN-α-producing DCs lead to reduced antitumor T cell priming, contributing to ICI resistance[51, 52]. Tumor cells can employ mechanisms to hinder T cell infiltration, involving epigenetic silencing and chemokine modification [53, 54, 55]

T cell exhaustion, characterized by loss of function, contributes to both primary and acquired resistance to ICI therapy[34]. PD-1/PD-L1 interactions induce T cell exhaustion, highlighting the importance of a diverse T cell repertoire in preventing tumor relapse[56]. The tumor microenvironment includes immunosuppressive cells, cytokines, and extracellular matrix components. Increased immunosuppressive cells and inhibitory cytokines contribute to the inhibition of the immune response[57, 58]. Responses to ICI therapy are adversely impacted by elevated immunoregulatory molecules, including VEGF, TGF-β, and TNF-α [34]. Additionally, the complexity of the immune landscape is highlighted by the involvement

of molecules like adenosine, IDO1, and B7-H4 in immunotherapy resistance [59, 60, 61]. ICI therapy resistance is linked to host-related factors such as gut microbiome, diet, antibiotic exposure, steroid use, and inflammatory status [62, 63]. Gut microbiome diversity and particular species are correlated with the outcomes of ICI therapy. Furthermore, antibiotic exposure alters the microbiota's makeup and suppresses the immune system [64–66]. The balance of immune cells in the tumor microenvironment is impacted by long-term steroid use, which also reduces the effectiveness of ICI [67]. Diet has a significant impact on immunological function and tumor growth. It also changes the makeup of the gut microbiome [68–70]. Immunotherapy resistance is linked to autoimmunity and chronic inflammation, which emphasizes the significance of maintaining a balanced immune homeostasis [71]. Immunocheckpoint inhibitor [ICI] resistance encompasses a variety of mechanisms that affect various stages of the immune response against tumors. One such mechanism is the upregulation of PD-L1, which affects therapy outcomes, and a high tumor mutational burden, which is linked to the effectiveness of ICIs.This understanding is essential for formulating strategies to overcome resistance and increase the effectiveness of immunotherapy.

Resistance to EGFR-targeted therapy in advanced lung cancer

EGFR mutations and primary resistance:

Primary resistance to EGFR-TKIs is associated with specific EGFR mutations, with the exon 20 insertion being a notable example, occurring in approximately 4% of NSCLC cases . This mutation confers intrinsic resistance to both reversible and irreversible inhibitors [72-74]..

Secondary resistance mechanisms:

Secondary resistance arises during treatment and includes mutations such as T790M, which occur in 50-60% of patients treated with first and second generation EGFR TKIs[75]. The T790M mutation affects inhibitor binding, alters affinity for certain inhibitors and increases affinity for ATP, providing a survival advantage [21]. Tertiary mutations such as C797S can confer sensitivity to certain irreversible binding compounds, but triple mutations can result in resistance to all generations of EGFR-TKIs [76–79]. Rare EGFR mutations, including D761Y, T854A and L747S, contribute to acquired resistance [80-83]. Loss of T790M is a resistance mechanism to third-generation osimertinib, and fourth-generation EGFR-TKIs are currently being developed to overcome T790M and C797S [84,85].

Bypassing of signaling pathways:

Activation of parallel or downstream signaling pathways such as cMET, KRAS, Axl, Her2, IGF-1R and the FGF family can induce resistance to EGFR-TKIs. The cMET signaling pathway activated by cMET amplification plays a role in intrinsic and acquired resistance [86]. KRAS mutations make KRAS constitutively active, leading to intrinsic resistance [88]. Upregulation of Axl serves as another intrinsic resistance mechanism [87]. Overexpression or amplification of the Her2 receptor contributes to resistance [89]. IGF-1R induces epithelial-mesenchymal transition [EMT] and confers intrinsic resistance [90]. The FGF family is involved in both intrinsic and acquired resistance [90].

