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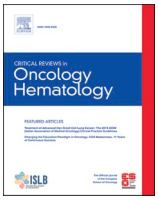

KRAS G12C-mutant driven non-small cell lung cancer (NSCLC)

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ABSTRACT

KRAS G12C mutations in non-small cell lung cancer (NSCLC) partially respond to *KRAS G12C* covalent inhibitors. However, early adaptive resistance occurs due to rewiring of signaling pathways, activating receptor tyrosine kinases, primarily EGFR, but also MET and ligands. Evidence indicates that treatment with *KRAS* G12C inhibitors (sotorasib) triggers the MRAS:SHOC2:PP1C trimeric complex. Activation of MRAS occurs from alterations in the Scribble and Hippo-dependent pathways, leading to YAP activation. Other mechanisms that involve STAT3 signaling are intertwined with the activation of MRAS. The high-resolution MRAS:SHOC2:PP1C crystallization structure allows in silico analysis for drug development. Activation of MRAS:SHOC2:PP1C is primarily Scribble-driven and downregulated by HUWE1. The reactivation of the MRAS complex is carried out by valosin containing protein (VCP). Exploring these pathways as therapeutic targets and their impact on different chemotherapeutic agents (carboplatin, paclitaxel) is crucial. Comutations in STK11/LKB1 often co-occur with *KRAS* G12C, jeopardizing the effect of immune checkpoint (anti-PD1/PDL1) inhibitors.

1. *KRAS* G12C covalent inhibitors in lung adenocarcinoma

KRAS is the most frequently mutated oncogene in approximately 25% of patients with lung adenocarcinoma (Rosell and Karachaliou, 2016). Its prevalence varies across regions, with Europe reporting around 30% among patients with lung adenocarcinoma, while lower rates are observed in Asian and Latin American countries (Frost et al., 2022; Carrot-Zhang et al., 2021). Additionally, significant geographical differences have been identified in the prevalence of the *KRAS* G12C mutation (8.9–19.5% in the US, 9.3–18.4% in Europe, 6.9–9.0% in Latin America, and 1.4–4.3% in Asia) for advanced lung adenocarcinoma (Lim et al., 2023), as recently reported in Germany and Colombia (Frost et al., 2022; Ruiz-Patiño et al., 2022). Consistent with several publications (Scheffler et al., 2019; Skoulidis et al., 2018), a recent comprehensive review shows that *KRAS* G12C-mutant lung adenocarcinoma (NSCLC) patients often harbor co-mutations, including STK11 (10.3–28%), Kelch-like ECH-associated protein 1(KEAP1) (6.3–23%), and, notably, TP53 (17.8–50%) (Lim et al., 2023).

In a co-clinical murine trial, cohorts of genetically engineered mice with either *KRAS*, *KRAS* and p53 (*KRAS*/p53) or *KRAS*/LKB1-mutant lung cancers were generated. The activation of *KRAS* G12D and inactivation of p53 or LKB1 in the lung epithelium was attained using nasal instillation of adenovirus encoding the CRE recombinase. In tumors with only *KRAS* mutations, treatment with docetaxel yielded a partial response rate of 30% in mice. However, mice bearing *KRAS* tumors with loss of p53 or LKB1 had lower responses to docetaxel (5% and 0%, respectively), and a greater number of these mice exhibited progressive disease as observed on magnetic resonance imaging (MRI). The addition of the mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor selumetinib to docetaxel increased the response rate to 92% in *KRAS*-

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mutant cancers and 61% in *KRAS*/p53 mice. In contrast, for *KRAS*/LKB1-mutant tumors, selumetinib plus docetaxel resulted in a significantly lower response rate, with only 33% of the mice attaining a partial response (Chen et al., 2012). However, in the SELECT-1 randomized trial, among patients with previously treated advanced *KRAS*-mutant NSCLC, the addition of selumetinib to docetaxel did not improve progression-free survival when compared to docetaxel alone (Jänne et al., 2017). Among the 510 randomized patients, median progression-free survival was 3.9 months with selumetinib plus docetaxel and 2.8 months with placebo plus docetaxel (a difference of 1.1. months; hazard ratio, 0.93; p = 0.44). Median overall survival was 8.7 months with selumetinib plus docetaxel and 7.9 months with placebo plus docetaxel (a difference of 0.9 months; hazard ratio, 1.05; p = 0.64) (Jänne et al., 2017). Response rate was 20% with selumetinib plus docetaxel, and 13.7% with placebo plus docetaxel (difference 6.4%; hazard ratio, 1.61; p = 0.05). Median duration of response was 2.9 months with selumetinib plus docetaxel and 4.5 months with placebo plus docetaxel. No differences were appreciated in progression-free survival between treatments by individual mutation subtype *KRAS* G12C, *KRAS* G12V or other *KRAS* mutations (Jänne et al., 2017).

