ISSN 2706-6819 Vol.8, Issue 1: 73-80, DOI: 10.25236/IJFM.2026.080109

Mechanisms of Resistance to Targeted Therapy and Advances in Combination Therapy for KRAS G12C Non-Small Cell Lung Cancer

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Abstract: *Lung cancer remains the leading cause of cancer incidence and mortality globally. Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer cases; designing treatment strategies for this disease is a significant focus. The KRAS gene is notably associated with a high mutation frequency in NSCLC, with the KRAS G12C subtype being the most prevalent. In recent years, several KRAS G12C inhibitors have received market approval and have shown promising antitumor efficacy; however, both primary and acquired resistance have hindered their long-term effectiveness. Therefore, a thorough investigation of the mechanisms underlying these resistance patterns, alongside the exploration of effective combination therapy strategies, is essential for enhancing patient prognosis. This article provides a systematic review of the resistance mechanisms to targeted therapies and the combination therapy strategies for KRAS G12C-mutated NSCLC, serving as a valuable reference for future research.*

Keywords: *Non-Small Cell Lung Cancer, KRAS G12C Inhibitors, Resistance Mechanisms, Combination Therapy*

1. Introduction

Lung cancer is the leading cause of cancer incidence and mortality worldwide. It can be classified into two types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for approximately 85% of cases[1]. In 2022, China reported 1,060,600 new cases of lung cancer and 733,300 deaths, accounting for 22.0% and 28.5% of all cancer cases and deaths, respectively[2]. In recent years, the discovery of driver genes and the advancement of targeted therapies have significantly reshaped the treatment landscape of NSCLC.

Kirsten rat sarcoma viral oncogene (KRAS) is another highly prevalent oncogenic driver gene in NSCLC, second only to epidermal growth factor receptor (EGFR). The protein encoded by KRAS promotes tumor cell proliferation, survival, and migration by activating downstream signaling pathways, including the Raf/MEK/ERK, PI3K/AKT/mTOR, and RalGDS/Ral pathways. KRAS mutations are predominantly concentrated at codons 12, 13, and 61, among which the G12C mutation (a substitution of glycine at position 12 with cysteine) is the most common subtype. The overall incidence of KRAS mutations in NSCLC patients is 12.1%, with the G12C mutation accounting for 29.6% of these cases [3]. The tens of thousands of new NSCLC cases diagnosed annually also present persistent challenges for therapeutic research targeting the MAPK pathway.

Since KRAS was first identified as a contributor in human cancer in 1982, it has long been regarded as an “undruggable” target due to its smooth protein surface and lack of drug-binding pockets. In 2021, Sotorasib, the world’s first KRAS G12C inhibitor, was approved by the U.S. Food and Drug Administration (FDA) [4], officially inaugurating the era of KRAS-targeted therapy. China has made remarkable progress in innovative drug research and development, with Fulzerasib, Garsorasib, and Glecirasib being successively approved for market launch. These inhibitors covalently bind to the cysteine residue in the Switch II pocket of KRAS, thereby inhibiting oncogenic signaling. Clinical data show that their objective response rates (ORR) typically range from 40% to 60%, while disease control rates (DCR) exceed 85% [5-8].

ISSN 2706-6819 Vol.8, Issue 1: 73-80, DOI: 10.25236/IJFM.2026.080109

However, primary or acquired resistance remains the primary cause of treatment failure with KRAS G12C inhibitors. Therefore, elucidating the underlying mechanisms of resistance and identifying effective combination therapy strategies have become the central focus of current research.

2. Research Progress on KRAS G12C Targeted Therapies

The KRAS G12C mutation disrupts the dynamic equilibrium between the inactive and active conformational states of the KRAS protein, leading to its sustained hyperactivation. Based on the functional activation status of KRAS, current KRAS G12C inhibitors are categorized into two major classes: OFF-state inhibitors and ON-state inhibitors.

KRAS G12C OFF-state inhibitors selectively recognize and covalently bind to the GDP-bound inactive form of KRAS, locking the protein in an inert conformation and thereby blocking persistent downstream oncogenic signaling. Clinically approved agents of this class are summarized in Table 1. In addition, multiple candidate molecules, including Divarasib (GDC-6036), Olomorasib (LY3537982), MK-1084, Opnurasib (JDQ443), D3S-001, and HRS-7058, are currently under clinical investigation.

