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KRAS G12C-Targeted Therapy Strategy for Lung Cancer: Mechanism, Clinical Practice and Challenges

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Abstract. Kirsten rat sarcoma viral oncogene homolog (KRAS) G12C mutations represent the most common driver alterations in non-small cell lung cancer and were long considered "undruggable" due to the lack of a suitable binding pocket on the protein surface. Recent structural breakthroughs have identified the Switch-II allosteric pocket, facilitating the development and clinical application of several covalent inhibitors—including Sotorasib, Adagrasib, and Divarasib—which have substantially improved outcomes for patients harboring this mutation. However, primary and acquired resistance remain major obstacles to long-term efficacy, with resistance mechanisms involving RTK-mediated adaptive signaling reactivation, aberrant PI3K–AKT–mTOR pathway activation, secondary genetic alterations, and other factors. Moreover, intratumoral heterogeneity, characterized by the coexistence of sensitive and resistant subclones, further complicates therapeutic responses. To overcome these challenges, combination strategies have become a major research focus, including the pairing of KRAS G12C inhibitors with immune checkpoint inhibitors, RTK-targeted agents, SHP2 inhibitors, or MEK inhibitors, aiming to block escape pathways and enhance antitumor immunity. Future directions emphasize optimizing combination regimens, exploring personalized immunotherapy, and developing next-generation inhibitors to prolong survival. This review systematically summarizes the molecular mechanisms driving KRAS G12C-mutant lung cancer, clinical applications of targeted drugs, resistance and heterogeneity challenges, and progress in combination therapy, providing a reference for clinical decision-making and further research in this field.

Keywords: KRAS G12C, Lung cancer, Mechanism, Clinical practice

1. Introduction

Pulmonary malignancy ranks as the leading fatal tumor condition across all global populations, which covers two primary pathological subgroups that carry distinct clinical traits, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [1]. Non-small cell lung cancer covers multiple histological subtypes which separate into glandular carcinoma, squamous cell carcinoma and giant cell carcinoma under pathological classification standards. Among all such tumor subtypes, lung adenocarcinoma holds the highest clinical prevalence rate which also presents the strongest correlation with abnormal gene alterations within the kirsten rat sarcoma viral oncogene homolog (KRAS) coding region.

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Clinical genomic screening which targets pulmonary tumor lesions regularly detects four core oncogenic driver mutations which include EGFR, ALK, c-ros oncogene 1 (ROS1) and KRAS as the top high-frequency mutated genetic markers in various lung tumor samples. Interestingly, mutation patterns vary between different patient populations: EGFR mutations are prevalent in Asian patients and KRAS mutations are prevalent in smokers and western patients. In addition to the significant epidemiological characteristics, KRAS mutations have different incidence rates under different pathological types, smoking history, race, gender, genetic background and tumor microenvironment (TME). Clinical analyses which assess disease duration without disease advancement and total lifespan length for patients who carry KRAS-mutated NSCLC was generated within a clinical trial which filters out all detected alterations related to epidermal growth factor receptor [2].

Current academic summaries which explore core tumor biomarkers will center on the specific KRAS G12C mutation that exists in multiple malignant tumor tissues. This unique mutational locus which features a uniform molecular exterior has for many years been classified as an untreatable molecular target that blocks pharmaceutical agents from achieving effective adhesion. The discovery of the unique Switch-II structural pocket has promoted the development of multiple targeted therapeutic agents which can form stable covalent connections with this key biological target, and mainstream targeted medications including Sotorasib, Adagrasib and Divarasib which exhibit prominent tumor-suppressing properties in practical clinical trials have gradually entered clinical application. Although some lung cancer patients with KRAS variations have shown positive clinical responses in the use of covalent inhibitors, there are still many challenges, such as drug resistance and other issues. These difficulties motivate the researchers to investigate the possibilities of more efficient control and elimination of tumor cells. Hence, the combination therapy has emerged as an ongoing trend today – combination of inhibitors of other signaling pathways with KRAS G12C inhibitors, and combination with monoclonal antibody in immunotherapy.

This article aims to systematically describe the mechanism, clinical application, tolerance mechanism of KRAS G12C inhibitors and the progress of combination therapy focusing on drug resistance. The goal is to continuously improve treatment options to offer patients with KRAS-mutated NSCLC improved chances of a cure and better quality of life.

