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KRAS mutations in non-small cell lung cancer: Translational aspects, current therapies and challenges for future research

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ABSTRACT

Mutations in the *KRAS* gene are prominent oncogenic drivers in non-small cell lung cancer (NSCLC), with multiple pathophysiological, clinical and prognostic implications. Although historically considered an "undruggable" target, recent research led to the development of specific *KRAS-G12C* inhibitors, like sotorasib and adagrasib which are currently approved for clinical use in patients affected by advanced NSCLC. However, the clinical utility of these drugs is often limited by resistance development through several biological mechanisms, including additional *KRAS* mutations, activation of compensatory pathways and metabolic reprogramming. In addition, the immunosuppressive tumor microenvironment (TME) in *KRAS*-mutant NSCLC reduces the efficacy of immune checkpoint inhibitors (ICIs), further complicating treatment and clinical outcomes. Combination therapy with *KRAS* inhibitors, ICIs, and other agents appears currently as an attractive option for overcoming resistance and improving survival in these patients. This review provides a detailed overview of *KRAS* genetic alterations in NSCLC, focusing on the involved molecular pathways, current and potential targeted therapies, challenges related to tumor heterogeneity, as well as ongoing research and future perspectives. In addition, the role of TME in generating treatment resistance is discussed, along with emerging therapeutic options that target non-*G12C KRAS* mutations or combine different pharmacological approaches to disrupt both oncogenic signaling and immune evasion.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, causing approximately 1.8 million deaths annually (Thandra et al., 2021). Despite advancements in screening, diagnosis, surgical techniques, targeted therapies, and immunotherapy, the overall 5-year survival rate for NSCLC remains under 25 %, mainly because of delays in early diagnosis and intrinsic treatment difficulties or acquired resistance after treatment initiation (Thandra et al., 2021; Paliogiannis et al., 2013; Araghi et al., 2023; Xiang et al., 2024). From a histological point of view, lung cancer is divided in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). According to the current World Health Organization (WHO) classification, NSCLC encompasses various histological subtypes, with adenocarcinoma being the most prevalent, particularly among non-smokers, followed by squamous cell carcinoma and large cell carcinoma (Thandra et al., 2021; Zhang et al., 2023). Profound intrinsic biological diversities across NSCLC histotypes cause consistent difficulties in both treatment decision-making and clinical management of NSCLC patients. Recent genomic profiling investigations, especially those from The Cancer Genome Atlas (TCGA) and other large-scale sequencing efforts, highlighted the underlying molecular complexity of NSCLC (Restrepo et al., 2023). These investigations discovered multiple actionable driver alterations, including mutations or fusions in *EGFR*, *BRAF*, *KRAS*, *ALK*, *ROS1*, *MET*, *RET* and *NTRK* genes, each of which contributes to various carcinogenic pathways (Fois et al., 2021; Friedlaender et al., 2024). The discovery of these

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biomarkers changed profoundly the approach to NSCLC treatment, as it led to the development of targeted therapies that have significantly improved clinical outcomes in NSCLC. In addition, novel immunotherapy agents, called immune checkpoint inhibitors (ICIs), added further improvements in survival outcomes in non – oncogene addicted cases (Putzu et al., 2023).

Among the clinically impacting driver genetic alterations, *KRAS* mutations are encountered in approximately 25–30 % of lung adenocarcinomas and were initially proven to be a challenging therapeutic target as they were resistant to targeted therapies (Fois et al., 2021; Santarpia et al., 2023). Indeed, *KRAS* has been labeled as an "undruggable" target for years, because of the lack of well-defined binding sites on the encoded protein surface, the high affinity for GTP, and the picomolar cell concentrations. In recent years, these issues were surmounted with the development of selective small-molecule inhibitors targeting the *KRAS-G12C* mutation, like sotorasib and adagrasib, adding new therapeutic options against NSCLC in clinical practice (Huang et al., 2021; Rathod et al., 2023). Nevertheless, the long-term efficacy of these drugs is tempered by early establishment of resistance mechanisms in majority of cases, thus reducing their curative potential. Therefore, even if KRAS-G12C inhibitors determined a substantial therapeutic achievement, additional research is essential to improve their clinical performance, overcome resistance, and explore new treatment strategies that could further improve survival outcomes in *KRAS*-mutant NSCLC.

This review provides a detailed overview of *KRAS* genetic alterations in NSCLC, focusing on the involved molecular pathways, current and potential targeted therapies, challenges related to tumor heterogeneity, as well as ongoing research and future perspectives. In addition, the role of tumor microenvironment (TME) in generating treatment resistance is discussed, along with emerging therapeutic options that combine different pharmacological approaches to disrupt both oncogenic signaling and immune evasion.

2. KRAS gene and main molecular pathways

2.1. *KRAS gene and protein*

The *KRAS* gene is a member of the RAS family of oncogenes and plays critical roles in several signal transduction pathways, regulating cellular growth, differentiation, and survival. *KRAS* is located on chromosome 12p12.1 and encodes a small GTPase that operates as a molecular switch, alternating between an inactive GDP-bound and an active GTP-bound state (Huang et al., 2021). This mechanism is crucial for the regulation of cell proliferation, survival, and differentiation, via

