REVIEW ARTICLE

Therapeutic Targets in Non-Small Cell Lung Cancer: Current Progress and Future Directions

Alvos Terapêuticos em Cancro do Pulmão Não Pequenas Células: Progressos Atuais e Direções Futuras

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https://doi.org/

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Recebido/Received: October 24th, 2024

Aceite/Accepted: December 4th, 2024

Publicado online/Published online: December 31st, 2024

Publicado/Published: December 31st, 2024

ABSTRACT

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, representing the majority of cancer-related deaths worldwide. Recent advances have shifted treatment paradigms from conventional chemotherapy to precision oncology approaches, particularly molecularly targeted therapies. This review focuses on pivotal molecular drivers such

RESUMO

O cancro do pulmão de células não pequenas (CPCNP) é responsável por aproximadamente 85% de todos os casos de cancro do pulmão, representando a maioria das mortes relacionadas com o cancro em todo o mundo. Os avanços recentes mudaram os paradigmas de tratamento da quimioterapia convencional para abordagens oncológicas de

as *EGFR, ALK, KRAS, MET, HER2*, and *RET*, synthesizing content from recent studies and editorial perspectives. Targeted therapies, particularly tyrosine kinase inhibitors (TKIs), have redefined patient care by improving progression-free and overall survival. However, resistance mechanisms remain a challenge, necessitating innovative strategies and combination approaches. This article integrates perspectives to provide a comprehensive overview of NSCLC target therapeutic progress and future directions.

Keywords:
Carcinoma, Non-Small-Cell Lung/ drug therapy; Carcinoma, Non-Small-Cell Lung/ genetics; Molecular Targeted Therapy; Precision Medicine; Protein Kinase Inhibitors/therapeutic use.

precisão, particularmente terapias molecularmente dirigidas. Esta revisão centra-se nas alterações acionáveis moleculares essenciais, EGFR, ALK, KRAS, MET, HER2 e RET, sintetizando conteúdo de estudos recentes e perspetivas editoriais. As terapêuticas dirigidas, particularmente os inibidores da tirosina quinase (TKIs), redefiniram os cuidados prestados aos doentes, melhorando a sobrevivência livre de progressão e a sobrevivência global. No entanto, os mecanismos de resistência continuam a ser um desafio, necessitando de estratégias inovadoras e abordagens combinadas. Este artigo integra perspetivas para fornecer uma visão abrangente do progresso terapêutico na terapêutica dirigida do CPCNP e das direções futuras.

Palavras-chave:
Carcinoma do Pulmão de células não pequenas/tratamento farmacológico; Carcinoma do pulmão de células não pequenas/genética; Terapêutica Molecular Dirigida; Medicina de Precisão; Inibidores da Proteína Quinase/uso terapêutico.

INTRODUCTION

Non-small cell lung cancer (NSCLC) remains a global health challenge, being the leading cause of cancer-related mortality. Historically treated with chemotherapy, advances in genomic technologies have transformed the treatment landscape. Actionable mutations in *EGFR, ALK, KRAS, MET, HER2*, and *RET* have enabled precision therapies that significantly improve clinical outcomes. This review merges recent editorial insights and research developments, focusing on established and emerging therapeutic targets in NSCLC.

Over the past few years, the treatment landscape for NSCLC has transformed dramatically. This evolution is largely due to significant advances in identifying specific genetic mutations and developing targeted therapies tailored to these alterations.[1] Previously, clinical efforts focused primarily on a few major mutations. However, it is clear that a broader spectrum of genetic changes plays a crucial role in managing patients and predicting their prognosis. This realization necessitates a comprehensive understanding of these mutations and their implications for therapeutic strategies.