2. KRAS gene-driven mechanisms of lung tumorigenesis

The rat sarcoma viral oncogene homolog, KRAS is the major subtype of rat sarcoma viral oncogene, RAS, which was originally identified in the 1960s [3]. KRAS is one of the most significant onco-drivers, especially in the case of non-small cell lung cancer (NSCLC) [1]. Mutations in KRAS are common in human malignant tumors, and are present in about 5% of lung adenocarcinomas (LUAD). There are also differences in the percentage of different types of cancer where KRAS mutations occur. Around 25% of NSCLC patients have KRAS mutations, most of which are in codons 12 and 13. The types of mutations are G12C, G12S, G13C, etc., G12C being the most common (40% of all KRAS mutations) [2]. The functional KRAS protein serves as a canonical molecular regulator which alternates dynamically between two distinct functional forms that attach to GTP molecules and GDP molecules respectively in biological environments. Specific protein molecules known as guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) which control the transformation of the two functional modes maintain the normal operation of this molecular regulatory mechanism. This core biological mechanism which modulates intracellular signal transmission can activate multiple tumor-promoting signal cascades which cover the typical MAPK and PI3K signaling axes inside human somatic cells [3, 4]. The

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G12C mutation results in the protein being permanently bound to GTP and constitutively active, causing uncontrolled growth of the cells [1].

Although the oncogenic mechanism of KRAS G12C is well understood, until recently it was considered "undruggable" [1]. This is attributed to two main reasons. Firstly, due to the absence of a hydrophobic pocket on the surface of the KRAS protein to which small-molecules can bind specifically; Second, for three decades of intensive study, no indirect approaches (blocking KRAS post-translational modification, blocking downstream effectors) have been proven clinically effective [1]. This deadlock for a long time prevented targeted treatments for lung cancer from developing.

3. KRAS-targeted therapy

3.1. Direct inhibitors targeting KRAS G12C

A major breakthrough in KRAS G12C-targeted therapy has resulted from recent advances, namely a major structural insight, which is the presence of a unique druggable pocket on the KRAS G12C protein, called the Switch-II pocket or P2 pocket, ideally suited for covalent small-molecule inhibition [1]. Such research progress which targets abnormal gene function has promoted the creation and clinical authorization of multiple targeted covalent therapeutic agents which act specifically on the KRAS G12C molecular subtype, which includes mainstream therapeutic candidates developed by major pharmaceutical enterprises such as Sotorasib (AMG 510/Lumakras), Adagrasib (MRTX849), and Divarasib [5-8]. The pharmacological working principles which guide these three targeted drugs have been fully validated through repeated biological verification, and these agents build stable covalent chemical connections with the cysteine-12 residue located within the Switch-II structural pocket of KRAS G12C which restricts the target protein to a silent GDP-coupled structural state that blocks the transmission of downstream biological signals and hinders the proliferative progression of tumor cells with gene mutations [5-7]. A large number of preclinical experimental explorations which focus on targeted tumor therapy have verified that Sotorasib and Adagrasib exert specific bioactive effects on cell strains that carry the KRAS G12C genetic variation while showing minimal pharmacological impacts on other cell lines with alternative KRAS gene alterations [1]. The most valuable clinical advantage which belongs to these two therapeutic agents lies in their stable metabolic characteristics inside human organisms which feature durable metabolic cycles and extensive tissue penetration capacity that support reliable and effective clinical treatment applications.

Sotorasib is an oral targeted drug, which irreversibly binds to KRAS G12C protein and inhibits the conduction of RAS/RAF signal pathway. The United States Food and Drug Administration issued official clinical approval for Sotorasib which targets adult patient populations that suffer from KRAS G12C-mutant NSCLC and have undergone prior systematic anti-tumor therapies [9]. Relevant clinical trial projects which enroll subjects with confirmed KRAS G12C genetic aberrations adopt standardized oral administration regimens of Sotorasib to observe therapeutic efficacy and clinical safety for refractory lung cancer cases. Key observational indicators which belong to the phase II clinical research system include core therapeutic response levels and long-term survival outcomes that reflect the drug's clinical application value for targeted tumor intervention. Multiple survival and response evaluation parameters which cover core clinical measurement dimensions can effectively prove the stable therapeutic efficacy of this targeted agent in managing advanced KRAS G12C-driven lung malignancy. But in total, 121 patients experienced adverse events related to Sotorasib treatment (TRAEs). Of them, 34 cases were grade 3, 2 cases

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were grade 4 and there were no fatal cases [3]. Additionally, preclinical data have also suggested that Sotorasib can modify the tumor microenvironment (TME) by establishing a pro-inflammatory microenvironment and promoting infiltration of T-cells, showing synergies in anti-tumour activity when combined with immune checkpoint inhibitors and suggesting new opportunities for combination therapy.