Additional mechanisms of resistance:

Additional mechanisms of resistance include activation of Yes-associated protein [YAP] and NF-kB pathways, mutations in PIK3CA, BRAF, loss of PTEN, and TP53. Resistance results from the decoupling of EGFR signaling from Akt signaling caused by PTEN loss. About 50% of NSCLC patients have TP53 mutations, which might affect survival and treatment. Both innate and acquired resistance are linked to YAP and the NF-kB pathway [21].

Resistance mechanisms resulting from histological changes:

The histological conversion of non-small cell lung cancer [NSCLC] to small cell lung cancer [SCLC], which happens in around 14% of patients, represents a distinct resistance mechanism [91]. While the EGFR mutation is preserved, this metamorphosis stops responding to EGFR TKIs. According to genetic research, TP53 and RB1 are frequently inactivated in transformed SCLC [92]. The optimal therapy for histological transformation remains uncertain, with platinum-etoposide chemotherapy and drug therapy showing promising results in some cases [91].

Resistance through aberrations in drug transporters:

Drug transporters, including organic anion transporters, OCT, ABC transporter superfamily and lysosomal sequestration, play a role in resistance to EGFR inhibitors in NSCLC . Gefitinib and erlotinib interact with ABCB1/PGP and ABCG2/BCRP and influence their function [21]

Lysosomal sequestration:

Lysosomal entrapment can activate lysosomal expression and regulatory mechanisms by causing lysosomal stress and shielding pharmacological targets resulting in resistance [93].

Resistance to chemotherapy

Chemotherapy remains the primary treatment for advanced non-small cell lung cancer [NSCLC] and first- and second-line treatment of small cell lung cancer [SCLC], despite increasing interest in non-cytotoxic therapeutics [94]. Chemotherapeutic agents used include alkylating agents [platinum compounds such as cisplatin and carboplatin], microtubule-targeting drugs [paclitaxel, docetaxel, and vinorelbine], antimetabolites [pemetrexed and gemcitabine], and topoisomerase inhibitors [etoposide]]. However, chemoresistance develops rapidly in lung cancer patients, compromising the effectiveness of these treatments [95]. The factors contributing to chemoresistance are diverse and include changes in drug influx and efflux, drug target changes, compartmentalization, epigenetic changes, etc. DNA damage [95]. Furthermore, the tumor microenvironment [TME], characterized by interactions between tumor and stromal cells, plays a crucial role in promoting chemoresistance through hypoxia, nutrient deprivation and vascular abnormalities [95]. Key mechanisms of chemoresistance include upregulation of the ERCC1-mediated DNA repair pathway contributes to resistance to platinum-based chemotherapeutics [95]. Drug efflux is controlled by the ATP-binding cassette [ABC] family of transporters, with upregulated expression of various transport proteins correlating with resistance to specific chemotherapeutic agents [96]. Glutathione S-transferase [GST] isozymes, particularly GSTP1, are involved in the detoxification and inactivation of platinum drugs, leading to chemotherapy resistance [95]. Activation of pro-survival signaling pathways such as EGFR, PI3K/Akt and MAPK, along with changes in cell cycle regulation and apoptosis, further contribute to chemoresistance [95]. Epigenetic regulation, microRNA dysregulation and the acquisition of epithelial-mesenchymal transition [EMT] and cancer stem cell [CSC]-like phenotypes also play a crucial role [95]..

Resistance to chemotherapy, especially platinum drugs based on cisplatin and carboplatin, mayinvolve activation of the NOTCH signal [95]. This pathway induces epithelial-mesenchymal transition [EMT] and upregulates drug transporters, resulting in reduced drug absorption and increased DNA repair mechanisms . The interaction between NOTCH and TP53 is crucial because loss of NUMB [a suppressor of NOTCH] can increase the concentration of the NOTCH receptor and decrease TP53, increasing chemoresistance. Microtubule-targeting inhibitors such as taxanes and vinca alkaloids encounter resistance mediated by ABC drug transporters. Activation of NOTCH1 downregulates miR-451, leading to increased drug resistance. Inhibition of NOTCH with gamma-secretase inhibitors can sensitize NSCLC cells to microtubule-targeting drugs. In addition, the tumor microenvironment and metabolic factors, including glycolysis and hypoxia, influence drug resistance through NOTCH signaling [95].