EGFR MUTATIONS

The discovery of epidermal growth factor receptor (*EGFR*) mutations has been a cornerstone of NSCLC treatment. These mutations, particularly exon 19 deletions and exon 21 L858R substitutions, lead to the constitutive activation of EGFR signaling pathways. This aberrant signaling drives tumor growth by promoting cell proliferation and inhibiting apoptosis, making EGFR a critical therapeutic target. Over the past two decades, therapies targeting *EGFR* mutations have transformed the treatment paradigm for NSCLC. First-generation TKIs, such as gefitinib and erlotinib, marked the beginning of EGFR-targeted treatment. These inhibitors showed significant improvements in progression-free survival (PFS) compared to chemotherapy, offering a new standard of care for patients with activating *EGFR* mutations. However, despite their initial success, resistance to first-generation TKIs invariably developed. The most common mechanism of acquired resistance was the emergence of the *T790M* mutation,

which altered the ATP-binding pocket of EGFR, reducing the efficacy of these drugs. To overcome T790M-mediated resistance, second-generation EGFR TKIs such as afatinib and dacomitinib were developed. These drugs irreversibly inhibit EGFR and other members of the ErbB family, demonstrating greater potency against resistant mutations. However, their clinical use was often limited by significant toxicities, particularly skin rash and diarrhea, requiring the need for development of more selective therapies. The advent of osimertinib, a third-generation EGFR TKI, revolutionized the management of *EGFR*-mutant NSCLC. Osimertinib specifically targets both activating *EGFR* mutations and the *T790M* resistance mutation, offering improved efficacy and reduced toxicity. It rapidly became the standard of care for patients with *EGFR* mutations, particularly following the landmark FLAURA trial. This trial demonstrated that osimertinib provided superior PFS and overall survival (OS) compared to first-generation TKIs like erlotinib and gefitinib.[2,3] Additionally, osimertinib's ability to penetrate the blood-brain barrier made it highly effective against CNS metastases, a common complication in *EGFR*-mutant NSCLC. Initially, there was considerable debate regarding the optimal sequencing of EGFR TKIs. Clinicians questioned whether patients should start with first-generation TKIs and reserve osimertinib for subsequent therapy upon progression with *T790M* mutation. However, accumulating evidence supported osimertinib as the preferred first-line treatment to maximize clinical benefits and prevent patients from progressing without receiving the most effective therapy available. This shift has become the consensus approach, further cemented by long-term survival data from the FLAURA trial.[2] Despite osimertinib's success, resistance inevitably develops, typically after 12–18 months of treatment. Mechanisms of resistance include MET amplification, HER2 amplification, and the emergence of *EGFR C797S* mutations, which interfere with osimertinib's binding. Current strategies to overcome these challenges focus on combination therapies. For instance, the combination of osimertinib with platinum-based chemotherapy and pemetrexed, investigated in the FLAURA2 trial, has shown promising results in enhancing both PFS and OS.[1] Other studies are exploring combinations with anti-angiogenic agents, such as bevacizumab, to disrupt the tumor microenvironment and delay resistance. Additionally, innovative approaches involving the use of bispecific antibodies, such as amivantamab, which target both EGFR and MET pathways, are being evaluated in clinical trials. These agents hold promise for addressing complex resistance mechanisms. Another approach involves combining osimertinib with immune checkpoint inhibitors to leverage the immune system's ability to combat tumor cells. However, this strategy is complicated by increased toxicity, such as pneumonitis, when combining these classes of drugs. Emerging fourth-generation *EGFR TKIs* are being designed to overcome resistance mutations such as *C797S* while maintaining activity against earlier *EGFR* alterations. Early-phase clinical trials of these agents are showing encouraging results, and they are likely to play a key role in future treatment strategies. The integration of liquid biopsies into clinical practice is another promising development. Liquid biopsies allow the detection of circulating tumor DNA (ctDNA), enabling real-time monitoring of resistance mutations and facilitating timely adjustments in therapy. This non-invasive approach improves precision and ensures that patients receive the most effective treatments tailored to their evolving tumor biology. In summary, while osimertinib has set a new benchmark for *EGFR*-mutant NSCLC, ongoing research is focused on extending its benefits through innovative combinations, novel agents, and advanced diagnostic tools. The evolving landscape of EGFR-targeted therapies highlights the importance of continuous innovation and personalized treatment approaches to improve outcomes for patients with *EGFR*-mutant NSCLC.