In lung adenocarcinoma, the distribution of *KRAS* mutant allele frequencies in codon 12 is higher for G12C, followed by G12V, then by *KRAS* G12D, G12A, G12S and G12R (Cook et al., 2021). *KRAS* activates downstream signaling pathways when GTP-bound. *KRAS* alternates between inactive GDP-bound states and active GTP-bound states regulated by guanine nucleotide exchange factors (GEF), such as SOS proteins, which catalyze the transition between *KRAS* and GTP-bound states. Additionally, GTPase activating proteins promote the hydrolysis of GTP-bound *KRAS,* converting it from the active state to an inactive GDP-bound state, thereby inhibiting the activity of *KRAS* (Fig. 1) (Rosell et al., 2021a). Cysteine, located at codon 12 of *KRAS* G12C, can be specifically inhibited in a covalent manner. In *KRAS* G12C mutants,

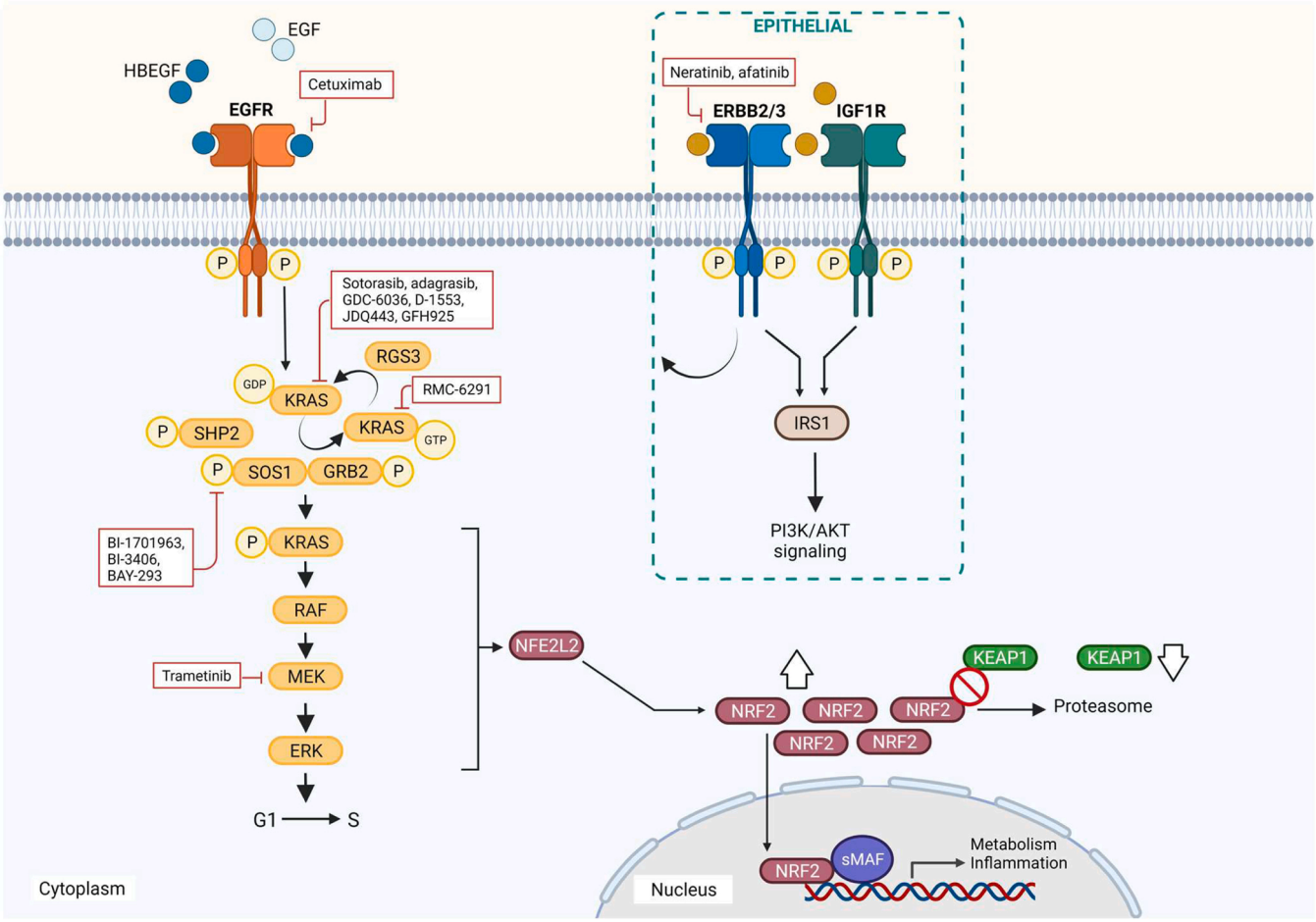

Fig. 1. The *KRAS* guanosine triphosphate hydrolase (GTPase) regulates downstream signaling by alternating *KRAS* between an inactive guanosine diphosphate (GDP)-bound state and an active state when bound to guanosine triphosphate(GTP). This process is regulated by guanine nucleotide exchange factors (GEFs), such as SOS1 (son of sevenless homolog 1), which catalyze the transition between the *KRAS* and GTP-bound states, and GTPase activating proteins (GAPs), which promote the hydrolysis of GTP bound to *KRAS*, converting the active state to an inactive GDP-bound state that inhibits *KRAS* activity. Regulator of G protein signaling 3 (RGS3) is a GAP that inactivates *KRAS*. Covalent *KRAS* inhibitors bind to the cysteine of *KRAS* G12C mutants to diminish the binding between GTP and *KRAS,* locking the *KRAS* G12C mutant in an inactive state. Map of marketed, clinical, and preclinical covalent inhibitors in signaling pathways, such as RAS-SOS (son of sevenless) inhibitors. Various genes that affect the GDP-bound state, such as epidermal growth factor receptor (EGFR), Src homology 2-containing protein tyrosine phosphatase 2 (SHP2), and others, become activated following *KRAS* inhibition (11). SHP2 is a non-receptor protein tyrosine phosphatase (PTP) encoded by PTPN11 gene. Inhibition of MEK1/2 with trametinib can elicit compensatory response through FGFR1-FRS2 feedback, ERBB2/3 activation of MEK and AKT, and induction of epithelial-mesenchymal transition (EMT). Nearly 20% of *KRAS* mutant lung adenocarcinomas carry loss-of-function in the gene encoding kelch-like ECH-associated protein 1(KEAP1), a negative regulator of nuclear factor erythroid 2-like-2 (NRF2). NRF2 regulates the expression of genes encoding enzymes involved in glycolysis and glutathione synthesis (11).
Other abbreviations: ERBB, Erb-b receptor tyrosine kinase; ERK, extracellular signal-regulated kinase; FGFR, fibroblast growth factor receptor; FRS, FGFR adopter protein; GBR2, growth factor receptor-bound protein 2; HBEGF, heparin-binding EGF; IGF-1R, insulin-like growth factor receptor; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; SMAF, small musculoaponeurotic fibrosarcoma. This figure was designed using BioRender.