The tumor microenvironment, hypoxia and changes in cancer metabolism, particularly PGC1α and glutamine metabolism, are associated with chemoresistance]. Furthermore, dysregulation of Notch and WNT/b-catenin signaling pathways, as well as variations in intracellular pathways involving miRNAs, contribute to chemotherapy resistance [95]. Also, metabolic reprogramming, communication within the tumor microenvironment, and microtubule alterations contribute to the complex landscape of chemoresistance [95].

Resistance to radiotherapy

Radiotherapy [RT] is a commonly used treatment for lung cancer, but its effectiveness is not always satisfactory. This is often due to radioresistance of the tumor, which can lead to subsequent recurrence and metastasis [97]. To overcome radioresistance, it is necessary to identify possible therapeutic targets and gain an understanding of the molecular and cellular mechanisms that contribute to the loss of radiosensitivity. Cancer cell survival is mediated in large part by survival and metastatic signaling pathways [98]. Lung cancer progression is linked to genetic changes in genes including PI3K, AKT, PTEN, EGFR, and KRAS as well as MET amplification and EML4-ALK rearrangements [99].

Targeting these pathways and overcoming radioresistance have been the subject of studies. For instance, in non-small cell lung cancer [NSCLC] cells, inhibition of vascular endothelial growth factor receptor 2 [VEGFR2] can downregulate AKT and ERK, suppress radiation-induced DSB repair, and increase radiosensitivity by causing G2/M phase arrest [100]. Radiosensitivity can be restored in lung adenocarcinoma cells and HIF1-α expression can be decreased by inhibiting mTOR [101]. According to research, RAC1, PI3K, MEK, and AKT can all be specifically overexpressed to increase radiosensitivity through preventing DSB repair [102]. Radiation resistance is partly explained by the complex balance of redox levels, which is marked by elevated ROS production and an activated antioxidant defense system in cancer cells. Radioresistance can be caused by mutations in Keap1 linked to Nrf2 activation, even though low-dose ionizing radiation can cause ROS production, which can then trigger autophagy and the Nrf2-HO-1 antioxidant pathway [103]. Radiation-sensitization of cancer cells has been studied using targeted inhibition of glutaminase or plant-derived compounds like ferulic acid [104].

Novel Mechanisms of Resistance

Molecular studies in recent years have revealed several genes and signaling pathways that contribute to chemoresistance in lung cancer, leading to a better understanding of the biology of tumor cells as well as the molecular mechanisms involved in their resistance to chemotherapeutic agents. Among these

mechanisms is the transfer of extracellular vesicles such as . Exosomes, between cancer cells and the surrounding non-cancerous cells are considered a new pathway. Exosomes can desirably function as signaling vesicles to transfer multiple molecules from normal cells to cancer cells and their microenvironment or vice versa. Using this ability, exosomes can influence the chemoresistance/chemosensitivity of cancer cells. Recently, it has been reported that noncoding RNAs [particularly microRNAs and long noncoding RNAs], as key molecules carried by exosomes, play an essential role in the process of drug resistance through the modulation of various proteins and their corresponding genes [105].

Strategies for Overcoming Resistance

Overcoming ICI Resistance

The complex network of signals that regulate immune responses includes various co-inhibitory and costimulatory molecules designed to prevent overreaction to self or foreign antigens. Enhancing the immune response against cancer can be achieved by directly blocking co-inhibitory signals or activating costimulatory signals. Both can be facilitated indirectly by triggering T cell priming[149].This process increases the number of responding T cells, thereby reducing co-inhibitory signals and increasing co-stimulatory signals. Furthermore, interventions in the tumor microenvironment and gut microbiota have the potential to alter the immune infiltrate and promote antitumor activity [106].