By contrast, KRAS G12C ON-state inhibitors directly target the GTP-bound activated form of KRAS. Theoretically, this mechanism enables them to overcome resistance driven by the reactivation of KRAS, a well-recognized limitation of OFF-state inhibitors. To date, no ON-state inhibitors have received marketing approval; representative investigational compounds include Elironrasib (RMC-6036/RMC-6291) and BBO-8520. Nevertheless, intrinsic and acquired resistance remains the predominant cause of treatment failure following monotherapy with KRAS G12C inhibitors. Accordingly, elucidating the underlying resistance mechanisms and developing rational combination therapeutic strategies have become the core focus of contemporary preclinical and clinical research.

Table 1: Approved KRAS G12C (OFF) inhibitors: efficacy and safety data.

Drug Name	Clinical Trial (Phase)	Patients (n)	ORR (95% CI)	mPFS* (month, 95% CI)	≥3 TRAEs(%)
Sotorasib (AMG 510)	CodeBreaK 100 (Phase II) [9]	124	37.1% (28.6-46.2)	6.8(5.1-8.2)	20.6%
	CodeBreaK 200 (Phase III) [7]	345	28.1%(21.5–35.4) vs. 13.2%(8.6–19.2) (docetaxel)	5.6(4.3-7.8) vs. 4.5(3.0-5.7) (docetaxel)	33.1% vs. 35.1% (docetaxel)
Adagrasib (MRTX849)	KRYSTAL-1 (Phase II) [10]	116	42.9%(NR)	6.5(4.7-8.4)	44.8%
	KRYSTAL-12 (Phase III) [11]	453	NR	5.5(4.5-6.7) vs. 3.8(2.7-4.7) (docetaxel)	47.0% vs. 45.7% (docetaxel)
Fulzerasib (IBI351/GFH925)	NCT05005234 (Phase II) [8]	116	49.1%(39.7–58.6%)	9.7(5.6-11.0)	41.4%
	NCT05504278(Phase III)	Study design: First-line treatment: Combination of Sintilimab ± chemotherapy versus chemotherapy alone to evaluate PFS benefit in advanced non-squamous NSCLC			
Garsorasib (D-1553)	NCT05383898 (Phase I/II) [6]	189	48.1% (40.8-55.5%)	9.07(7.39-9.76)	49.2%
Glecirasib (JAB-21822)	NCT05009329 (Phase IIb) [5]	119	47.9% (38.5-57.3%)	8.2(5.5-13.1)	38.7%
	NCT06416410 (Phase III)	Study design: First-line treatment: Comparing efficacy with standard immunochemotherapy combined with Cetrotinib in treatment-naive patients			
Sosimerasib (JMKX001899)	ChiCTR2200059986 (Phase II) [12]	145	52.4% (44.0-60.8%)	7.2 months (5.6- not evaluated)	40.0%

**Note: NR = Not reported; mPFS = median progression-free survival; TRAEs = treatment-related adverse events.*

3. Mechanisms of Resistance to KRAS G12C Inhibitors

Based on the timing of resistance onset, the mechanisms of resistance to KRAS G12C inhibitors are

ISSN 2706-6819 Vol.8, Issue 1: 73-80, DOI: 10.25236/IJFM.2026.080109

categorized into primary resistance (present before treatment) and acquired resistance (developing after treatment) [13]. Both types of resistance involve multidimensional alterations in genes, signaling pathways, cellular phenotypes, and the tumor microenvironment.

Notably, primary and acquired resistance remain the predominant cause of treatment failure in patients receiving KRAS G12C inhibitor monotherapy. Therefore, elucidating the underlying molecular mechanisms of resistance and identifying rational combination therapeutic strategies have become the core focus of contemporary research in this field.

3.1. Mechanisms of Primary Resistance

STK11/LKB1, TP53, and KEAP1 are the most common co-mutated genes in KRAS G12C-mutated NSCLC, with mutation rates of 47%, 39%, and 30%, respectively[14,15]. Clinical data indicate that STK11 or KEAP1 mutations are associated with poor prognosis, particularly in patients with dual mutations. Although TP53 mutations are common, they are not significantly associated with clinical drug resistance. Apart from KEAP1/STK11 co-mutations, tumor cells with abnormally activated receptor tyrosine kinases (RTKs) exhibit low dependence on the KRAS pathway and instead activate downstream MAPK/PI3K-AKT pathways through compensatory bypass mechanisms, leading to poor treatment response. Furthermore, approximately 8% of patients with KRAS G12C mutations harbor co-mutations at other sites (primarily G12V), of which 70% are in the cis-configuration and 22% in the trans-configuration[16]. Such co-existing mutations significantly reduce the sensitivity of tumor cells to inhibitors.