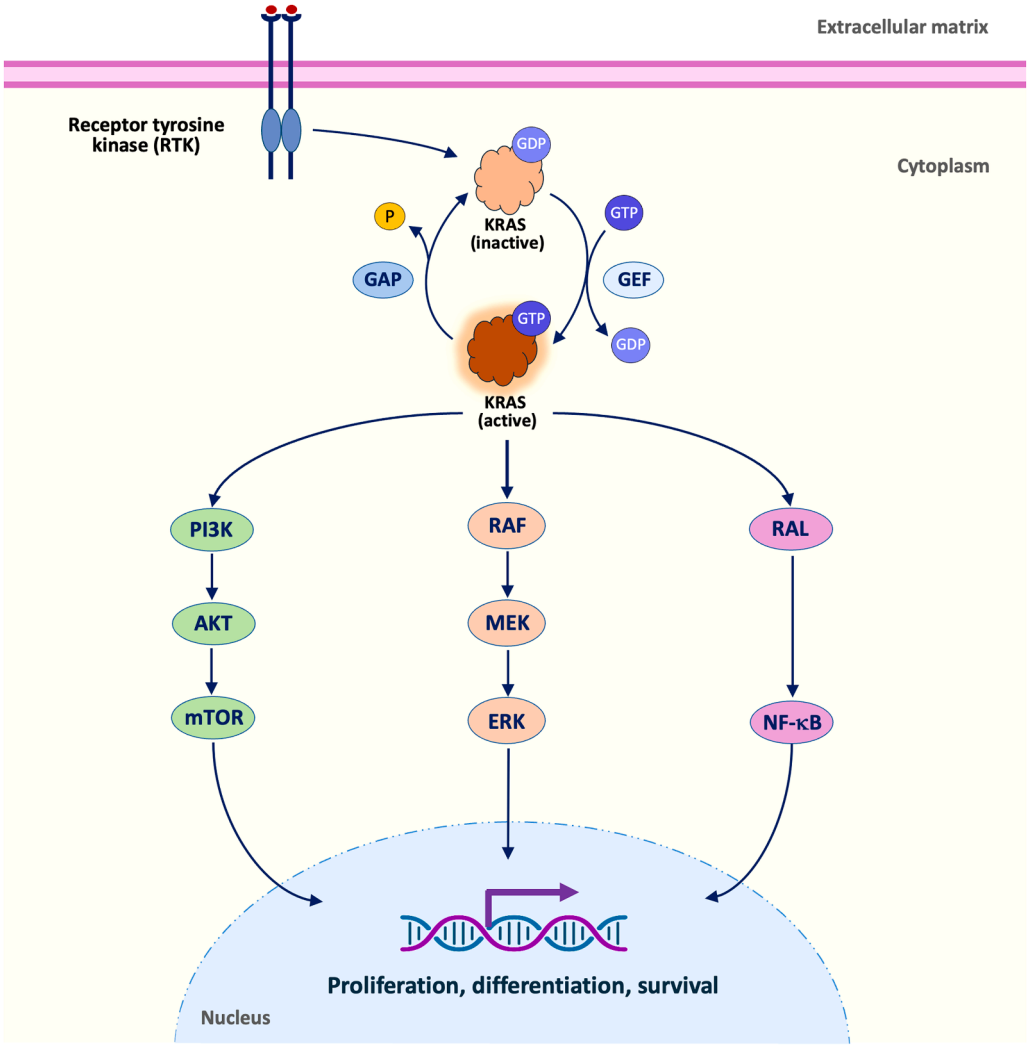

Fig. 1. KRAS activation cycle and downstream signaling pathways. The figure illustrates KRAS cycling between an inactive GDP-bound state and an active GTP-bound state, regulated by GEFs and GAPs. Upon activation by a receptor tyrosine kinase (RTK), active KRAS triggers key signaling pathways - including PI3K-AKT-mTOR, RAF-MEK-ERK, and RAL-NF-κB - leading to cellular processes like proliferation, differentiation, and survival. GAP, GTPase-activating proteins; GEF, guanine nucleotide exchange factors; GDP, guanosine diphosphate; GTP, guanosine triphosphate; RAL, RAS-like proteins.

different signaling pathways (Li et al. 2022b). Under physiological conditions, KRAS activity is strictly controlled by guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs), ensuring that KRAS alternates between its active and inactive states to guarantee cellular homeostasis (Huang et al., 2021) (Fig. 1). *KRAS* mutations lead to the constitutive activation of the encoded protein, which in turn induces oncogenesis by increasing downstream signaling cascades such as the RAF-MEK-ERK and PI3K-AKT-mTOR pathways (Ferreira et al., 2022). As shown in Fig. 1, activated KRAS in turn can also activate RAL proteins, which are small GTPases that have been implicated in the control of cell proliferation and reported to contribute to the RAS-mediated oncogenic transformation (Wolthuis et al., 1998). Analogously to RAS proteins, RAL proteins become biologically active upon change of their status from GDP-bound to GTP-bound and act as important mediators of RAS-induced proliferative signals (Henry et al., 2000). Activated RAL induces the oncogenic activation of NF-kB which is an important pleiotropic transcription factor; upon activation, NF-kB can enhance the transcription of a wide variety of genes, including those involved in the control of cell proliferation and, mostly, in the regulation of apoptotic processes underlying cell survival among different tumor types (Palmieri et al., 2009).

These molecular pathways are crucial for cell proliferation and survival, and their dysregulation leads to the aggressive biological and clinical behavior of *KRAS*-mutant tumors. For this reason, *KRAS* mutations have been commonly associated with poor prognosis, though the clinical outcome may vary according to the different treatments (standard chemotherapy, immune checkpoint inhibitors, and targeted therapies) patients undergo (Fois et al., 2021; Santarpia et al., 2023; Li et al., 2022a).

KRAS is frequently mutated in several human cancers, especially in NSCLC, pancreatic ductal adenocarcinoma (PDAC), and colorectal cancer (CRC) (Fois et al., 2021; Palomba et al., 2016a; Luo, 2021; Sini et al., 2024). In NSCLC, *KRAS* is mutated in about one fourth of adenocarcinomas, whereas prevalence of the other most frequent oncogenic driver alterations has been reported as follows: EGFR (about 15 % in Western countries), ALK (5 %), MET (3 %), BRAF (3 %), ROS1 (2 %), HER2 (2 %), RET (2 %), PIK3CA (2 %), and NTRK1 (1 %) (Pakkala and Ramalingam, 2018; Otano et al., 2023).

The *KRAS-G12C* mutation is common in NSCLC (up to 15 % of cases), while the *G12D* mutation is more common in CRC and PDAC (Colombino et al., 2019; Fois et al., 2021; Palomba et al., 2016b; Luo, 2021; Sini et al., 2024). Overall, about two fifths of *KRAS*-mutant lung adenocarcinomas are represented by the *KRAS-G12C* variant; the other most frequent oncogenic *KRAS* mutations are *G12D* (about 18 %) and *G12V* (15 %) (Pakkala and Ramalingam, 2018; Otano et al., 2023).

Codon 12 mutations are the most prevalent in NSCLC and are

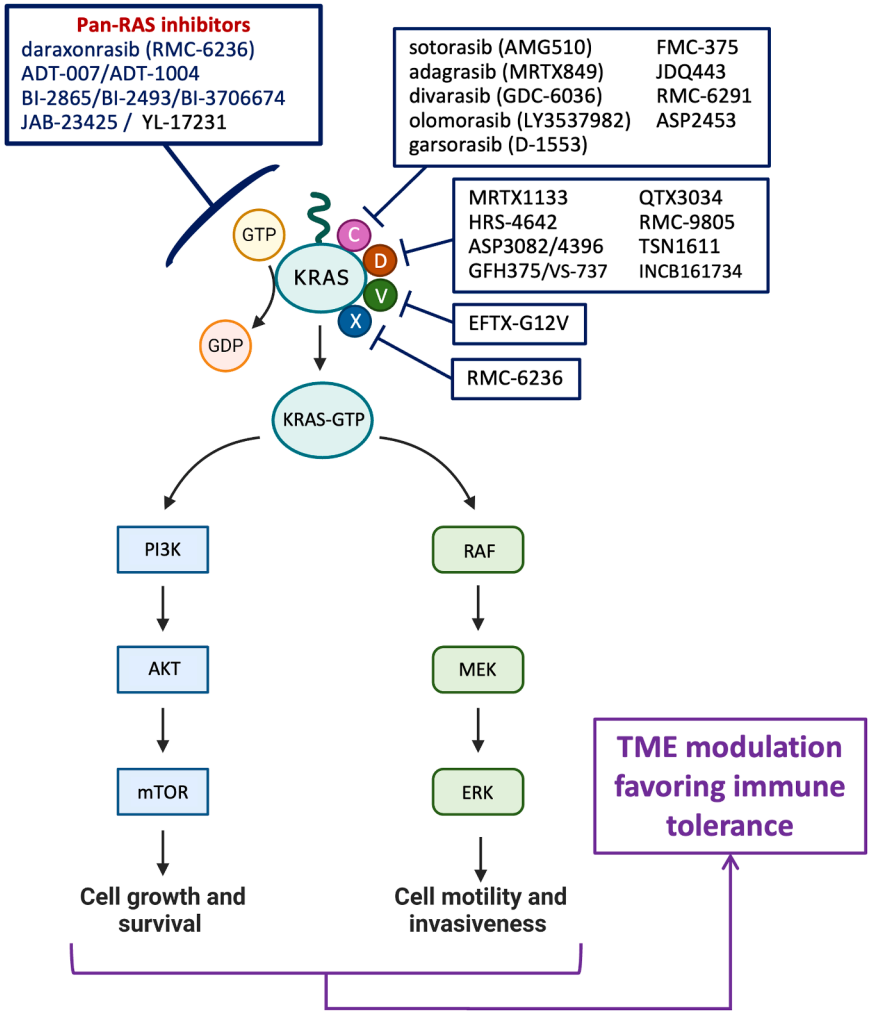

Fig. 2. KRAS-driven pathways and KRAS-mutant inhibitors. The figure shows RAS activation through GTP binding, leading to the downstream signaling of two major pathways: the PI3K-AKT pathway, which promotes cell growth and survival, and the RAF-MEK-ERK pathway, which drives cell motility and invasiveness. RAS activation is regulated by the exchange of GDP for GTP, transitioning it into an active state that triggers these critical cellular processes. Effect of *KRAS* activation on tumor microenvironment (TME) is reported. KRAS inhibitors specific for the main mutations (G12C, G12D, G12V, and G12 regardless the amino acid change) are listed.