Adagrasib was granted FDA Breakthrough Therapy Designation for the same indication. In the realm of targeted oncology, the KRAS G12C variant represents a common driver in lung adenocarcinoma. Among patients who have non-small-cell lung cancer and who possess that specific mutation, the therapeutic agent named Adagrasib has undergone clinical evaluation in several phases. The first set of data, which came from a combined Phase I and Phase II project that was organized into two separate parts, enrolled a certain quantity of subjects whose tumors were measurable and whose responses could be reliably judged. From that preliminary research, the proportions of cases that achieved partial shrinkage and that remained stable were derived, and these proportions were documented together with the bibliographic notes [10, 11]. A rate of 94% of patients treated with Adagrasib had a TRAE of some type, with 47% being grade 3 or higher. Moreover, Adagrasib has shown exemplary efficacy in preventing metastasis of brain cancers. Clinical data which originate from the KRYSTAL-1 research trial reveal that Adagrasib possesses powerful transmembrane permeability which allows therapeutic molecules to cross the complete blood-brain barrier structure and generate effective tumor-inhibiting activities within human central nervous system tissues. Such unique pharmacological properties which distinguish this targeted medication from common anti-cancer drugs fully illustrate the core clinical value of Adagrasib for routine lung cancer management which further highlights its promising clinical prospects for patient groups which suffer from malignant tumor brain metastasis complications.

Divarasib (GDC-6036) is another oral drug that targets KRAS G12C and is able to bind irreversibly to the mutated cysteine residue to inhibit the signal pathway by locking KRAS G12C protein in an inactive state [12]. On April 1, 2024, 65 advanced KRAS G12C+ NSCLC patients were taking Divarasib (50-400 mg) once daily. In all patients, it revealed an ORR of 55.6%, mDOR of 18 months and mPFS of 13.8 months [12]. In terms of safety, 94% of patients had at least one TRAE with 17% of patients having grade 3 to 4 TRAEs, such as diarrhoea and vomiting.

3.2. Application of ICIs in KRAS mutant NSCLC

Immune checkpoint inhibitors (ICIs) represent a class of novel anti-tumor pharmaceuticals which activate human immune defense functions by blocking specific immune checkpoint molecular pathways that limit endogenous immune responses. These mainstream immunotherapeutic agents which serve as core clinical treatment options for multiple malignancies primarily target two key immune regulatory molecules which include programmed cell death protein 1 and programmed cell death ligand 1 (PD-L1) within human immune microenvironments. Drugs include Pembrolizumab, Ipilimumab, and Atezolizumab, with Ipilimumab being a drug that targets the pathway of the cytotoxic T-lymphocyte-associated antigen pathway [2].

If KRAS is mutated, the pathway (RAF-MEK-ERK) is activated and leads to an increase in the translation of PD-L1. Patients with NSCLC have a direct correlation between the expression of PD-L1 and KRAS mutation [4]. The antigen recognition by T cells leads to the production of IFN which causes tumor cells to express PD-L1 in high levels. The PD-L1 biomarker which appears on the outer membrane of malignant tumor cells can interact with the PD-1 molecule which locates on the exterior layer of T lymphocytes to transmit suppressive biological signals within immune circulation. This immune regulatory process which interferes with normal lymphocyte functions can

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hinder the clonal expansion of T lymphocytes, lower the release level of immune cytokines, and weaken the immune clearance capacity which targets malignant tumor lesions in human bodies. Immune checkpoint inhibitors (ICIs) can restore the anti-tumor immune function which gets suppressed by negative immune regulation through interfering with the mutual combination process of PD-L1 and its corresponding receptors [2].