3.2. Acquired resistance

3.2.1. KRAS Secondary Mutations and Amplifications, Cross-RAS Family Mutations

Secondary KRAS mutations (e.g., G12D, G12V, G12F) exhibit distinct drug specificity by restructuring the Switch II pocket conformation to block drug binding[17]. Additionally, cross-RAS family mutations (NRAS, MRAS) and BRAF mutations are detected in up to 63% of resistant patients and often drive bypass signaling to evade inhibition [18]. In contrast, KRAS gene amplification sustains oncogenic signaling by increasing copy number. Crucially, in Ba/F3 cell model experiments, 87.3% of resistant clones harbored secondary KRAS mutations, and the mutation sites were correlated with the inducing drugs [17]; drug-specific mutations can be targeted with sequential therapy as needed.

3.2.2. Bypass Activation

Bypass activation exhibits multi-level, network-based characteristics and can be described into three aspects: (1) At the RTK level, MET, EGFR/FGFR2, and RET/ALK fusions are the primary drivers[19],(2) At the downstream signaling nodes, NRAS/BRAF activation and NF1/PTEN loss both lead to sustained activation of the PI3K-mTOR pathway[19]; (3) Alternative signaling axes, such as YAP1/TAZ-TEAD and the SRC family, mediate resistance through transcriptional reprogramming and tumor microenvironment remodeling[20,21]. In actual clinical cases, multiple mechanisms interact synergistically, forming the basis for combined targeted therapeutic strategies.

3.2.3. Altered Cellular Plasticity

Epithelial-mesenchymal transition (EMT)-related genes are significantly enriched in Sotorasib-resistant cells. TGF-β induction or TWIST/SNAI1 overexpression can trigger EMT; however, some studies suggest its predictive value is inferior to that of KRAS co-mutations. Resistance is mediated by downregulating KRAS activity and by maintaining the PI3K/AKT pathway [22]. Reversing EMT-mediated resistance can be achieved by combining treatments to inhibit the synergistic activation of the AKT-p38 signaling pathway, or by co-administering KRAS G12C inhibitors with FGFR inhibitors and heat shock protein 90 (HSP90) inhibitors [23,24].

Schoenfeld et al. were the first to report that adenosquamous transition (AST) in drug-resistant samples is associated with poor prognosis. Patients with high baseline expression of AST-related features exhibited low ORR to adagrasib and poor prognosis[25]. Analysis shows that the rate of acquired MAPK pathway gene mutations in NSCLC is significantly lower than in colorectal cancer (CRC), highlighting the central role of other resistance mechanisms, such as AST, in NSCLC treatment[26]. The mechanism underlying KRAS decoupling following AST remains unclear. Therefore, future efforts should integrate multi-omics approaches to dynamically analyze the AST process and identify new strategies for epigenetic intervention[25].

ISSN 2706-6819 Vol.8, Issue 1: 73-80, DOI: 10.25236/IJFM.2026.080109

3.2.4. Adaptive Resistance: Rapid Signal Reactivation

Following KRAS inhibition, tumor cells can rapidly reactivate RAS signaling—through mechanisms such as wild-type RAS activation or KRAS re-mutation—to restore proliferative capacity. Abnormal cholesterol metabolism can block phosphotyrosine (pTyr) signal feedback activation, thereby enhancing the cytotoxicity of MAPK pathway inhibitors against resistant cells[27].

3.2.5. Mechanisms of Tumor Microenvironment (TME)-Mediated Resistance

The continuous secretion of hepatocyte growth factor (HGF) by fibroblasts activates the MET-PI3K pathway in tumor cells, thereby reducing the efficacy of drug therapy[28]. Concurrently, Sotorasib treatment induces upregulation of PD-L1 on tumor cells, creating an immunosuppressive microenvironment via the JAK2/STAT3/IL-6 pathway, thereby reducing $CD8^+$ T-cell infiltration and promoting immune evasion [29]. Collectively, these factors form a "stromal-immune" dual resistance barrier.