ALK REARRANGEMENTS

ALK rearrangements, involving gene fusions like *EML4-ALK,* are present in approximately 3%–5% of NSCLC cases. These genetic alterations drive tumorigenesis by activating ALK signaling pathways, which promote cell proliferation and survival. ALK inhibitors have revolutionized the management of these patients, offering targeted approaches that significantly improve clinical outcomes. Crizotinib, the first ALK-targeting agent, demonstrated remarkable efficacy in early clinical trials by providing substantial tumor response rates and progression-free survival (PFS). However, its limitations became apparent over time, including poor central nervous system (CNS) penetration and the emergence of resistance mechanisms, such as secondary *ALK* mutations and

bypass signaling pathways.[5] Second-generation ALK inhibitors, such as alectinib, brigatinib, and ceritinib, have addressed some of these limitations. These agents offer improved CNS activity, a critical advantage for ALK-positive patients who are at high risk of brain metastases. Alectinib has shown superiority over crizotinib in the ALEX trial, significantly extending PFS and reducing the risk of CNS progression.[6] Brigatinib also demonstrated robust efficacy in the ALTA-1L trial, making it a compelling option for first-line treatment. Lorlatinib, a third-generation ALK inhibitor, was evaluated in the CROWN trial and established as a promising first-line therapy for ALK-positive NSCLC. This drug offers enhanced CNS protection and prolonged disease control compared to earlier agents.[5] Its ability to overcome a broad spectrum of ALK resistance mutations underscores its utility in both first-line and refractory settings. Despite its effectiveness, lorlatinib is associated with neurocognitive and metabolic side effects, including mood alterations and hyperlipidemia, which can impact patient quality of life. To maximize the benefits of ALK inhibitors, combination strategies and sequential approaches are being explored. For instance, ongoing studies are investigating the integration of ALK inhibitors with MET or EGFR inhibitors to address overlapping resistance mechanisms. Additionally, combining targeted therapies with immune checkpoint inhibitors holds potential for enhancing therapeutic efficacy, though concerns about toxicity must be carefully managed. Looking ahead, the development of next-generation ALK inhibitors with even greater selectivity and resistance profiles remains a priority. Biomarker-driven approaches, such as liquid biopsies to monitor *ALK* mutation dynamics, are expected to further personalize treatment and optimize long-term outcomes for patients with ALK-positive NSCLC.

KRAS MUTATIONS

KRAS mutations, particularly *KRAS* G12C, represent one of the most common oncogenic drivers in NSCLC, occurring in approximately 25%–30% of lung adenocarcinomas. These mutations play a central role in tumorigenesis by activating downstream signaling pathways, including the MAPK and PI3K/AKT pathways, which drive cell proliferation, survival, and resistance to apoptosis. Historically, KRAS was considered an "undruggable" target due to the structural properties of the KRAS protein and the difficulty in identifying suitable binding sites for small molecules. However, recent advances in drug discovery have led to the development of selective KRAS inhibitors, marking a breakthrough in NSCLC treatment. KRAS G12C inhibitors, such as sotorasib and adagrasib, have emerged as promising therapies for this subset of patients. These agents irreversibly bind to the mutant *KRAS* protein in its inactive GDP-bound state, effectively preventing its activation and subsequent signaling. Sotorasib was the first KRAS G12C inhibitor to receive FDA approval based on its efficacy in previously treated NSCLC patients, with clinical trials showing objective response rates (ORR) of approximately 37% and a median progression-free survival (PFS) of 6.8 months.[7] Adagrasib has demonstrated similar efficacy, with the added advantage of improved CNS penetration, making it a valuable option for patients with brain metastases. Despite these advances, resistance to KRAS G12C inhibitors often develops, limiting their long-term efficacy. Resistance mechanisms include bypass signaling through pathways such as *EGFR, MET*, or *HER2* amplification, as well as the emergence of secondary mutations within the *KRAS* protein itself. To address these challenges, combination strategies are being actively investigated. For example, combining KRAS inhibitors with SHP2 inhibitors can block upstream signaling pathways, while the addition of MEK inhibitors targets downstream signaling cascades, potentially overcoming resistance. Early-phase clinical trials are exploring these combinations, showing encouraging preclinical and clinical results. Expanding the scope of KRAS-targeted therapies, researchers are developing inhibitors for other *KRAS* variants, such as *KRAS* G13D and *KRAS* Q61H. These mutations, although less common than *KRAS* G12C, are also significant drivers of tumor progression. Novel agents targeting these variants are currently in preclinical and early-phase clinical trials, which may broaden therapeutic options for patients with KRAS-driven NSCLC.[8] In addition to targeted therapies, immunotherapy has emerged as a key treatment modality for patients with *KRAS* mutations. *KRAS*-mutant tumors, particularly in patients with a history of smoking, often exhibit high tumor mutational burden (TMB) and elevated PD-L1 expression, making them more responsive to immune checkpoint inhibitors. Clinical trials such as KEYNOTE-042 and KEYNOTE-189 have demonstrated the efficacy of pembrolizumab, either alone or in combination with chemotherapy, in improving