small molecules covalently bound to the mutant cystine, bind to GDP-bound K*RAS* proteins. This binding reduces the affinity between GTP and *KRAS*, hence preventing GEF from catalyzing the replacement of GDP with GTP, thereby locking the *KRAS* G12C mutant in an inactive state. Binding of these inhibitors to *KRAS* G12C disrupts both effector binding switch I and switch II regions, subverting the native nucleotide preference to favor GDP over GTP and impairing binding to RAF (Ostrem et al., 2013). (Fig. 1). The discovery of covalent inhibitors for *KRAS* G12C represents a giant leap in the treatment of *KRAS* G12C tumors (Ostrem et al., 2013; Canon et al., 2019). Treatment with the *KRAS* G12C inhibitor 12 decreased viability in lung cancer cell lines containing G12C mutations (H1792, H358, H23 and Calu-1) and increased apoptosis compared to the group without G12C mutations (H1473, H1299 and A549). It is worth noting that H1792, which was highly sensitive to the *KRAS* G12C inhibitor, exhibited low levels of *KRAS*-GTP. This observation is consistent with the preferential binding of Shokat's inhibitors to *KRAS*-GDP. The half-maximum effective concentration (EC_{50}) for compound 12 in H1792 cells was 0.32 + /- 0.01 μM) (Ostrem et al., 2013). *KRAS*-dependent A549 and independent (H1299) cell lines lacking G12C were insensitive to compound 12 (Ostrem et al., 2013).

The direct inhibition of *KRAS* G12C was demonstrated by ARS-1620. The X-crystal structure of the *KRAS* G12C-ARS-1620 covalent complex revealed a notable hydrogen bonding interaction between ARS-1620 and His95 (Canon et al., 2019). This discovery led to the development of AMG-510 (sotorasib) as an optimized His95 groove-binding molecule. The highly optimized isopropyl-methylpyridine substituent of AMG-510, which occupies the His95 groove, forms a continuous network of 25 ligand-protein van der Waals contacts extending from the backbone of helix 2 (His95, Tyr96) to the backbone of the flexible switch II loop (Canon et al., 2019). In two *KRAS* G12C cell lines, NCI-H358 and MIA PaCa-2, AMG-510 strongly impaired cellular viability (half--maximum inhibitory concentration [IC_{50}]=0.0006 μM and 0.009 μM, respectively. AMG-510 was profiled in 22 cell lines that had heterozygous or homozygous *KRAS* G12C, *KRAS* mutations other than *KRAS* G12C, or wild-type *KRAS*. Treatment with AMG-510 for 2 h showed that basal p-ERK was inhibited in all *KRAS* G12C cell lines, with IC_{50} values ranging from 0.0010 μM to 0.123 μM. AMG-510 did not inhibit p-ERK in any of the non-*KRAS* G12C cell lines (IC_{50} > 10 uM) (Canon et al., 2019). In cell viability assays, AMG-510 impaired the growth of all *KRAS* G12C cell lines except SW1573, with IC_{50} values ranging from 0.004 μM to 0.032 μM. Non-*KRAS* G12C cell lines were insensitive to AMG-510 (Canon et al., 2019).

2. EGFR deregulation and efficacy of KRAS G12C covalent inhibitors

The effects on cellular signaling in NCI-H358 or MIA PaCa2 after 4- or 24-hour treatment with a serial titration of AMG-510 showed an accumulation of active EGFR (p-EGFR (Y1068)). Inhibition of AKT phosphorylation was apparent in one cell line, while an increase in cleaved caspase-3 was noted at 24 h in both cell lines, suggesting the induction of apoptosis (Canon et al., 2019). In time course studies, treatment with AMG-510 at 0.1 μM elicited rapid (<2 h) and sustained (>24 h) effects on MAPK and EGFR pathway signaling in NCI-H358 and MIA PaCa-2 cells (Canon et al., 2019).

Intriguingly, it was reported that *KRAS* G12C-mutant organoids are selectively responsive to covalent G12C inhibitors only when EGFR is suppressed (Zafra et al., 2020). KP-G12C organoids were insensitive to treatment with the *KRAS* G12C inhibitor ARS-1620 alone, showing no effect on morphology, proliferation, or organoid size. While ARS-1620 selectively reduced RAS-GTP levels in KP-G12C organoids but not in KP-G12D organoids, it did not inhibit ERK1/2 or AKT phosphorylation, which could be attributed to receptor-mediated pathway activation (Zafra et al., 2020). Likewise, the combination of the G12C inhibitor with gefitinib (EGFR tyrosine kinase inhibitor) induced further reduction in RAS-GTP levels, abrogated proliferation, and eliminated all organoids within 6 days of treatment. As reviewed in previous lines of research, upstream signaling through receptor tyrosine kinase activation can hinder downstream *KRAS* G12C inhibitor signaling effects due to feedback deregulation (Zafra et al., 2020).