4. Combination Therapy Strategies Based on Mechanisms of Resistance

Given the multifaceted resistance mechanisms associated with KRAS G12C inhibitors, current combination therapy strategies focus on targeting signaling pathways as the core approach, supplemented by efforts to remodel the tumor microenvironment and overcome cellular plasticity. Several such studies have entered the clinical phase and demonstrate promising potential for widespread application.

4.1. Combination Strategies Targeting MAPK Pathway Reactivation

Feedback reactivation of the MAPK pathway is the core mechanism of resistance to KRAS G12C inhibitors. Combined inhibition of upstream and downstream nodes in this pathway can effectively block signal escape and enhance inhibitor efficacy.

4.1.1. MEK Inhibitors

Mechanistically, combining MEK inhibition with KRAS G12C inhibitors can prevent post-treatment feedback reactivation of the ERK pathway, thereby enhancing efficacy. Trametinib (GSK1120212), an allosteric inhibitor of MEK1/2, has demonstrated preclinical activity in KRAS-mutant NSCLC; however, Phase II trials showed poorer safety and a shorter duration of response compared with docetaxel [30]. A Phase Ib study of the combination of trametinib and Sotorasib demonstrated that this regimen is safe and exhibits antitumor activity[31]. However, existing combination data remain limited to early-phase clinical trials; further clinical studies are needed to validate the actual benefits of this combination strategy and to optimize dosing to balance efficacy and toxicity.

4.1.2. SHP2 inhibitors

The combination of SHP2 inhibitors and KRAS G12C inhibitors can synergistically overcome HER2-mediated resistance while remodeling the tumor microenvironment and enhancing immune regulation, thereby significantly improving antitumor efficacy [32]. A clinical trial of JDQ443 combined with TNO155 enrolled patients who had failed prior treatments (including some who had received KRAS G12C inhibitors). The median duration of treatment was 18 weeks, and 88% of patients experienced treatment-related adverse events, indicating preliminary clinical potential [33]. Further studies found that a multi-drug combination regimen (including a PD-1 inhibitor) led to greater tumor regression.

4.1.3. EGFR Inhibitors

Following KRAS inhibition, tumor cells can form a bypass signal by upregulating and activating EGFR, thereby sustaining ERK phosphorylation and reactivating the MAPK pathway, leading to drug resistance[34]. Fulzerasib combined with cetuximab has demonstrated synergistic effects in preclinical studies, but high YAP1/MRAS expression can attenuate its efficacy [34]. An international multicenter Phase II trial confirmed that this regimen achieves durable responses with a favorable safety profile as first-line treatment for KRAS G12C-mutated NSCLC[35]. A Phase III trial is currently underway to evaluate its efficacy in patients with a PD-L1 Tumor Proportion Score (TPS) <50%[35].

ISSN 2706-6819 Vol.8, Issue 1: 73-80, DOI: 10.25236/IJFM.2026.080109

4.2. Combined Strategies Targeting Cell Cycle Dysregulation

4.2.1. CDK4/6 inhibitors

The incidence of central nervous system (CNS) metastases in patients with KRAS G12C-mutated NSCLC can reach 40%, and the prognosis is poorer than in KRAS wild-type patients[36]. Homozygous deletion of cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) leads to uncontrolled cell-cycle progression and may be closely associated with an increased risk of brain metastases. Adagrasib in combination with abemaciclib exerts near-synergistic effects in brain metastasis models, reducing tumor burden and prolonging overall survival; however, its efficacy is affected by CDKN2A/B homozygous deletion status, and caution must be exercised regarding drug-drug interactions between the two (Adagrasib may increase abemaciclib exposure) [37].

4.2.2. Farnesyltransferase Inhibitors

Combined with KRAS G12C inhibitors, they demonstrate synergistic effects in cell lines and 2D/3D models. Mechanistically, by inhibiting compensatory HRAS reactivation and blocking mTOR downstream signaling, they synergize with KRAS G12C inhibitors to induce cell cycle arrest and apoptosis and to inhibit tumor cell migration, thereby significantly enhancing therapeutic efficacy against KRAS G12C-mutated tumors [38].