associated with specific biological characteristics; the *KRAS-G12C* is linked to smoking-related lung cancers with distinct biochemical properties, such as selective activation of the RAL-GEF pathway and lower PI3K-AKT activity in comparison to other variants (Tang et al., 2024; Addeo et al., 2021).

2.2. RAF-MEK-ERK pathway

The RAF-MEK-ERK pathway, also referred to as the mitogen-activated protein kinase (MAPK) signaling cascade, is a critical downstream pathway of KRAS, playing a pivotal role in regulating cell proliferation, differentiation, and survival (McCubrey et al., 2007) The pathway is activated when KRAS, in its GTP-bound state, directly interacts with the RAF family of kinases (ARAF, BRAF, and CRAF/RAF1) (Simanshu and Morrison, 2022). This interaction triggers the phosphorylation and activation of RAF kinases, which promote a sequential phosphorylation of downstream MEK1/2 and subsequently ERK1/2 into the cascade (Fig. 2) (Wu and Park, 2015; Zhao and Luo, 2022). Once activated, ERK translocates to the nucleus, where it phosphorylates and regulates various transcription factors, ultimately controlling the expression of genes involved in cell cycle progression, growth, and differentiation (Mebratu and Tesfaigzi, 2009). Dysregulation of this pathway through *KRAS* mutations leads to constitutive signaling and oncogenesis. Chronic ERK activation also promotes cell motility and invasiveness, enhancing the metastatic potential of *KRAS*-mutant tumors.

Given its focal involvement in *KRAS*-driven oncogenesis, the RAF-MEK-ERK pathway has been a major target for drug development (Song Y et al., 2022). MEK inhibitors - such as cobimetinib, trametinib and binimetinib - have been designed to block the pathway at the MEK level, therefore blocking ERK activation (Gonzalez-Del Pino et al., 2021). These inhibitors provided survival benefits in cancers with *BRAF* mutations, but their impact in *KRAS*-mutant tumors is limited due to compensatory mechanisms and the activation of parallel pathways, such as PI3K-AKT-mTOR (Kun et al., 2021; Rittler et al., 2020). Resistance to MEK inhibitors in *KRAS*-mutant tumors is typically reported due to the activation of upstream or downstream components of the pathway. For example, feedback reactivation of RAF or mutations in ERK can sustain signaling even while MEK is suppressed (Yaeger and Corcoran, 2019). Additionally, activation of alternative receptor tyrosine kinases (RTKs), such as EGFR or MET, can overcome the blocking of the RAF-MEK-ERK pathway, allowing cancer cells to sustain proliferative signaling (Song Y et al., 2022; Song KW et al., 2022). To address these issues, combination treatments targeting both the RAF-MEK-ERK pathway and other critical survival pathways have been proposed and will be discussed later.

2.3. PI3K-AKT-mTOR pathway

Another key signaling transduction cascade influenced by *KRAS* mutations is the PI3K-AKT-mTOR pathway, which regulates cell growth, metabolism, and survival (Fig. 2). This pathway is triggered when KRAS activates phosphoinositide 3-kinase (PI3K), a lipid kinase that phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3) (Akinleye et al., 2013; He et al., 2021). The creation of PIP3 serves as a docking site for AKT (also known as protein kinase B), allowing its phosphorylation by phosphoinositide-dependent kinase-1 (PDK1) (Akinleye et al., 2013). Once phosphorylated and fully active, AKT orchestrates multiple downstream processes; among others, the most significant targets of AKT are the mTOR (mechanistic target of rapamycin) complexes, which plays a vital role in regulating cellular survival, cell proliferation, and metabolism (Saxton and Sabatini, 2017). In details, mTOR exists in two distinct complexes, mTORC1 and mTORC2, both of which are important for maintaining cellular growth through distinct downstream effects: mTORC1 is important for controlling protein synthesis by activating S6 kinase and inhibiting 4EBP1, which enhances the translation of mRNA, while mTORC2 governs cell survival and metabolism through AKT feedback loops (Kim et al., 2017).

In the setting of *KRAS*-mutant cancers, mutations lead to continuing activation of PI3K, promoting persistent AKT and mTOR signaling, enabling uncontrolled cell proliferation, inhibition of apoptosis, along with enhanced metabolic activity. Aberrant signaling through this pathway not only fuels tumor formation but also promotes metabolic alterations that allow cancer cells to thrive under nutrient-limited circumstances, further improving tumor aggressiveness. The PI3K-AKT-mTOR pathway also plays a vital role in maintaining cellular survival by inhibiting apoptotic events. Activated AKT phosphorylates and inactivates pro-apoptotic proteins, such as BAD and caspase-9 (Kim et al., 2001; Zhang et al., 2011). By suppressing apoptosis, *KRAS*-mutant tumors can escape the programmed cell death and continue to grow despite cellular damage or extracellular anti-proliferation stimuli (Ferreira et al., 2022; Ash et al., 2024).

Several PI3K inhibitors, like alpelisib and buparlisib, and mTOR inhibitors, like everolimus and rapamycin, have been developed to interrupt this signaling cascade (Curigliano et al., 2021; Ye et al., 2023). Recently, new drugs have been demonstrated to be active in inhibiting the PI3K-AKT-mTOR cascade: *a*) inavolisib, a selective oral inhibitor of the PIK3CA-encoded p110α protein that is also capable of promoting the degradation of mutated p110α, thus inducing a more prolonged inhibition of the PI3K-dependent pathway (Song KW et al., 2022; Song Y et al., 2022; Hanan et al., 2022; Jhaveri et al., 2025); b) capivasertib is an oral small molecule that inhibits all three AKT isoforms, promoting the dephosphorylation of the downstream effectors into the pathway in preclinical models (Davies et al., 2012) and among breast cancer patients carrying an altered AKT pathway (inactivating PTEN deletions, activating PIK3CA or AKT mutations) (Turner et al., 2023); c) ipatasertib, a highly selective inhibitor targeting mutated AKT1 in different types of cancer (McCourt et al., 2025).