Adagrasib (MRTX849) is another potent covalent inhibitor of *KRAS* G12C, which irreversibly and selectively binds to and locks it in its inactive, GDP-bound state. MRTX849 demonstrated tumor regression exceeding 30% volume reduction from baseline in 17 out of 26 (65%) *KRAS* G12C-positive cell line and patient-derived xenograft models. Additionally, objective responses were observed in patients with *KRAS* G12C lung and colon adenocarcinomas (Hallin et al., 2020). The response to MRTX849 was categorized as sensitive, partially sensitive (e.g., H2030 [*KRAS* G12C, p53 mutated and LKB1 mutated]), or treatment refractory (e.g., SW1573 lung cancer cell line [*KRAS* G12C, P53 wild-type and LKB1 wild-type]). Neither the *KRAS*-mutant allele frequency nor the presence of TP53, STK11, or CDKN2A mutations predicted the antitumoral activity of MRTX849 (Hallin et al., 2020). As mentioned earlier, the RAS pathway's negative feedback signaling is mediated by ERK1/2 pathway target genes, including dual-specificity phosphatases (DUSP) and Sprouty (SPRY) proteins (Hallin et al., 2020). The MRTX849 and afatinib combination demonstrated significantly greater antitumor efficacy compared to either single agent in all five analyzed cell lines, even resulting in complete or near-complete responses to the combination (Hallin et al., 2020). The MRTX2122 partially sensitive H2122 cells were treated with increasing concentrations of MRTX849, either alone or in the presence of afatinib (200 nmol/L, IC_{90}). The mobility shift in *KRAS* protein was examined densitometrically from immunoblots. A shift in the concentration response to MRTX849 was evident in the presence of afatinib, indicating that the combination increased the fraction of modified *KRAS* G12C, plausibly for the intervention of HER family receptors in extrinsic regulation of *KRAS* G12C-GTP loading. The KRAS-dependent signaling effect of the combination was further investigated in H2030, H2122, H358, and KYSE-410, where afatinib clearly inhibited phosphorylation of EGFR (Y1068) and HER2 (Y1248) (Hallin et al., 2020).

Fulzerasib (GFH925) is an irreversible small molecule inhibitor for *KRAS* G12C mutation blocking *KRAS* pathway signaling (pERK IC50: 37 nM) by covalently inhibiting the GDP/GTP nucleotide exchange on *KRAS* G12C (IC50: 29 nM), trapping *KRAS* in the inactive GDP-bound form (RAS-GTP IC50: 74 nM), and therefore inhibits the growth of *KRAS* G12C-mutant tumor cell lines (IC50: 2–20 nM). GFH925 also demonstrated potent anti-tumor activity in multiple *KRAS* G12C-mutant tumor models including MIA Paca-2 CDX, human lung adenocarcinoma NCI-H358 CDX, colorectal adenocarcinoma SW837 CDX, and lung cancer LU2529 PDX models, with minimum effective doses of 1 mg/kg, 3 mg/kg, 10 mg/kg and 2 mg/kg, respectively. Cetuximab (1mpk, ip. biw) combined with GFH925 (0.3mpk, po, qd) was also tested in in vivo models with NCI-H2122 CDX Tumor and MIA Paca-2 CDX Tumor showing substantial synergetic effect (Genfleet Therapeutics internal data), which could potentially position the *KRAS* G12C inhibitor with better efficacy and safety treating advanced NSCLC patients in the front setting considering low risk of drug-drug interaction between antibody and small molecule. The phase II study (KROCUS) treating NSCLC patients with *KRAS* G12C mutation is ongoing with preliminary encouraging data (NCT05756153).