4.3. Combined Strategies for Remodeling the Tumor Microenvironment

4.3.1. Immune Checkpoint Inhibitors

The KRAS G12C mutation can induce high PD-L1 expression, promoting the formation of an immunosuppressive tumor microenvironment, which in turn leads to varying responses to targeted therapy. This treatment limitation can be reversed by immune checkpoint inhibitors (ICIs). Preclinical studies have confirmed that combining KRAS G12C inhibitors with anti-PD-1 therapy yields synergistic effects, and clinical trials have further validated this enhanced efficacy [39]. The core targets of ICIs include: programmed cell death protein 1 (PD-1)/ programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Data analysis indicates that this non-CTLA-4-targeted combination strategy yields greater benefits in patients with high tumor mutational burden (TMB)[40], high PD-L1 expression[41], and no STK11/KEAP1 co-mutations[42]. Notably, for the immune-resistant subgroup with STK11/KEAP1 co-mutations, anti-CTLA-4 therapy may overcome resistance by activating alternative immune pathways; relevant clinical studies are currently underway [43].

4.3.2. Combined Strategies to Overcome Phenotypic Plasticity—Combination with Chemotherapy

Chemotherapy can target drug-resistant phenotypes such as EMT and AST, complementing KRAS G12C inhibitors to address tumor heterogeneity. Preclinical studies have shown that the combination of KRAS inhibitors and chemotherapy reduces the survival of resistant cells [44] and significantly inhibits tumor growth [44]. Challenges remain in clinical translation: cell line models struggle to accurately simulate the immune microenvironment, tumor heterogeneity, and pharmacokinetic variability, which can introduce biases in clinical trial design. Further elucidation of resistance mechanisms is needed, along with validation using patient-derived xenograft (PDX) models, and optimization of dosing schedules and combination dosages through adaptive clinical trial designs.

5. Conclusions and Outlook

The emergence of KRAS G12C inhibitors has indeed provided a novel therapeutic option for patients with KRAS G12C-mutated non-small cell lung cancer (NSCLC); however, monotherapy is associated with inherent limitations, including limited long-term clinical benefits and a high risk of resistance development. With the in-depth exploration of resistance mechanisms and the continuous expansion of combination therapy strategies, these approaches have gradually become the key pathway to overcoming clinical resistance. At present, multiple emerging therapeutic strategies—including broad-spectrum antitumor approaches such as targeted antibody–drug conjugates, adoptive cell therapy, and personalized immunotherapy, as well as innovative interventions targeting the KRAS pathway, such as pan-KRAS inhibitors, PROTACs, mRNA vaccines, and metabolic modulation—have demonstrated promising potential for clinical translation.

Current research on KRAS resistance mechanisms comprehensively covers multiple dimensions, including genetic alterations, signaling pathway dysregulation, cellular phenotypic changes, and tumor

ISSN 2706-6819 Vol.8, Issue 1: 73-80, DOI: 10.25236/IJFM.2026.080109

microenvironment remodeling. Circulating tumor DNA (ctDNA) sequencing and predictive biomarkers have played a tangible role in guiding precision therapy; however, current treatment strategies still face considerable challenges, such as limited long-term efficacy, insufficient clinical validation of combination regimens, and inadequate therapeutic options for specific patient subgroups (e.g., those with poor-prognosis brain/bone metastases and STK11/KEAP1 co-mutations).

Future research efforts should focus on deepening the understanding of resistance mechanisms, accelerating the clinical translation of novel therapeutic technologies, and optimizing the dosing sequences and combination regimens of combination therapies, thereby promoting a paradigm shift in treatment toward "precision resistance prevention." The treatment of KRAS G12C-mutated NSCLC has now entered a new era characterized by "targeted therapy as the mainstay and combination therapy as an adjuvant." The next phase of research should aim to improve the long-term survival of patients and provide higher-quality clinical solutions.

Based on the timing of resistance onset, the mechanisms of resistance to KRAS G12C inhibitors are categorized into primary resistance and acquired resistance [13]. Both types of resistance involve multidimensional alterations in genes, signaling pathways, cellular phenotypes, and the tumor microenvironment. Notably, primary and acquired resistance remain the predominant cause of treatment failure in patients receiving KRAS G12C inhibitor monotherapy. Therefore, elucidating the underlying molecular mechanisms of resistance and identifying rational combination therapeutic strategies have become the core focus of contemporary research in this field.

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