However, as observed for the RAF-MEK-ERK system, malignancies can develop resistance to inhibitors of the PI3K-AKT-mTOR pathway through feedback loops or compensatory activation of parallel pathways. For instance, reduction of mTORC1 often leads to the activation of PI3K through feedback, which reactivates AKT signaling, decreasing the efficiency of mTOR inhibitors in the long term (Rozengurt et al., 2014; Carracedo et al., 2008). This system is intimately interlaced with other signaling networks, including the RAF-MEK-ERK pathway. There is an extensive interaction between these two pathways, and their mutual activation in *KRAS*-mutant tumors contributes to treatment resistance. The suppression of one route may result in compensatory activation of the other, necessitating combination therapies that target both the PI3K-AKT-mTOR and RAF-MEK-ERK pathways to prevent tumor cells from adapting to single-agent treatments (Li et al., 2022b; Steelman et al., 2011). The interplay between these pathways highlights again the need for combination treatments that can target multiple points within the signaling network.

2.4. Interplay between intracellular alterations and extracellular modifications

The main molecular alterations activating the canonical signaling transduction cascades controlling tumor cell proliferation and survival (MAPK and PIK-AKT pathways) have been demonstrated to modulate the tumor microenvironment (TME) mostly toward a tumor immune tolerance in different tumor types (Sumimoto et al., 2006; Akbay et al., 2013; Avery et al., 2022; Palmieri et al., 2015). The TME in NSCLC carrying *EGFR* mutations has been demonstrated to present a markedly reduced content of tumor-infiltrating lymphocytes (TILs) - mostly due to a combination of lack of T-cell activating interferon-gamma (IFN) signature, low expression levels of chemokines involved in T cell attraction, and increased expression of CD73, which in turn increases conversion of AMP to immunosuppressive adenosine - and increased activity of suppressive regulatory T cells (Tregs) (Akbay et al., 2013;

Madeddu et al., 2022).

Overall, *EGFR* mutations are associated with immunosuppressive TME with limited T cell infiltration, low tumor mutation burden (TMB), and low PD-L1 expression, promoting cancer immune escape (Madeddu et al., 2022; Otano et al., 2023). In lung adenocarcinomas, two additional oncogene-associated changes have been reported to affect the TME immune status (Vesely et al., 2011; Otano et al., 2023). *KRAS* and *TP53* co-mutations are associated with high TMB, intermediate-to-high PD-L1 expression, and abundant T cell infiltration, promoting an inflamed status of TME (high IFN levels, preponderance of stimuli activating the immune system). *KRAS* and *STK11* and/or *KEAP1* co-mutations are associated with a high TMB and low-to-intermediate PD-L1 expression, but a low density of tumor-infiltrating T cells, poor secretion of pro-inflammatory chemokines and cytokines (including IFN-dependent effectors), enrichment of immunosuppressive factors, and recruitment of immunosuppressive cells such as T-regs and myeloid-derived suppressor cells (MDSCs) (Otano et al., 2023).

Analogously to the BRAF-V600 inhibitors in melanoma, which has been proven to promote either a reversion of the BRAF-mutant driven TME immunosuppression - through CD73 downregulation and depletion of both T-regs and MDSCs - either an increased levels of PD-L1 (Mandalà et al., 2017; Ascierto and Dummer, 2018), KRAS-G12C inhibitors have been reported to induce the upregulation of PD-L1 expression in many preclinical studies and clinical trials (Li et al., 2025), suggesting that combination or sequence of immunotherapy with inhibitors of the PD-1/PD-L1 axis and KRAS-G12C inhibitors may represent a viable strategy.

In summary, crosstalk between tumor cells (with their heterogeneous molecular alterations), stromal cells, and immune cells can modify pro- or anti-survival signals as well as impact on treatment outcomes (responsiveness to immune checkpoint inhibitors, resistance to tyrosine-kinase inhibitors, etc.). Interactions and impact of the TME on the molecular pathways involved in *KRAS*-mutant tumors will be further discussed later in this review.

3. KRAS mutations and targeted therapies in NSCLC

3.1. KRAS as prognostic biomarker and therapeutic target in NSCLC

The prevalence and distribution of *KRAS* mutations in NSCLC has been investigated extensively and shows significant variation based on regional, environmental, and patient-specific characteristics. In Western populations, *KRAS* mutations are discovered in around 25–30 % of lung adenocarcinomas, contrasting with East Asian populations, where the prevalence is significantly lower, ranging between 5 % and 15 % (Paliogiannis et al., 2022; Fois et al., 2021). This gap is largely attributable to variations in smoking patterns, environmental exposures, and genetic predispositions. In individuals with a strong smoking history, the incidence of *KRAS* mutations can reach up to 30 %, with the *G12C* variation being particularly frequent (Fois et al., 2021; Kuśnierczyk, 2023). Studies showed that approximately 35 % of smokers with NSCLC possess KRAS mutations, particularly *G12C*, while among non-smokers the most frequent driver genetic alterations detected involve other genes, like *EGFR*, *ALK* and *ROS1* (Fois et al., 2021; Friedlaender, et al., 2024). Therefore, *KRAS* mutations are generally considered mutually exclusive with *EGFR*, *ALK* and *ROS1* genetic alterations, despite the results of some studies revealing a certain degree of co-occurrence (Paliogiannis et al., 2022). This underlines the need for carrying out routine comprehensive genomic profiling in patients affected by NSCLC, at least those with locally advanced or metastatic stage disease, for guiding personalized treatment strategies and estimating the prognostic impact of driver genetic alterations.

Unlike *EGFR* aberrations, *KRAS* mutations do not seem to have any gender or age predilection, even though young women have been reported to display a higher susceptibility to the transversion mutation *G12C* (Paliogiannis et al., 2022). As mentioned before, this mutation is frequent mutation among smokers, suggesting an increased susceptibility to tobacco carcinogenesis in women compared to men. In any case, the *KRAS-G12C* variant is one of the most common oncogenic mutations in NSCLC, accounting alone for about 13–15 % of the global genetic alterations occurring in NSCLC (Lim et al., 2023). This mutation, characterized by a glycine-to-cysteine substitution at codon 12, locks *KRAS* in its active GTP-bound state, perpetually activating the downstream signaling pathways described, promoting uncontrolled cell proliferation (Huang et al., 2021; Ferreira et al., 2022).

The clinical impact of *KRAS* mutations in NSCLC is the subject of extensive research in recent years. Numerous studies, conducted on both Western and Asian populations, have sought to examine the prognostic and predictive significance of *KRAS* mutations and their various subtypes; the issue remains controversial with some studies indicating minimal differences in outcomes between *KRAS*-mutant and *KRAS* wild-type patients, while others showed that *KRAS* mutations have significant prognostic implications.

In a 2023 report by Veccia et al., patients with *KRAS* mutations exhibited only a slight difference in survival outcomes compared to their wild-type counterparts (Veccia et al., 2023). Progression-free survival (PFS) was found to be comparable between the two groups (7.2 months in *KRAS* wild-type patients versus 8.8 months in *KRAS*-mutant patients), while overall survival (OS) was approximately equivalent (14.9 months against 14.7 months, respectively). Similar results were observed when comparing individuals with *KRAS-G12C* mutation to those with other variants. These findings align with those of previous investigations, supporting the hypothesis that *KRAS* mutations do not universally impact clinical outcomes (Paliogiannis et al., 2022). Interestingly, in the study by Paliogiannis et al. a moderate advantage in survival was detected in non-*G12C* patients undergoing immunotherapy.