Combating co-inhibitory signals

The first co-inhibitory molecules to be identified, CTLA-4 and PD-1, were therapeutically targeted to counteract co-inhibitory signals. Peripheral tolerance maintenance is the primary role of PD-1, whereas CTLA-4 is involved in early T cell priming. It has been demonstrated that combined PD-1 and CTLA-4 blockade is beneficial in treating a variety of solid tumors, including non-small cell lung cancer [NSCLC]. Nivolumab plus ipilimumab, for instance, increased overall survival in advanced PD-L1-positive NSCLC [107]. Moreover, this combination demonstrated efficacy in treating other cancers, indicating the possibility of overcoming immunotherapy resistance [108]. Emerging co-inhibitory signals like LAG3, TIGIT, TIM3, VISTA, and Siglec-15 are promising targets in addition to PD-1 and CTLA-4. These signals have various immunomodulatory roles, but they all have the following characteristics in common: they upregulate in tumor samples, they suppress T cell activation, and their blockade increases the effectiveness of traditional immune checkpoint inhibitors [41]. While there is a lack of clinical data on novel checkpoint inhibitors in non-small cell lung cancer [NSCLC], preliminary study findings point to possible benefits [109].

Enhancement of co-stimulatory signals

While blocking co-inhibitory signals has shown clinical activity, the amplification of co-stimulatory signals remains experimental. Targeted molecules such as OX40, CD137, CD40, GITR and ICOS from the TNFR family of the immunoglobulin superfamily are intended to increase the antitumor activity of T cells and NK cells. These signals generally lack intrinsic enzymatic activity and rely on signaling adapters for their stimulatory effects [110]. Encouraging preclinical data supports the potential of these costimulatory signals, but clinical confirmation is still pending [111].

Improving T cell priming

Novel drug combinations and adoptive cell therapy [ACT] are two ways to strengthen the immune response against cancer. A stronger antitumor response and enhanced T cell priming are the outcomes of ACT, which entails the isolation, enlargement, and reinfusion of T lymphocytes [112].

Gut microbiota conditioning

Preclinical evidence suggests that gut microbiota composition can predict responses to immune checkpoint blockade and immunogenic chemotherapies[113].Certain bacterial species such as Akkermansia muciniphila, Bifidobacterium spp. And Faecalibacterium prausnitzii have been associated with treatment benefits [113]. The association between the use of broad-spectrum antibiotics and unfavorable outcomes in NSCLC patients undergoing anti-PD-1 treatment highlights the possible influence of the gut microbiota on the effectiveness of treatment [114].

Immune stimulation byChemotherapy and Radiotherapy

Chemotherapy, an established strategy in NSCLC treatment, possesses immunostimulatory properties, mainly due to the release of immunogenic molecules from dying tumor cells, which is referred to as "immunogenic cell death" or by various complex off-target effects on immune cells. The complex off-target effects on immune cells vary depending on the chemotherapy drug[115]. Combinations of chemotherapy and immunotherapy have been extensively studied, with ongoing work to identify the optimal chemotherapeutic agents for synergistic immune stimulation [115]. Recent clinical reports suggest that chemotherapy can even revert previous resistance to PD-1 blockade, necessitating further investigation through well-designed randomized clinical trials [116].

Radiotherapy induces cell damage leading to increased release of tumor antigens and increased antigen presentation [41]. Radiation-triggered innate immune responses further stimulate T cell migration to the tumor site, thereby promoting antigen recognition and specific activation of antitumor T cells. The observed abscopal effect, in which non-irradiated tumor sites respond to immunotherapy after radiotherapy, highlights the potential synergy of radiation and immunotherapy [117]. Furthermore, there is promisein combining radiation and immunotherapy is driven by the prospect of antigen-induced activation of the systemic immune response [117].

Tumor microenvironment conditioning

The tumour microenvironment [TME] comprises tumour cells, various immune cell types, signaling molecules, vessels, and stroma [118]. Interactions among these components influence the effectiveness of immune antitumour activity, suggesting that targeting TME signaling molecules like enzymes, oncogenes, chemokines, cytokines, and growth factors could enhance immune activation [119].