3. Efficacy of inhibitors of KRASG12C in clinical trials of patients with KRAS G12C NSCLC

A phase 1 trial (CodeBreak 100) of sotorasib (AMG-510) included 59 patients with NSCLC, 42 with colorectal, and 28 with other tumors harboring the *KRAS* G12C mutation. Patients had already received a median of 3 (range 0–11) previous lines of anticancer treatment for metastatic disease. In the subgroup with NSCLC, 32.2% had an objective response (complete or partial response) and 88.1% had disease control (objective response or stable disease). The median progression-free

survival was 6.3 months. In the subgroup with colorectal cancer, 7.1% had response, and 73% had disease control. Response was also noted in patients with pancreatic, endometrial, and appendiceal cancers and melanoma. Treatment adverse events were seen in 56.6% of the patients (Hong et al., 2020). The response with a daily dose of 960 mg resulted higher than across lower doses used in the study (160, 360 and 760 mg). The first assessment of response to sotorasib was performed at week 6 measured by computed tomography or magnetic resonance imaging. The median time to response was 1.4 months and the median duration of response was 10.9 months (Hong et al., 2020). In the phase 2 trial (CodeBreak 100) sotorasib was administered orally at a dose of 960 mg once daily in patients with *KRAS* G12C-mutant advanced NSCLC previously treated with standard therapies (platinum-based chemotherapy and inhibitors of programmed death 1 PD-1]) (Skoulidis et al., 2021). An objective response was recorded in 37.1% (46 of 126 patients), including 3.2% complete response and 33.9% who had a partial response. The median duration of response was 11.1 months. Disease control was seen in 80.6% of patients. The median progression-free survival was 6.8 months, and the median overall survival was 12.5 months. Efficacy was seen in subgroups with mutated STK11, KEAP1 or TP53. Although response was lower among patients with mutated KEAP1 (Skoulidis et al., 2021), long-term benefits were associated with lower baseline circulating tumor DNA levels, across *KRAS* G12V VAF (variant allelic frequency) levels, PD-L1 expression, and in patients with STK11 and/or KEAP1 comutations (Dy et al., 2023). According to guidelines, second-line treatment in NSCLC relies on docetaxel. Recently, a study was conducted to revisit the effect of docetaxel in patients with *KRAS* G12C-mutant advanced NSCLC (Gray et al., 2023). In the study, de-identified databases derived from United States electronic health records were used to assess clinicopathological characteristics and outcomes of NSCLC patients with *KRAS* mutations treated with second-line docetaxel between January 1, 2011, and March 31, 2021. Out of the 677 patients with *KRAS*-mutant NSCLC who received second-line docetaxel treatment, 295 (43.6%) had the *KRAS* G12C mutation, while 382 (56.4%) had *KRAS* non-G12C mutations. In the *KRAS* G12C group, the median overall survival and median progression-free survival after receiving docetaxel were 6 and 3.4 months, respectively (Gray et al., 2023).

A phase 3 trial comparing sotorasib with docetaxel in patients previously treated with advanced or metastatic NSCLC with *KRAS* G12C mutation (CodeBreak 200) indicated an increase in the progression-free survival for sotorasib, compared with docetaxel (median progression-free survival 5.6 months versus 4.5 months; hazard ratio 0.66; $p = 0.0017$). Overall survival was not different between the treatment groups (10.6 months in the sotorasib group and 11.3 months in the docetaxel group). The overall response rate was 28.1% in the sotorasib group and 13.2% in the docetaxel group (de Langen et al., 2023).