The impact of *KRAS* mutations on the outcomes of immunotherapy has been investigated in several studies. Sun et al., reported that patients with *KRAS* wild-type tumors who were treated with first-line ICIs exhibited a markedly longer PFS (20 months), compared to those with *KRAS* mutations (7.2 months, $p = 0009$) (Sun et al., 2022). Similarly, a significant improvement in PFS and OS among patients with *KRAS* mutations who were treated with ICIs compared to those with wild-type *KRAS* malignancies has been reported (Torralvo et al., 2019). In the study by Torralvo et al., patients with *KRAS-G12C* mutations exhibited a considerably longer PFS (19.1 months), compared to those with G13C (7.8 months) or G12V (9.4 months) mutations. Also, Elkrief et al., demonstrated that patients with *G12C* mutations showed a higher response rate to ICI/chemotherapy combinations, with a PFS of 6.8 months versus 5.4 months in other *KRAS* mutation subtypes, and an OS of 15 months versus 12 months, respectively (Elkrief et al., 2023). Discrepancies in clinical results across trials are indicative of the complexity inherent in *KRAS* subgroups and their intricate interactions with a multitude of treatment regimens.

Despite *KRAS* mutations promote molecular and metabolic alterations that have been generally associated to a more aggressive behavior of cancers, the coexistence of mutations or alterations in effectors of other interacting gene pathways may be probably responsible of the differences in predictive and prognostic roles of the mutated *KRAS*. The response rates of various therapeutic approaches in prominent studies investigating *KRAS*-mutant NSCLC are summarized in Table 1. The main targeted drugs against *KRAS* mutations, those already approved for clinical use and others under investigation in advanced trials, are reported in Fig. 2 and discussed below.

3.2. Sotorasib and adagrasib

Sotorasib (AMG 510) and adagrasib (MRTX849) are two covalent inhibitors that target the cysteine residue at codon 12 in the KRAS-G12C mutant protein with precision, trapping KRAS in its inactive GDP-bound form (Fig. 3) (Awad et al., 2021). This results in the prevention of reactivation of oncogenic signaling, which effectively limits the

Table 1
Response rates of different therapeutic regimens involving KRAS in NSCLC.

Therapeutic Regimen	ORR	PFS (months)	Remarks
Sotorasib (AMG 510)	36 %	5.6	High initial response, resistance frequently observed
Adagrasib (MRTX849)	43 %	6.5	Longer response duration compared to Sotorasib, effective in cases with brain metastases
Sotorasib + Immunotherapy (anti-PD−1)	~50 %	7.2	Potential improvement with combination therapy, but with more frequent adverse events
Divarasib (GDC−6036) + Cetuximab	62.5 %	5.6	Targeted combination to reduce MAPK pathway reactivation
Standard Chemotherapy (Platinum-based)	~20–30 %	4–5	Lower response in KRAS-mutant patients compared to direct inhibitors

ORR: overall response rate; PFS: progression-free survival.

proliferation of cancer cells. The two drugs have demonstrated consistent outcomes in clinical trials, particularly against NSCLC. Sotorasib, the first to receive FDA approval for clinical use in 2021, has demonstrated an overall response rate of 37 % in patients with *KRAS-G12C*--mutant NSCLC, with a median response duration of 11.1 months (Desai et al., 2023). Similarly, adagrasib has demonstrated improved outcomes, with a 45 % response rate in patients with NSCLC during early-phase clinical trials (Awad et al., 2021). These drugs display lengthy half-lives and good tissue distribution, which contribute to their efficacy in preventing tumor growth. Despite their initial effectiveness, both sotorasib and adagrasib are limited by intrinsic and acquired resistance (Mohanty et al., 2023).

3.3. Divarasib and olomorasib

Divarasib is a novel inhibitor that preferentially targets the *KRAS-G12C* mutation by creating a covalent connection with the reactive cysteine residue at codon 12 (Sacher et al., 2023). This covalent connection stabilizes KRAS in its inactive GDP-bound state, hence inhibiting the reactivation of oncogenic signaling pathways that drive tumor growth and survival. In comparison to earlier inhibitors, like sotorasib and adagrasib, divarasib has showed greater performance in vitro, displaying a 5- to 20-fold improvement in effectiveness and a 50-fold enhancement in selectivity (Brazel and Nagasaka, 2024). This makes it an attractive option for the treatment of *KRAS-G12C*-mutant cancers. In a 2023 trial conducted by Sacher, divarasib revealed considerable therapeutic effectiveness (Sacher et al., 2023); among patients with *KRAS-G12C*-mutant NSCLC, 2 % achieved full responses, 59 % demonstrated partial responses, 29 % indicated disease stabilization, and 7 % exhibited progression of disease.

Divarasib has also been tested in combination with cetuximab, an *EGFR* inhibitor, with the purpose of limiting the adaptive feedback reactivation of the MAPK pathway that often occurs following *KRAS-G12C* suppression. The combination showed improved anticancer activity in comparison to divarasib alone; in patients who had not had

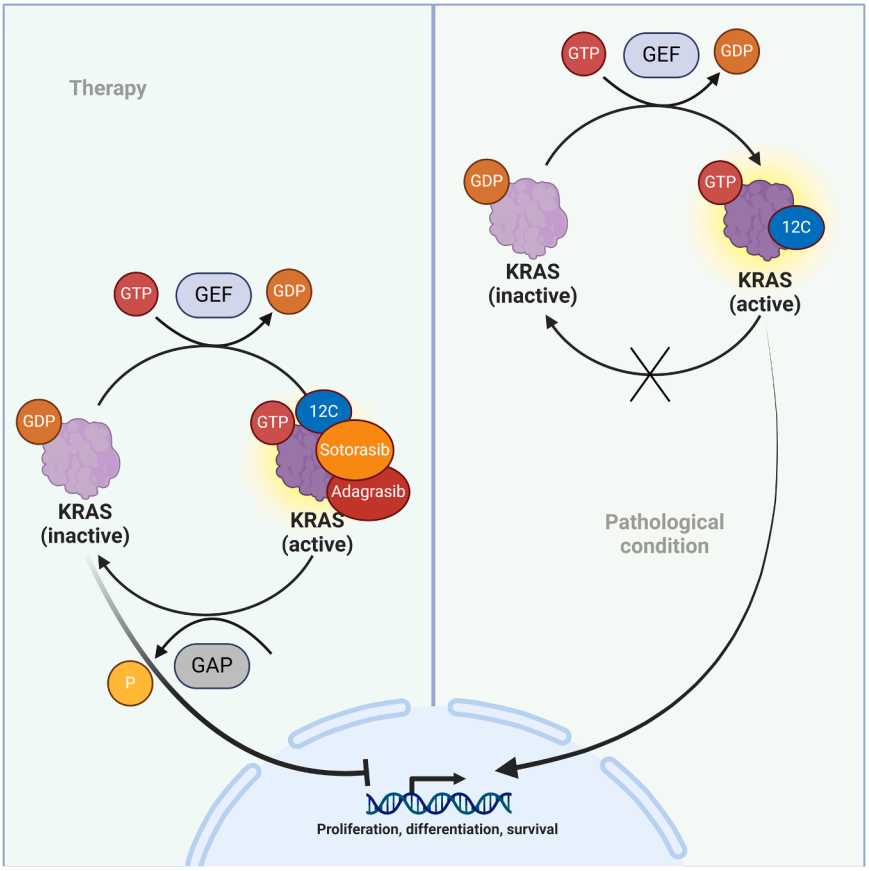

Fig. 3. Mechanism of KRAS-G12C inhibition by targeted therapies. The figure illustrates the cycle of KRAS activation and the mechanism of action of KRAS-G12C inhibitors like sotorasib and adagrasib. On the left, during therapy, inhibitors bind specifically to the KRAS-G12C mutation, locking it in its inactive GDP-bound state, thereby preventing further activation and signaling. This blocks downstream pathways involved in cell proliferation, differentiation, and survival. On the right, the pathological condition is shown where, in the absence of inhibitors, KRAS-G12C remains active, leading to continuous signaling and tumor progression.

prior treatment, monotherapy with divarasib generated a response rate of 35.9 %, whereas the combination with cetuximab resulted in a 62.5 % response rate (Desai et al., 2024).