overall survival for these patients. Consequently, immunotherapy remains a cornerstone of first-line treatment for *KRAS*-mutant NSCLC, with KRAS inhibitors typically reserved for subsequent lines of therapy. Emerging strategies for *KRAS*-mutant NSCLC include the integration of antibody-drug conjugates (ADCs) and synthetic lethality approaches. ADCs targeting specific surface antigens on KRAS-mutant tumors may offer a novel therapeutic avenue, delivering cytotoxic agents directly to cancer cells while sparing normal tissue. Synthetic lethality approaches exploit vulnerabilities in *KRAS*-mutant tumors by targeting co-dependent pathways, such as DNA damage repair mechanisms, to induce tumor cell death. These strategies are currently under investigation in early-phase clinical trials. The role of liquid biopsies in managing *KRAS*-mutant NSCLC is also gaining prominence. Liquid biopsies enable the detection of circulating tumor DNA (ctDNA), allowing for the real-time monitoring of resistance mutations and treatment response. This non-invasive approach facilitates dynamic treatment adjustments and helps optimize outcomes for patients with evolving resistance profiles. While KRAS-targeted therapies represent a significant step forward, their modest response rates and the emergence of resistance highlight the need for continued innovation. Future research should focus on refining combination strategies, developing next-generation inhibitors, and identifying predictive biomarkers to better stratify patients who are most likely to benefit from KRAS-targeted therapies. Additionally, integrating advanced diagnostic tools such as liquid biopsies and incorporating artificial intelligence into treatment planning may further enhance therapeutic precision. In conclusion, the management of *KRAS*-mutant NSCLC has undergone a paradigm shift with the advent of KRAS inhibitors and the integration of immunotherapy. Continued advancements in targeted therapies, combination strategies, and diagnostic approaches hold the promise of further improving outcomes for this challenging subset of NSCLC patients.