Overcoming targeted therapy resistance

Overcoming EGFR-TKI resistance:

Recent advances in strategies to overcome EGFR-TKI resistance in lung cancer have led to the emergence of irreversible EGFR inhibitors, particularly second-generation EGFR-TKIs such as Afatinib, dacomitinib and neratinib, developed to combat T790M-mediated resistance. These inhibitors form irreversible covalent bonds with the cysteine residue at position 797 of the EGFR gene, thereby overcoming resistance by maintaining the affinity between ATP and the double mutant EGFR [120].

Use of third-generation EGFR tyrosine kinase inhibitors to overcome resistance

EGF816 [nazartinib]: EGF816, an irreversible EGFR inhibitor, selectively targets L858R, exon 19 deletion and T790M mutations. Its scope extends to exploring efficacy against exon 20 insertion mutations, which are known for their intrinsic resistance to first and second generation inhibitors [121].

Olmutinib [HM61713]: Olmutinib, originally approved in South Korea, showed promise in phase II ELUXA trials for T790M-positive NSCLC patients. Of note, 54% of evaluable patients demonstrated an objective response and 90% achieved disease control, with a median duration of response of 8.3 months and a median PFS of 6.9 months [122]. However, studies were stopped due to serious skin toxicities, including toxic epidermolytic necrosis and Stevens-Johnson syndrome, affecting its use despite initial approval [122]. The less favorable side effect profile compared to osimertinib impaired its clinical benefit.

Mavelertinib [PF-0647775]:PF-0647775, a third Generation EGFR TKI is being evaluated for mutated EGFR ex19del or L858R with or without T790M mutation. Preliminary data from dose escalation showed an ORR of 42.3% and promising responses in combination with palbociclib, a CDK4/6 inhibitor [46]. Grade 3 adverse events were observed at doses above 150 mg, primarily diarrhea [12.4%] and skin toxicities [30.8%]. Further analyses will examine the efficacy and tolerability of the compound, particularly in combination strategies [123].

Overcoming ALK drug resistance:

Strategies to overcome Off-target mechanism mediated ALK -TKI resistance

Downstream signaling pathway activation

Tumors that develop resistance to lorlatinib harbor mutations in several members of the MAP kinase signaling pathway [NRAS, KRAS, MEK and MAP3K]. Combinatorial strategies such as lorlatinib with MEK inhibitors such as binimetinib, cobimetinib or trametinib are currently being investigated [124]. Studies are currently underway to combine lorlatinib with binimetinib [NCT0429119], and alectinib with cobimetinib [NCT03202940].

Parallel Pathway activation

MET amplification [METamp] is associated with acquired resistance to next-generation ALK inhibitors such as alectinib [125]. The combination of lorlatinib with crizotinib is being tested in ALK-positive NSCLC with METamp [NCT04292119]. Similar approaches to combining VEGF inhibitors such as bevacizumab with ALK-TKIs are being investigated [NCT04227028].

SHP2, mTOR, and VEGF inhibition

Inhibition of SHP2 with compounds like PF-07284892 and TNO155 in combination with lorlatinib [NCT04800822, NCT04292119] is being investigatedas a possible strategy. Alterations in mTOR and

NF2 suggest a role for mTOR inhibitors [e.g. ceritinib with everolimus in NCT02321501]. Combinations of ALK-TKIs with VEGF inhibitors, such as brigatinib with bevacizumab, are also being investigated [NCT04227028].

ADCs [Antibody Drug Conjugates]

ADCs such as telisotuzumab vedotin [MET targeting] and datopotamab deruxtecan [Trop-2- targeting] are promising. Telisotuzumab in combination with osimertinib showed efficacy in c-MET-overexpressing EGFR-mutated NSCLC. Trastuzumab deruxtecan [T-DXd] is being investigated in HER2-mutated NSCLC [DESTINY-Lung 02, NCT04644237].