Olomorasib is a second-generation covalent *KRAS-G12C* inhibitor with efficacy in both monotherapy and combination with immunotherapy in several *KRAS-G12C*-mutant malignancies. In a recent trial by Hollebeque et al., monotherapy with olomorasib revealed an objective response rate of approximately 40 % in patients with gastrointestinal and pancreatic malignancies; the addition of cetuximab to olomorasib considerably boosted the global therapeutic effectiveness (Hollebecque et al., 2024). A phase Ib trial including 64 advanced-stage NSCLC patients examined the combination of olomorasib and pembrolizumab, an immune checkpoint inhibitor; in the cohort of patients treated with olomorasib plus pembrolizumab as first-line therapy, the objective response rate was 77 % (Burns et al., 2024). Notwithstanding the high response rates, the PFS in metastatic patients receiving first-line combination therapy was 3.6 months. The safety profiles of both divarasib and olomorasib have been shown to be manageable, with gastrointestinal toxicity and skin rash being the most reported adverse events. Globally both divarasib and olomorasib are well tolerated and represent interesting options for combination therapy targeting to improve the treatment landscape for KRAS-G12C-mutant cancers. The key characteristics of the main *KRAS* inhibitors evaluated in clinical trials are summarized, including their mechanism of action and early clinical outcomes (Table 2).

3.4. Additional KRAS-G12C inhibitors

Garsorasib (D-1553) has been reported to exert a remarkable antitumor activity with a significant tumor regression; in preclinical models, combination of garsorasib and chemotherapy was found to achieve a deeper and prolonged tumor growth inhibition (Shi et al., 2023). In a phase 1–2 clinical trial, garsorasib was demonstrated to produce an objective response rate > 40 % and a median progression-free survival (mPFS) of about 8 months in patients with advanced or metastatic KRAS-G12C mutated tumors (Li et al., 2024) (Table 2).

Preliminary data on additional selective and irreversible KRAS-G12C inhibitors - such as FMC-375, JDQ443, and RMC-6291 - revealed an acceptable safety profile and a promising clinical activity of these new compounds in cohorts of NSCLC patients (Wasiak et al., 2025). Finally, an additional anti-KRAS-G12C, ASP2453, with more potent effects on tumor regression in preclinical models has been reported (Wasiak et al., 2025)

3.5. Non-G12C and other KRAS inhibitors

Although the development of new inhibitors has been primarily focused on the G12C mutation, attention has been recently focused on other mutations within the KRAS G12–13 codons.

The G12D mutation causes modifications into the kinase pocket of the KRAS protein that has long represented an obstacle in developing a covalent and effective inhibitor. Some KRAS-G12D inhibitors - such as HRS-4642, MRTX1133, QTX3034, RMC-9805, and TSN1611 - have been developed in recent years and are being test in phase 1–2 trials either as single agents either in combination with an anti-EGFR like cetuximab or a proteasome inhibitor like carfilzomib (Hallin et al., 2022; Wasiak et al., 2025).

Despite the intrinsic causative mechanisms are still unknown, *KRAS* codon 13 mutations, particularly the G13D mutation, appear to have a worse prognosis than those with codon 12 mutations, with an increased tendency to metastasis formation and association with relatively low levels of tumor-infiltrating lymphocytes, overall contributing to a higher risk for cancer recurrence (Hwang et al., 2025). Since a close interaction between the oncogenic KRAS-G13D mutation and the HER2-dependent pathway has been demonstrated, a small molecule inhibitor of the HER2-KRAS axis able to induce transcriptional downregulation of HER2 and KRAS has been recently described (Hwang et al., 2025). This in addition to other anti-HER inhibitors, such as afatinib and neratinib, though a limited efficacy was reported for these drugs in preclinical models (Jayachandran et al., 2025).

Overall, KRAS-G12V represents the second most common *KRAS* mutation in cancer, but the only inhibitor developed against this alteration is an EGFR-directed RNA interference/RNAi molecule (EFTX-G12V) that selectively inhibits KRAS-G12V expression and has recently been shown to possess significant preclinical activity (Stanland et al., 2025).

Finally, mutations activating KRAS have been reported to upregulate Polo-like Kinase 1 (PLK1), which is a serine/threonine protein kinase

Table 2
Overview of key KRAS-G12C inhibitors in clinical trials.

Drug [reference]	Inhibition type	Target	Mechanism of action and types of evaluated patients	Clinical outcomes
Sotorasib (AMG 510) [A]	Covalent	KRAS-G12C	Binds to the mutant cysteine, locking KRAS in its inactive GDP-bound state; patients who had received both prior chemotherapy and immunotherapy	ORR 36 %, DOR 10 months in Phase 2 trial; ORR 28 %, mPFS 5.6 months in Phase 3 trial
Adagrasib (MRTX849) [B]	Covalent	KRAS-G12C	Irreversible binding to KRAS-G12C in the inactive state; patients previously treated with chemotherapy and immunotherapy	ORR 43 %, mPFS 6.5 months in Phase 2 trial; ORR 32 %, mPFS 5.5 months in Phase 3 trial
Divarasib (GDC−6036) [C]	Covalent	KRAS-G12C	Irreversible bond with inactive KRAS; patients who had received previous platinum chemotherapy and immuno-therapy with PD−1/PD-L1 inhibitors	ORR 56 %, DOR 18 months, median PFS 15.3 months, as monotherapy; ORR 62.5 % in combination with cetuximab
Olomorasib (LY3537982) [D, E]	Covalent	KRAS-G12C	Irreversible binding to KRAS-G12C, in combination with immunotherapy (pembrolizumab)	ORR 40 % as monotherapy; 75 % combined with pembrolizumab in a Phase1/2 study
Garsorasib (D−1553) [F]	Covalent	KRAS-G12C	Irreversible and selective binding GDP-bound KRAS-G12C in patients previously treated with platinum-based chemotherapy and immune checkpoint inhibitors	ORR 41 %, DOR 7.1 months, mPFS 8.2 months, as mono-therapy in Phase 1–2 trial

DOR: median duration of response; mPFS: median progression-free survival; ORR: overall response rate. References: [A], Brazel et al., 2023; [B], Luo and Arter, 2024; [C], Desai et al., 2024; [D], Sacher et al., 2025; [E], Shaverdashvili and Burns, 2025; [F], Li et al., 2024

that controls multiple aspects of the cell cycle and has become an important therapeutic target, with subsequent development of several PLK1 inhibitors being currently in various stages of development and testing (Jayachandran et al., 2025).

3.6. Pan-RAS inhibitors

Recently, several inhibitors targeting both mutated and wild-type RAS proteins - KRAS but also NRAS and HRAS isoforms - have been developed. Such pan-RAS inhibitors have been designed to warrantee a more complete suppression of the RAS signaling cascade independently of the *RAS* mutational status (Kim et al., 2023). These inhibitors are capable of binding both the inactive (GDP-bound) and the active (GTP-bound) forms of the KRAS protein; when binding to the inactive KRAS protein, they block the nucleotide exchange and prevent KRAS activation regardless of the wild-type state or the different types of occurring gene mutations (Kim et al., 2023).