HER2 ALTERATIONS

HER2 (human epidermal growth factor receptor 2) mutations and amplifications, although less common in NSCLC, represent significant actionable therapeutic opportunities. *HER2* alterations occur in approximately 2%–4% of lung adenocarcinomas and are associated with aggressive tumor behavior and poorer prognosis. These genetic alterations lead to the constitutive activation of HER2 signaling pathways, promoting uncontrolled tumor growth and resistance to apoptosis. The rarity of HER2 alterations in NSCLC has historically limited the development of targeted therapies, but recent advancements have brought new therapeutic options to the forefront. Antibody-drug conjugates (ADCs), such as trastuzumab deruxtecan (T-DXd), have revolutionized the treatment landscape for HER2-driven tumors. T-DXd combines a HER2-targeting antibody with a potent cytotoxic payload, delivering chemotherapy directly to HER2-expressing cells while minimizing off-target effects. Clinical trials have demonstrated the efficacy of T-DXd in patients with *HER2*-mutant NSCLC, including those with CNS metastases, a common and challenging complication in this population. The DESTINY-Lung01 trial reported an objective response rate (ORR) of 54.9% and a median progression-free survival (PFS) of 8.2 months, underscoring the potential of T-DXd in this setting.9 Emerging data suggest that ADCs may play an even broader role in earlier lines of therapy. Trials such as DESTINY-Lung04 are investigating the use of T-DXd in combination with immune checkpoint inhibitors and chemotherapy to enhance therapeutic efficacy. Preliminary results indicate that this combination may provide synergistic benefits, improving response rates and extending survival outcomes.10 Beyond trastuzumab deruxtecan, other ADCs targeting HER2 are showing promise. Agents such as trastuzumab emtansine (T-DM1) and novel HER2-targeting ADCs are in clinical development, aiming to improve efficacy while reducing toxicity. These next-generation ADCs incorporate advanced linker technologies and more potent cytotoxic payloads, potentially overcoming resistance mechanisms observed with first-generation ADCs. In addition to ADCs, small-molecule HER2 inhibitors are being actively explored. Agents such as poziotinib and pyrotinib have demonstrated clinical activity in HER2-mutant NSCLC, particularly in patients with exon 20 insertions, a subset known for its resistance to earlier HER2-targeted therapies. These drugs offer an oral treatment option and have shown efficacy in heavily pretreated populations, though challenges related to toxicity, including diarrhea and rash, remain. Combination strategies are also under investigation to optimize outcomes for patients with HER2-driven NSCLC. Combining HER2-targeting agents with MEK inhibitors or PI3K

inhibitors may enhance anti-tumor activity by simultaneously targeting multiple pathways involved in tumor growth and survival. Early-phase trials are evaluating these combinations, and preliminary results suggest potential benefits in overcoming resistance. CNS metastases are a frequent and challenging complication in patients with HER2-driven NSCLC. The ability of HER2-targeted therapies to penetrate the blood-brain barrier is critical for achieving effective disease control in this setting. Trastuzumab deruxtecan has shown promising activity in CNS metastases, with emerging data indicating significant intracranial responses. Similarly, poziotinib and pyrotinib have demonstrated CNS efficacy, providing additional options for patients with brain involvement. The development of biomarkers to better identify patients with HER2-driven NSCLC and predict responses to HER2-targeted therapies remains a key area of research. Liquid biopsies capable of detecting circulating tumor DNA (ctDNA) with *HER2* mutations are being explored as a non-invasive diagnostic tool. These advancements could enable real-time monitoring of treatment response and resistance, further personalizing therapy. In conclusion, *HER2* alterations in NSCLC present significant therapeutic opportunities, with advances in ADCs, small-molecule inhibitors, and combination strategies driving progress in this field. Continued innovation and clinical research are essential to fully realize the potential of HER2-targeted therapies, improving outcomes for this challenging subset of NSCLC patients.