Chemotherapy

Platinum-based chemotherapy, particularly platinum/pemetrexed-based therapies, may have a role in ALK-TKI-resistant disease [126]. In some cases, histological transformation to ALK-positive SCLC occurs, justifying platinum-based chemotherapy [126].

Immunotherapy

While single-agent immune checkpoint inhibitors have limited efficacy in EGFR/ALK-altered NSCLC, combining immunotherapy with chemotherapy or targeted therapy, as shown in IMPower150, could improve outcomes in ALK-positive NSCLC [127] .

Strategies to overcome resistance to KRAS G12C inhibitors:

KRAS, a common genetic alteration in NSCLC, has been a difficult target due to its elusive structure. However, promising results are achieved with G12C-KRAS inhibitors such as sotorasib and adagrasib as shown below .

Targeting acquired resistance to KRAS G12C inhibitors

The potential of sotorasib to enhance the therapeutic efficacy of agents that are specifically targeted against KRAS G12C has been clarified in a study [128]. Particularly in H358 cells and NCI-H1373 spheroid models, sotorasib demonstrated synergy with a number of targeted therapies, such as afatinib, RMC-4550 [an SHP2 inhibitor], and trametinib [a MEK inhibitor][128]. Interestingly, compared to monotherapies, the combination of sotorasib and MEK inhibitor significantly reduced the tumor volume in H358 xenograft models. Moreover, sotorasib unexpectedly improved the therapeutic efficacy of carboplatin in vivo [128].

Adagrasib, another KRAS-G12C inhibitor, also demonstrated improved efficacy in combination with various targeted agents such as afatinib and RMC-4550 and demonstrated superior antitumor activity compared to monotherapies in xenograft models of NSCLC and esophageal squamous cell carcinoma [129]. Furthermore, research into downstream KRAS effectors revealed mTOR and cyclin D family members as potential targets for enhancing adagrasib efficacy in vivo [129].

Targeting RTKs involved in evasion of signaling pathways and epithelial-mesenchymal transition.

Acquired resistance to KRAS G12C inhibitors often involves adaptive strategies, such as KRAS secondary mutations or activation of upstream effectors such as RTKs, leading to bypasses of signaling

pathways or epithelial-mesenchymal transition [EMT][130]. Several therapeutic strategies have been proposed to treat acquired resistance, focusing on combination therapies targeting specific RTKs or upstream and downstream effectors of KRAS G12C [130]. Studies investigating the effects of targeting RTK-mediated acquired resistance found that combined treatment with sotorasib and crizotinib in H23 sotorasib-resistant cells with MET amplification showed superior inhibition of ERK, AKT and MET compared to monotherapies [130].This combination therapy significantly reduced tumor growth in MET-amplified H23 sotorasib-resistant xenograft models..These studies highlight the potential of targeting specific RTKs in overcoming acquired resistance to KRAS G12C inhibitors

Targeting SHP2 and SOS to Overcome Acquired Resistance to KRAS G12C Inhibitors

SHP2, a protein tyrosine phosphatase, plays a critical role in the RAS activation pathway through its interaction with activated RTKs and subsequent activation of SOS1. The combination of SHP2 inhibitors such as RMC-4550 or TNO-155 with KRAS-G12C inhibitors showed improved efficacy compared to monotherapies in preclinical studies [130]. Notably, RMC-4550 in combination with AMG-510 achieved high synergy values in both monolayer cell line and KRAS-G12C spheroid models [130]. Furthermore, SHP099 and TNO-155 showed promising results in overcoming acquired resistance to sotorasib, with a significant reduction in tumor growth and suppression of PI3K-AKT, MAPK, and S6 phosphorylation [130]. These results suggest that targeting SHP2 may be a viable strategy to prevent or delay acquired resistance to KRAS-G12C inhibitors. SOS1, an important guanine nucleotide exchange factor for KRAS activation, emerged as a potential target to overcome acquired resistance [130]. BI-3406, a selective SOS1 inhibitor, demonstrated efficacy in various KRAS mutant models and showed promise in preventing adaptive resistance to MEK inhibition and overcoming acquired resistance to KRAS G12C inhibitors in combination with downstream effectors such as trametinib [130].These preclinical rationales present novel strategies to reverse or delay the emergence of acquired resistance to sotorasib and adagrasib.