Pan-RAS inhibitors usually bind the RAS proteins in a non-covalent manner; the main exponents of these multi-selective drugs - actually, investigated in preclinical studies and, for some of them, in clinical trials - are reported in Fig. 2 and briefly presented below:

- daraxonrasib (RMC-6236) is a nonsteroidal inhibitor of the active (GTP-bound) form of either mutated or wild-type RAS protein. In clinical trials, daraxonrasib showed promising efficacy in pancreatic and lung cancers (Cregg et al., 2025); the antiproliferative effects through inhibition of RAS-dependent signaling cascades - including also the AKT pathway - have been reported in other malignancies like osteosarcoma (Jung et al., 2025);
- ADT-007 is a first-in-class pan-RAS inhibitor, which works by blocking the GTP activation and, in turn, by suppressing the constitutive stimulation of the MAPK/AKT pathways and tumor growth in cancers carrying wild-type, mutant, or activated RAS proteins (Foote et al., 2025). An oral prodrug of ADT-007, ADT-1004, also showed greater efficacy than sotorasib, adagrasib, and MRTX1133 in preclinical models of pancreatic ductal adenocarcinoma (Bandi et al., 2025);
- BI-2865 and BI-2493 are potent inhibitors acting against wild-type KRAS and a wide range of KRAS mutants, with no activity on HRAS and NRAS in preclinical studies on xenograft models of pancreatic adenocarcinoma (Bröker et al., 2025). Although these compounds were found to improve the toxicity profile due to their higher selectivity, compensatory activation of the other RAS isoforms contributes to reducing the effectiveness of the KRAS inhibition (Kim et al., 2023; Bröker et al., 2025);
- BI-3706674 is another pan-KRAS inhibitor that binds the inactive (GDP-bound) form of KRAS, particularly active against tumors harboring *KRAS*-G12V mutations and *KRAS* wild-type gene amplifications in phase I trial (Krupa et al., 2025);
- JAB-23425 is another highly potent pan-KRAS inhibitor, which is active against all the most relevant non-G12C *KRAS* mutations as well as against both active and inactive KRAS proteins; it has been demonstrated to be particularly effective - inducing a strong reduction of the downstream ERK phosphorylation into the MAPK signaling pathway - in *KRAS*-mutant cells of NSCLC tumors (Mina et al., 2025);
- YL-17231 is a pan-RAS inhibitor that has shown a marked antiproliferative activity in resistant *KRAS*-mutated cell lines; further investigations in clinical trials are awaited (Krupa et al., 2025).

4. Co-occurring mutations and their clinical implications in KRAS-mutant NSCLC

The oncogenic activity of *KRAS* mutations is further modulated by co-occurring mutations in other genes, especially those involving tumor suppressor genes like *TP53*, *STK11*, and *KEAP1* (Shen et al., 2021). Skoulidis and colleagues, conducted investigations with the objective of detecting co-mutation patterns in patients with *KRAS*-mutant malignancies; their research identified over 350 genes that are frequently co-mutated in conjunction with KRAS, with a median of eight co-mutations per tumor (Skoulidis et al., 2015). The most common co-mutations include variants in *TP53*, *STK11*, *KEAP1*, *SMARCA4*, *CDKN2A*, *RBM10*, and *PTPRD*, which illustrate the genetic complexity of *KRAS*-mutant cancers (Arbour et al., 2018). In addition, three different subgroups have been proposed according to the type of *KRAS* co-mutations identified: the KP subgroup is characterized by *TP53* mutations, the KL subgroup is distinguished for the inactivation of *STK11* and *KEAP1*, and the KC subgroup is characterized by alterations in *CDKN2A/B* and *NKX2–1* (Skoulidis et al., 2015). These subgroups reflect diverse biological activities and therapeutic responses, underscoring the importance of examining the entire mutational profile in patients with NSCLC. As also mentioned before, *STK11* co-mutations are associated with an "immunologically cold" TME, characterized by low immune cell infiltration and resistance to immune checkpoint inhibitors, while *TP53* co-mutations are linked to a more inflamed ("immunologically hot") TME, potentially increasing responsiveness to immunotherapy (Proulx-Rocray et al. 2023; Ma et al., 2021). Approximately 37 % of cases exhibit co-mutations involving *KRAS* and *TP53*, 9 % involve *KRAS* and *STK11*, and 6 % include *KRAS* and *KEAP1* (Arbour et al., 2018); Negrao et al., reported that *KRAS* co-mutations of *KEAP1*, *SMARCA4*, and *CDKN2A* were highly prevalent, either as single mutations or in combination (Negrao et al., 2023). Globally, *STK11* and *KEAP1* co-mutations seem to have a detrimental impact on clinical outcomes, while *TP53* mutations showed controversial results (Skoulidis et al., 2015; Arbour et al., 2018).

In subsequent studies focused on *TP53* and *STK11* co-mutations, the presence of *TP53* co-mutations was associated with improved PFS in patients receiving immunotherapy combined with chemotherapy, with a median PFS of 18.7 months (Sun et al., 2022). In contrast, *STK11* co-mutations were linked to increased PFS in patients treated with chemotherapy and bevacizumab (PFS = 7 months); however, in patients treated with ICI/chemotherapy regimens, those harboring *STK11* co-mutations demonstrated significantly worse outcomes compared to *STK11* wild-type patients (PFS = 4.4 months versus 19.1 months) (Sun et al., 2022).

A further study on patients with *KRAS-G12C* mutations treated with chemotherapy and ICIs showed a median PFS and OS of 6.8 months and 15 months, respectively (Elkrief, et al., 2023). However, individuals with *KEAP1* and *STK11* co-mutations, either separately or in combination, were associated with poorer outcomes, indicating a significant negative impact on both PFS and OS. Additional investigations showed that co-mutations in *KEAP1*, *SMARCA4*, and *CDKN2A*, determining the so called "KSC-mutated" group, exhibited a diminished response to targeted therapies and demonstrated inferior overall survival (OS = 6.9 months compared to 13 months in wild-type patients) and PFS (2.8 months versus 5.9 months) (Negrao et al., 2023).

5. Mechanisms of resistance to KRAS targeted therapies

As previously mentioned, the clinical efficacy of sotorasib and adagrasib - the two drugs with longer clinical use - is often limited by the early establishment of resistance (Mohanty et al., 2023). All main molecular factors that contribute to the mechanisms of resistance to KRAS-G12C inhibitors can be grouped in four classes (Blaquier et al., 2021; Li et al., 2025):

a. genetic factors: secondary *KRAS* mutations (Y96C/D, H95D, R68S) or *KRAS-G12C* amplification, both altering the KRAS conformation and reducing the capability of binding the inhibitor; mutations in other driver genes such as those into the MAPK (BRAF-V600, MAP2K1-K57N/-Q56P, MAP2K1-E102_103del) or the PI3K/AKT

(PIK3CA-H1047R) pathways, bypassing the KRAS dependence for cell proliferation.
b. epigenetic changes: hypermethylation, silencing genes that control cell proliferation; histone acetylation, inhibiting genes involved in cell differentiation; increased levels of non-coding RNAs, inhibiting tumor suppressor and regulatory genes.
c. activation of signal transduction cascades as consequence of alterations in upstream receptor tyrosine kinases: mainly, EGFR and HER2 stimulation, MET amplification, and RET mutation.
d. modification of the TME toward an immune tolerance status: upregulation of the PD-L1 expression and/or recruitment of immunosuppressive factors and cells.