MET ALTERATIONS

MET (mesenchymal-epithelial transition) alterations, including exon 14 skipping mutations and amplifications, are associated with aggressive tumor biology, poor prognosis, and resistance to conventional therapies. These alterations lead to dysregulated MET signaling, promoting uncontrolled tumor growth, invasion, and metastasis. *MET* exon 14 skipping mutations, present in approximately 3%–4% of NSCLC cases, impair the degradation of the MET receptor, resulting in its prolonged activation. MET amplifications, on the other hand, occur in a wider range of tumors, either as primary oncogenic drivers or secondary resistance mechanisms to EGFR-targeted therapies. Introducing MET inhibitors, such as capmatinib and tepotinib, has significantly improved outcomes for patients with MET-driven NSCLC. These selective MET tyrosine kinase inhibitors (TKIs) have demonstrated robust efficacy, particularly in treatment-naïve patients with *MET* exon 14 skipping mutations. In clinical trials, capmatinib achieved an objective response rate (ORR) of 68% in treatment-naïve patients and 41% in previously treated patients, with durable responses observed across cohorts. Similarly, tepotinib showed an ORR of 43% in advanced NSCLC patients with MET exon 14 skipping mutations, with encouraging progression-free survival (PFS) and central nervous system (CNS) activity.[11] Despite the success of MET inhibitors, resistance often emerges, either through secondary *MET* mutations, bypass signaling via other pathways (such as EGFR or HER2 amplification), or histological transformation. To address these challenges, combination strategies are being explored. For instance, combining MET inhibitors with EGFR or ALK inhibitors offers a promising approach for tumors with co-occurring mutations or amplifications. Preclinical studies suggest that dual inhibition of MET and EGFR pathways can synergistically suppress tumor growth and delay the emergence of resistance. Using liquid biopsies to detect circulating tumor DNA (ctDNA) with *MET* exon 14 skipping mutations or amplifications is revolutionizing the management of MET-driven NSCLC. Research into next-generation MET inhibitors aims to address the limitations of current therapies, including overcoming resistance mutations and improving CNS penetration. Early-phase trials of novel MET inhibitors, such as savolitinib and amivantamab (a bispecific antibody targeting EGFR and MET), have shown promising activity in patients with resistant disease. These agents are expected to expand treatment options for patients with MET-driven NSCLC. Additionally, targeting the tumor microenvironment (TME) in MET-altered NSCLC is emerging as a complementary therapeutic strategy. MET-driven tumors often create an immunosuppressive microenvironment, facilitating immune evasion and metastasis. Therapeutic interventions aimed at reprogramming the TME, such as combining MET inhibitors with TME-modulating agents, are under investigation and may enhance treatment efficacy. CNS metastases are a common complication in patients with MET-driven NSCLC, requiring therapies with robust CNS penetration. Both capmatinib and tepotinib have shown activity against CNS metastases, providing an important treatment option for these patients. Ongoing trials

are evaluating the potential of next-generation MET inhibitors to further improve CNS efficacy, addressing a critical unmet need in this population. MET alterations represent a significant therapeutic target in NSCLC, with the advent of MET inhibitors marking a major milestone in precision oncology. While challenges related to resistance and CNS metastases persist, ongoing research into combination strategies, next-generation inhibitors, and advanced diagnostics holds promise for improving outcomes. As the field evolves, integrating these innovations into clinical practice will be essential to optimizing care for patients with MET-driven NSCLC.[12]