Immunotherapy for KRAS-mutant NSCLC

Immunotherapy has emerged as a promising approach for the treatment of KRAS-mutated non-small cell lung cancer [NSCLC], particularly in patients with a history of tobacco use, high tumor mutation burden [TMB], increased PD-L1 expression, and a pro-inflammatory microenvironment [131]. In fact, KRAS-G12C mutant patients have showed positive responses to immune checkpoint inhibitors [ICIs][130].

Combination approaches to overcome resistance

The goal of combining immunotherapy with targeted therapy, radiation therapy, and chemotherapy is to improve treatment outcomes when battling resistance. New treatment plans, such as combining chemotherapy with EGFR-TKIs and ICIs, are being investigated in ongoing clinical trials in an effort to increase therapeutic efficacy [132]. In terms of overall survival [OS], progression-free survival [PFS], and objective response rate [ORR], clinical trials examining combination approaches in patients with lung cancer have demonstrated encouraging results [133,134]. A median OS of 22.0 months and a median PFS of 9.0 months were observed in the Keynote 189 trial when platinum, pemetrexed, and pembrolizumab were combined in phase III [133]. In a similar vein, the Keynote 407 trial assessed pembrolizumab, [nab]-paclitaxel, and carboplatin in phase III and found that the median OS was 15.9 months, while the

median PFS was 6.04 months [134]. Carbaplatin, nab-paclitaxel, and atezolizumab were assessed in Impower 130, a different phase III trial, which revealed a median OS of 18.6 months and a median PFS of 7.0 months [135]. Furthermore, the Impower-150 trial assessed atezolizumab, bevacizumab, paclitaxel, and carboplatin in phase III and found that the median OS was 19.2 months, and the median PFS was 8.3 months [127]. Pembrolizumab, platinum, and pemetrexed together, in phase III produced a median OS of 12 months and a median PFS of 8. 8 months [136]. The CheckMate 9LA trial evaluated nivolumab, ipilimumab and two cycles of chemotherapy in phase III and showed a median OS of 15.6 months [137]. In phase II [Javelin Medley VEGF], the combination of avelumab and axitinib showed an ORR of 31.7% and a median PFS of 5.5 months [138]. Nivolumab combined with ipilimumab in phase III [CheckMate 227] showed a median OS of 17.1 months [139]. Furthermore, the combination of pembrolizumab and stereotactic body radiation therapy [SBRT] in phase II [PEMBRO-RT] demonstrated a median OS of 15.9 months and a median PFS of 6.6 months [140]. Resistance to chemotherapy in lung cancer can be addressed through combination approaches. Studies have shown that the addition of pembrolizumab to chemotherapy, such as carboplatin and paclitaxel or nab-paclitaxel, extends life expectancy in patients with metastatic squamous cell carcinoma and NSCLC [141]

Conclusion:

In conclusion, overcoming resistance in NSCLC is a major challenge due to its complexity. Our research identifies key pathways and mechanisms involved in resistance to targeted therapies, immunotherapy, chemotherapy and radiotherapy. For targeted therapies such as ALK inhibitors, consideration of both on-target and off-target mechanisms is crucial. Strategies such as fourth-generation TKIs and combination therapies show promise in overcoming resistance. Understanding and treating primary and acquired resistance mechanisms is crucial in immunotherapy. Targeting co-inhibitory signals and strengthening the immune response through various approaches offer potential solutions. Challenges and opportunities in overcoming resistance to chemotherapy and radiotherapy highlight the need for targeted interventions and combination strategies. Therefore, continued research and clinical trials are crucial for refining treatment approaches for NSCLC. By comprehensively addressing resistance mechanisms, we can improve patient outcomes and quality of life.

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