Trying to further synthesize the events that lead to the development of pharmacological resistance, one can divide them into two general mechanisms:

a) reactivation of *KRAS*-driven signaling;
b) activation of alternate compensatory pathways, including alternative metabolic pathways that has also been advocated as a potential resistance mechanism (Ash et al., 2024).

Both primary and acquired resistance can act through all these mechanisms, limiting the duration of responses to therapy and mining long-term oncological outcomes.

5.1. Reactivation of KRAS-driven signaling in KRAS-mutant cancer

One of the main mechanisms of acquired resistance to *KRAS* inhibitors is the onset of secondary mutations in the *KRAS* gene itself. These mutations often arise in regions of the protein that compromise the efficient binding of the inhibitor restoring, therefore, KRAS signaling. For example, mutations at codon 12 (like *G12V* or *G12D*) can occur during therapy with *G12C* inhibitors, leading to drug resistance (Awad et al., 2021; Zhu et al., 2022). These mutations disrupt the structure of the KRAS protein, rendering the treatment ineffective and allowing uncontrolled oncogenic signaling. A recent study detected multiple secondary *KRAS* mutations in patients treated with sotorasib, including changes at codons 13 and 61, which impair the drug's binding site and contribute to KRAS reactivation (Zhang and Nagasaka, 2021). This reactivation maintains the function of MAPK and PI3K-AKT pathways, allowing the tumor to survive and continue growing. The development of next-generation inhibitors which can target a wider variety of *KRAS* mutations or the discovery of inhibitors that can bind irreversibly, regardless of potential conformational alterations of the protein, are attractive approaches to overcome this type of resistance.

5.2. Activation of alternative pathways as a resistance mechanism in KRAS-mutant cancer

A recently discovered mechanism of resistance to *KRAS* inhibitors involves metabolic reprogramming within cancer cells (Ash et al., 2024; Kerk et al., 2021). *KRAS*-mutant cells are known to rely substantially on altered metabolic pathways to enable their rapid proliferation and survival under conditions of food shortage or treatment-induced stress. Upon *KRAS* inhibition, cancer cells modify their metabolic dependency by upregulating pathways such as glycolysis, oxidative phosphorylation or autophagy, to compensate the lack of *KRAS*-driven metabolic support. Autophagy has been discovered as a survival strategy in *KRAS*-mutant tumors treated with *KRAS* inhibitors, as it provides nutrition and energy to cancer cells by recycling intracellular components.

6. Insights on the role of tumor microenvironment in KRAS-mutant NSCLC

The TME in *KRAS*-mutant cancers is characterized by tendency to a "hot" immune profile, with significant infiltration of immune cells (Dias Carvalho et al., 2019; Xu et al., 2024). This probably depends on the production of a wide range of cytokines, chemokines, and pro-inflammatory factors, that are upregulated by *KRAS*-dependent signaling pathways (Hamarsheh et al., 2020; Yi et al., 2024). The presence of more abundant immune cells in TME could suggest a robust anti-tumor response; instead, a fraction of these cells exhibits immunosuppressive properties (Gun et al., 2019; Alvero et al., 2024). Key immune cell populations that contribute to this suppression include Tregs, MDSCs, tumor-associated macrophages (TAMs), neutrophils, and mast cells (Tie et al., 2022). The oncogenic signaling of *KRAS* promotes the expression of numerous immunomodulatory factors within tumor cells, which shape the TME into an immunosuppressive environment. This transformation is largely mediated through alternative signaling pathways such as IFN-MYC, NF-kB, and MAPK.

The IFN-MYC pathway alters the immune landscape by inhibiting interferon signaling, leading to the exclusion of T cells, B cells, and natural killer (NK) cells, while promoting macrophage infiltration (Zhao et al., 2021). Additionally, the NF-kB pathway is a key regulator of cytokine and chemokine expression, contributing to the recruitment of immune cells that support tumor growth (Ebrahimi et al., 2024). The MAPK pathway further promotes immunosuppression by driving the production of transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10), both of which activate Tregs, enhancing the immune evasion capabilities of the tumor (Tie et al., 2022). Another critical aspect of *KRAS*-mutant tumors is the upregulation of PD-L1, a checkpoint protein that allows tumors to evade immune surveillance by inhibiting T cell activity (Chen et al., 2017). This hyperexpression of PD-L1 creates a barrier to effective immune responses, facilitating the tumor's ability to escape immune-mediated destruction (Falk et al., 2018). These insights underscore the complexity of the immune modulation in KRAS-mutant tumors and further highlight the potential for targeting the TME in combination with existing *KRAS*-targeted therapies to improve therapeutic outcomes. Actually, therapeutic approaches in NSCLC patients carrying *KRAS* mutations foresee PD-(L)1 blockade ± platinum-based chemotherapy as first-line treatment and *KRAS* allele specific inhibitors as second-line therapy (Ricciuti et al., 2022).

7. Conclusions and future perspectives

The treatment landscape for *KRAS*-mutant NSCLC has changed significantly in recent years with the development of targeted *KRAS-G12C* inhibitors like sotorasib and adagrasib. These drugs have offered a valid therapy to patients who previously had limited treatment options. However, the advent of treatment resistance remains a great challenge for the achievement of durable responses. Both innate and acquired resistance mechanisms, through secondary mutations of *KRAS*, compensatory signaling pathways and metabolic reprogramming, need to be further investigated and overcome. Understanding the molecular basis of resistance has opened new research horizons, especially in testing combination therapy approaches. Combination therapies targeting different pathways, such as PI3K-AKT-mTOR or MAPK, showed encouraging results in preclinical models and early clinical trials (Molina-Arcas et al., 2019). For example, the combination of *KRAS-G12C* inhibitors with *MEK* inhibitors (e.g., trametinib or cobimetinib) or *PI3K* inhibitors (e.g., alpelisib) is being investigated with the objective of eliciting more durable responses by blocking both the primary and compensatory pathways in several cancer types (Xiao et al., 2024; Miyazaki et al., 2025; Baars et al., 2025). In addition, research into next-generation *KRAS* inhibitors that can overcome resistance mutations or drugs that target tumor heterogeneity and the TME, is currently ongoing.

Furthermore, recent trials have explored the potential of combining *KRAS* inhibitors with immunotherapies, particularly anti-PD-1 or anti-PD-L1 antibodies (Chmielewska et al., 2023). As mentioned before, it has been reported that *KRAS* mutations, particularly the *G12C* variant,

are associated with the development of an immunosuppressive TME by induction of high levels of immune evasion factors, particularly PD-L1. Although ICIs have demonstrated only modest efficacy as monotherapies in the context of *KRAS*-mutant malignancies, the combination of ICIs with KRAS inhibitors has theoretically the potential to enhance immune-mediated tumor clearance. This combination can reactivate exhausted T lymphocytes, while concurrently reducing tumor cell growth and survival through the inhibition of *KRAS*. Preclinical data indicate that KRAS inhibitors may facilitate immune cell penetration into tumors and enhance the production of pro-inflammatory cytokines, thereby creating a more conducive environment for immunotherapy (Pereira et al., 2022). Further trials are needed to evaluate these combinations with the objective of overcoming the immunosuppressive obstacles presented by the TME in KRAS-mutant cancers.

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