RET AND ROS1 FUSIONS

RET (rearranged during transfection) and ROS1 (c-ros oncogene 1) fusions, while relatively rare in NSCLC, represent distinct oncogenic drivers that offer significant opportunities for targeted therapy. RET fusions are observed in approximately 1%–2% of NSCLC cases, while ROS1 rearrangements occur in 1%–3% of patients, predominantly in younger individuals with minimal or no smoking history. Both alterations are associated with tumorigenesis through constitutive activation of their respective tyrosine kinase domains, driving uncontrolled cell proliferation and survival. The development of highly selective RET inhibitors, such as pralsetinib and selpercatinib, has significantly advanced the management of RET-positive NSCLC. These agents were specifically designed to target RET alterations while sparing other kinases, reducing off-target effects and improving tolerability. Clinical trials have demonstrated their robust efficacy. Selpercatinib, for instance, achieved objective response rates (ORRs) of approximately 64% in treatment-naïve patients and 85% in previously treated patients with RET-positive NSCLC. Similarly, pralsetinib showed ORRs of 61% in treatment-naïve patients and 70% in pretreated patients, with durable responses observed across cohorts. Both selpercatinib and pralsetinib have shown activity against CNS metastases, a common complication in RET-positive NSCLC. Their ability to penetrate the blood-brain barrier addresses a critical need for patients with intracranial disease. While these therapies are generally well-tolerated, side effects such as hypertension, liver enzyme elevations, and fatigue require monitoring and management. Next-generation RET inhibitors are under development to address resistance mechanisms, such as secondary mutations in the RET kinase domain. These emerging agents aim to improve efficacy and overcome limitations of first-generation therapies. ROS1 rearrangements are highly actionable targets in NSCLC, with first-generation ROS1 inhibitors like crizotinib providing significant clinical benefit. Crizotinib demonstrated an ORR of approximately 72% and a median progression-free survival (PFS) of 19.3 months in ROS1-positive NSCLC. However, resistance often develops due to secondary ROS1 mutations, activation of bypass signaling pathways, or inadequate CNS penetration. Next-generation ROS1 inhibitors, such as repotrectinib and lorlatinib, have shown promise in overcoming these limitations. Repotrectinib is designed to address acquired resistance mutations, such as *ROS1 G2032R*, while maintaining activity against the primary ROS1 fusion. It has demonstrated encouraging intracranial efficacy, making it a valuable option for patients with CNS metastases. Lorlatinib, originally developed as an ALK inhibitor, has shown efficacy in ROS1-positive NSCLC, particularly in patients with advanced or resistant disease. Combination therapies are being explored to optimize outcomes for RET- and ROS1-positive NSCLC. Combining RET or ROS1 inhibitors with immune checkpoint inhibitors or anti-angiogenic agents, such as VEGF inhibitors, may enhance anti-tumor activity. Preclinical studies suggest that dual targeting of RET or ROS1 and other pathways involved in tumor progression can delay resistance and prolong disease control. CNS metastases remain a significant challenge in patients with RET and ROS1 fusions. Both selpercatinib and pralsetinib have demonstrated CNS activity, providing an effective treatment option for patients with brain involvement. Similarly, repotrectinib has shown robust intracranial responses, addressing an unmet need for ROS1-positive patients with CNS metastases. Ongoing research aims to improve the durability of responses to RET and ROS1 inhibitors and develop strategies to overcome resistance. The integration of liquid biopsies for real-time detection of resistance mutations and advanced imaging techniques to monitor CNS disease progression are expected to play a pivotal role in the management of RET- and ROS1-positive NSCLC. Additionally, the development of bispecific antibodies targeting multiple oncogenic drivers holds the potential for addressing complex resistance mechanisms.[13]

CONCLUSION

The integration of targeted therapies with emerging technologies and innovative combinations represents the future of NSCLC treatment. Advances in EGFR, ALK, KRAS, HER2, MET, RET, and ROS1-targeted therapies have significantly improved patient outcomes. However, resistance to these therapies remains a major obstacle in NSCLC management. Secondary mutations, bypass pathway activations, and histological transformations frequently drive therapeutic failures. For instance, MET amplification often undermines EGFR-targeted therapies.[14] Emerging approaches to combat resistance include rotating targeted agents, combining therapies with complementary mechanisms, and leveraging liquid biopsies for real-time monitoring. Novel biomarkers and adaptive treatment strategies are essential for personalized therapy, ensuring long-term disease control.[15] Antibody-drug conjugates (ADCs) and novel small molecules are reshaping the NSCLC treatment landscape. ADCs such as datopotamab deruxtecan and telisotuzumab vedotin target specific tumor antigens, offering new hope for patients with refractory disease.[16] In parallel, synthetic lethality–based approaches, which exploit tumor-specific vulnerabilities, are emerging as promising strategies to overcome therapy resistance.[17] Small molecules targeting previously "undruggable" mutations are entering clinical trials, broadening the spectrum of actionable targets. Moreover, liquid biopsies are revolutionizing NSCLC management by enabling the detection of circulating tumor DNA (ctDNA) and tumor-derived exosomes. This non-invasive approach facilitates the real-time monitoring of tumor dynamics, resistance mutations, and minimal residual disease. Continued research and a multidisciplinary approach are critical to overcoming resistance and optimizing precision oncology. The ongoing evolution of NSCLC management underscores the importance of comprehensive genetic profiling, patient-centered care, and global collaboration.

Ethical Disclosures:

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

Responsabilidades Éticas:

Conflitos de Interesse: *Os autores declaram não possuir conflitos de interesse.*

Suporte Financeiro: *O presente trabalho não foi suportado por nenhum subsídio o bolsa ou bolsa.*

Proveniência e Revisão por Pares: *Não comissionado; revisão externa por pares.*

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