In real-world clinical treatment which focus on targeted immunotherapy for lung malignancies, patient groups which carry the specific KRAS G12C genetic variation can achieve superior therapeutic reactivity toward ICI-based immunotherapies when compared with populations that harbor alternative KRAS mutation subtypes. Relevant clinical statistical analyses which evaluate long-term survival benefits can confirm obvious statistical disparities in overall survival outcomes between these distinct patient subgroups during standardized clinical intervention [2].

3.3. Combination therapy

3.3.1. Combination with immunotherapy

Targeted therapeutic agents combined with immune checkpoint inhibitors represent an emerging clinical strategy of combined immunotherapy which two mainstream targeted drugs are matched with different PD-1 or PD-L1 inhibitors to carry out clinical explorations. These clinical follow-up data observe the tumor remission status, long-term survival outcomes and safety tolerance performance of each combined administration regimen which confirm the considerable anti-tumor benefits delivered by such combined treatment modes [3].

Table 1. Comparison of clinical characteristics of direct inhibitors of KRAS G12C

Inhibitors	Mechanism	Key efficacy indicators	TRAEs	Ref.
Sotorasib	Irreversibly bind CYS-12 in the Switch-II pocket, lock KRAS G12C in the inactive GDP-bound state, and block the RAS/RAF signaling pathway	Objective response rate 41%. Median duration of response 12.3 months. Median progression-free survival 6.3 months. Median overall survival 12.5 months. 2-year survival rate 33% in overall	The incidence of Treatment-Related Adverse Events (TRAEs) of any grade was relatively high (121/174 cases reported), including 34 cases of grade 3 and 2 cases of grade 4, with no fatal incidents	[11]
Adagrasib	Covalently binds to CYS-12 of KRAS G12C, locking it in the inactive GDP-bound state and suppressing downstream signals; It can penetrate the blood-brain barrier	Partial response rate 45% (stage I/II). Disease stability rate 51%. Median progression-free survival in the Phase III trial 5.49 months, Objective response rate 31.9%. Effective for brain metastases	The incidence rate of TRAEs at any level is 94%, among which grade ≥3 accounts for 47%. Common symptoms include nausea, diarrhea and elevated ALT	[6,12]
Divarasib	Irreversibly bind the mutant cysteine residue, lock KRAS G12C in an inactive state, and block the signaling pathway	Objective response rate 55.6%. Median duration of response 18 months. Median progression-free survival 13.8 months	The incidence rate of TRAEs at any level is 94%, among which grades 3-4 account for 17%. The main symptoms are diarrhea and vomiting	[12]

Various grades of treatment-related adverse events maintain relatively high occurrence rates which some severe adverse responses will force partial subjects to stop the whole set of combined medication plans (Table 1). The combined regimen of Divarasib matched with Pembrolizumab is undergoing verification inside a large phase III controlled clinical trial which stratifies participants based on multiple clinical features to compare two intervention modes including targeted

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immunotherapy and chemoimmunotherapy. This targeted inhibitor shows favorable anti-tumor effects and medication safety in its previous clinical applications which this trial screens the optimal combined treatment strategy without chemotherapy and with better overall tolerance for relevant patients [12].

3.3.2. Combination with RTK-targeted therapy

As KRAS inhibitors inhibit KRAS protein that locks it in GDP-bound inactive state, it is easy to bypass the inhibition by activating tyrosine kinase receptors (RTKs). Moreover, KRAS G12C inhibition results in strong rebound of phospho-ERK. This type of drug resistance mechanism is called primary drug resistance and also the reason for the poor responses of KRAS G12C-mutated NSCLC [3]. Afatinib acts as a targeted kinase inhibitor which can block signal pathways related to epidermal growth factor receptors inside human tumor cells. This pharmaceutical agent can be matched with KRAS-targeted preparations for the treatment of lung cancer populations that carry corresponding gene mutations. The combined administration regimen tends to trigger digestive tract related adverse reactions which partial users will terminate the whole treatment due to severe intestinal discomfort. Controlled observations are conducted under groups with distinct dosing ratios which compare the differences in tumor remission effects brought by various dose combinations.

3.3.3. Combination with an SHP2-targeted therapy

SHP2 is a protein upstream of RTK and KRAS, an essential phosphatase to activate RAS. Suppression of KRAS G12C causes drug resistance to be bypassed through activation of RAS signaling by upstream RTK via SHP2. But, when SHP2 is inhibited, the upstream feedback loop is prevented, and KRAS G12C inhibitors are effective. The phase Ib clinical research named KontRASt-01 carries out combined medication exploration which matches SHP2 targeted inhibitors with KRAS G12C inhibitors for enrolled patients carrying corresponding gene mutations. The enrolled population includes patients diagnosed with non-small cell lung cancer which are divided into subgroups according to previous medication history for comparative efficacy analysis. This combined treatment regimen induces adverse reactions related to blood cells and peripheral tissues which granulocyte reduction ranks as the most prominent type among all severe adverse events [3].

3.3.4. Combination with an MEK-targeted therapy

MEK is a downstream effector of the RAS-RAF-MEK-ERK pathway. However, KRAS G12C inhibitors only transiently suppress ERK activity and within 24 hours. There is rapid rebound, causing primary resistance. Combined MEK inhibition maintains pathway suppression. The sub-cohort research of CodeBreak 101 carries out efficacy observation which combines MEK pathway inhibitors with KRAS G12C targeted drugs for solid tumor populations with prior systematic treatment history. The lung cancer subgroups show distinct tumor remission performances which are divided according to the previous application of targeted KRAS G12C inhibitors. This combined therapeutic approach easily triggers adverse reactions of digestive tract and skin types which partial severe toxic responses will force some participants to discontinue the whole combined medication regimen [3].

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4. Main challenges: resistance and heterogeneity

4.1. Drug resistance

Although KRAS G12C inhibitors have shown good clinical activity, intrinsic or acquired resistance is unavoidable, and is the primary limitation of prolonged clinical benefit [4]. Various preclinical explorations and clinical researches clarify the diverse and complicated drug resistance mechanisms of KRAS G12C targeted agents which divide all relevant pathological pathways into three core categories for systematic classification.

• RTK-mediated adaptive activation of KRAS G12C: Aberrant activation of RTKs (such as EGFR, Aurora Kinase A (AURKA) or other members of the RTK family) can activate newly synthesized KRAS G12C protein or wild-type RAS isoforms to their active GTP-bound state to evade the blockade of inhibitors [8]. Importantly, increased GDP-GTP exchange is a direct downstream effect of many RTKs mediated by PTPN11/SHP2, which is a major downstream effector of many RTKs and is directly and centrally involved in this adaptive resistance.

• The PI3K-AKT-mTOR pathway is a known pathway of Sotorasib resistance as oncogenic signaling can be re-routed through other pathways (including epithelial–mesenchymal transition (EMT)). More importantly, when EMT occurs, either PI3K or ERK signaling gets activated in a cell-type dependent manner, which results in resistance to Sotorasib and ARS1620, another KRAS G12C inhibitor [8].

• Acquired Genetic Alterations: Secondary mutations in the KRAS gene (Y96D/C/S, G12D/R/V etc.) directly modify the structure of the Switch-II pocket, making the binding of inhibitor impossible [11]. Other hereditary events that also can result in resistance include amplification or mutation of the KRAS G12C gene, amplification or mutation of bypass oncogenes (e.g., MET), and gene fusions (e.g., ALK), and mutations in the KEAP1/NFE2L2 pathway.

4.2. Tumor heterogeneity

Intratumoral heterogeneity acts as the key root that leads to the drug resistance manifestations of targeted KRAS G12C therapeutic agents [4]. Relevant cellular sequencing analyses verify the existence of multiple cell subpopulations with differentiated traits inside tumor tissues which these cell groups can dominate the adaptive drug resistance responses generated toward targeted pharmaceutical preparations. Intra-tumoral heterogeneity means that within the tumor microenvironment, there are drug sensitive and drug resistant subclones. In the presence of KRAS G12C inhibitors, the sensitive clones are eradicated and the resistant subclones quickly become the predominant population and clinical progression occurs [4].

It is well supported by the clinical evidence. Within 38 patients treated with Adagrasib monotherapy, 45% of patients developed detectable resistance mechanisms, with 18% of patients having multiple, overlapping genetic changes. This discovery is indicative of the great heterogeneity in the evolution of resistance [11].

5. Conclusion

G12C site mutations are the most common mutations in KRAS-mutated NSCLC, making it the most prevalent type of lung cancer in all lung cancer types, particularly in smokers. In the early years the G12C site was considered "undruggable" because of its smooth surface. As basic and therapeutic

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research areas for KRAS-mutant NSCLC have developed, the Switch-II site has been found, which offers covalently binding sites. This promoted the advent of covalent inhibitors such as Sotorasib.

However, cancer cells can become primary drug-resistant, because they activate other signaling pathways which makes the inhibitors ineffective. Thus, combination therapy has become the main direction of research for the treatment of KRAS-mutated NSCLC. The article expands on that, explanation of how combination therapy is being explored to prevent other bypass pathways so that the effect of KRAS G12C inhibitors can be seen. A large number of clinical explorations carry out combined treatment designs which match KRAS G12C targeted preparations with therapeutic agents acting on upstream, downstream and collateral signaling pathways of core tumor cascades. These research schemes can also cooperate with monoclonal antibodies which build diversified combined intervention modes based on tumor immunotherapy principles.

Various combination therapies are available which have varying effects on individuals with different stages of the disease; all have had positive clinical outcomes. The next step in future research is towards specific immunotherapy for KRAS mutations in combination with ICIs and targeted therapy for increasing the life expectancy of patients with KRAS-mutated NSCLC. To conclude, more detailed studies into the role of immunotherapy in KRAS mutated NSCLC are likely to bring hope and a better future to patients.

References

[1] Liu, J., Kang, R., & Tang, D.-L. (2022). The KRAS-G12C inhibitor: Activity and resistance. *Cancer Gene Therapy, 29*(7), 875–878.

[2] Yang, X.-Y., Tang, Z.-W., & Ma, L. (2025). Advances in immunotherapy of KRAS-mutated non-small cell lung cancer. *Chinese Journal of Lung Cancer, 28*(5), 343–352.

[3] Miyashita, H., Kato, S., & Hong, D. S. (2024). KRAS G12C inhibitor combination therapies: Current evidence and challenge. *Frontiers in Oncology, 14*, 1380584.

[4] Tansou, R., Kubo, T., & Nishida, H. (2025). Lipid-siRNA conjugates targeting high PD-L1 expression as potential novel immune checkpoint inhibitors. *Biomolecules, 15*(2), 293.

[5] Saleh, K., Kordahi, M., Felefly, T., Kourie, H. R., & Khalife, N. (2021). KRAS-targeted therapies in advanced solid cancers: Drug the undruggable? *Pharmacogenomics, 22*, 587–590.

[6] Moore, A. R., Rosenberg, S. C., McCormick, F., & Malek, S. (2020). RAS-targeted therapies: Is the undruggable drugged? *Nature Reviews Drug Discovery, 19*, 533–552.

[7] Fell, J. B., Fischer, J. P., Baer, B. R., Blake, J. F., Bouhana, K., & Briere, D. M. (2020). Identification of the clinical development candidate MRTX849, a covalent KRAS(G12C) inhibitor for the treatment of cancer. *Journal of Medicinal Chemistry, 63*, 6679-6693.

[8] Dunnett-Kane, V., Nicola, P., Blackhall, F., & Lindsay, C. (2021). Mechanisms of resistance to KRAS(G12C) inhibitors. *Cancers, 13*, 151.

[9] Hong, D. S., Fakih, M. G., Strickler, J. H., Desai, J., Durm, G. A., & Shapiro, G. I. (2020). KRAS(G12C) inhibition with sotorasib in advanced solid tumors. *New England Journal of Medicine, 383*, 1207-1217.

[10] Skoulidis, F., Li, B.-T., Dy, G. K., Price, T. J., Falchook, G. S., & Wolf, J. (2021). Sotorasib for lung cancers with KRAS p.G12C mutation. *New England Journal of Medicine, 384*, 2371-2381.

[11] Shiravand, Y., Khodadadi, F., & Kashani, S. M. A. (2022). Immune checkpoint inhibitors in cancer therapy. *Current Oncology, 29*(5), 3044-3060.

[12] Liu, Y., Huang, Z., Chen, L.-L., & Song, Q.-B. (2025). Therapeutic progress in advanced KRAS G12C-mutant non-small cell lung cancer. *Cancer Research on Prevention and Treatment, 52*(12), 1012-1020.