The recommended phase 2 dose of adagrasib (MRTX849) was 600 mg twice a day based on the results of a phase 1 study (KRYSTAL-1) in NSCLC, colorectal cancer, and other tumors harboring the *KRAS* G12C mutation. Eight out of 15 patients (53.3%) with *KRAS* G12C-mutant NSCLC attained a partial response. The median duration of response was 16.4 months. The median progression-free survival was 11.1 months. The most common adverse events were nausea (80%), diarrhea (70%), vomiting (50%), and fatigue (45%) (Ou et al., 2022). Patients with *KRAS*-mutant NSCLC have a high propensity to develop brain metastasis. In a retrospective database analysis of patients with *KRAS*-mutant NSCLC treated at Massachusetts General Hospital between May 2015 and October 2019, a total of 374 patients were reviewed. Among them, 40% (149 patients) had *KRAS* G12C mutations, while the remaining 60% (225 patients) had *KRAS*-mutant non-G12C tumors. The average age at the initial diagnosis of lung cancer was 68 years, with a range of 29–91 years. Among the patients, 58% were female, 88% were of white ethnicity, and 82% were heavy smokers with a history of more than 10 pack-years. A total of 318 patients (85%) received a histologic diagnosis of adenocarcinoma, and 249 patients (67%) were diagnosed with stage IV (metastatic) disease at the time of their initial cancer diagnosis. Importantly, there were no notable differences in these characteristics between patients with the G12C mutation and those with non-G12C mutations. Moreover, it is worth noting that 40% (150 patients) developed brain metastasis at some point, and there were no discernible differences in the frequency of brain metastases based on genotype (*KRAS* G12C and non-G12C patients). Most patients demonstrated synchronous brain metastasis; defined as detection within 3 months of the initial diagnosis of metastatic disease, while 23% developed metachronous brain metastasis (Sabari et al., 2022). Multiple in vivo models and clinical trial data indicate that adagrasib can penetrate the central nervous system (Sabari et al., 2022).

In the registrational phase 2 study, adagrasib (600 mg orally twice daily) was administered to patients with *KRAS* G12C-mutant NSCLC who had been previously treated (98% had previously received chemotherapy and immunotherapy). Of the 112 patients, 48 (42.9%) had a partial response. The median duration of response was 8.5 months, and the median progression-free survival was 6.5 months, with a median overall survival of 12.6 months. Among 33 patients with previously treated, stable central nervous system metastases, the intracranial response rate was 33.3% (Jänne et al., 2022). Response rates in patients with co-occurring alterations in STK11, KEAP1, TP53, and CDKN2A were 40.5%, 28.6%, 51.4% and 58.3, respectively. Responses were lower for those who had STK11 wild-type with a KEAP1 co-mutation (14.3%) (Jänne et al., 2022). In the sub-group analysis of response, it was 45.8% among former smokers (44/96 patients) and only 9.1% (1/11 patients) current smokers (Jänne et al., 2022). Intriguingly, the major metabolite of NNK, a tobacco-specific lung carcinogen, 4-(methylnitrosamino)− 1-(3-pyridyl)− 1-butanol (NNAL), induces LKB1 phosphorylation (S428) in lung cancer cells with wild-type LKB1 in an isomer-dependent manner, (R)-NNAL via β-adrenergic-mediated PKA activation (Bian et al., 2022). The effects of NNAL on LKB1 deactivation could be further analyzed in lung cancer patients who continue to smoke (Bian et al., 2022). While NNAL is not detectable in the plasma samples from non-smokers, it was detected in the plasma samples from all smokers (Bian et al., 2022). Previously, it was noted that β_2-adrenergic receptors promote EGFR tyrosine kinase inhibitor resistance via inactivating LKB1, increasing CREB (cyclic adenosine 3',5'-monophosphate response element-binding protein) and enhancing tumor secreted (Nilsson et al., 2017).

Divarasib (GDC-6036) is another covalent *KRAS* G12C inhibitor that, in a phase 1 study, was administered orally once daily at doses ranging from 50 to 400 mg. Among patients with NSCLC, a response was observed in 53.4% of patients, and the median progression-free survival was 13.1 months. Among patients with colorectal cancer, a confirmed response was noted in 29.1% of patients, and the median progression-free survival was 5.6 months. Serial assessments of circulating tumor DNA demonstrated that declines in *KRAS* G12C variant allele frequency were associated with response. All patients with a partial response, across all tumor types, had a *KRAS* G12C variant allele frequency of less than 1% on day 1 of cycle 3 (Sacher et al., 2023). Responses to divarasib were also observed across subgroups defined by PD-L1 status and the presence of co-occurring mutations (TP53, STK11, and KEAP1). A total of 16 patients (3 with NSCLC, 9 with colorectal cancer, and 4 with other solid tumors) had at least one possible mechanism of resistance identified, such as *KRAS* copy number gain or amplification (Sacher et al., 2023). Divarasib is being investigated in combination with other anticancer therapies: atezolizumab, cetuximab, bevacizumab, erlotinib, GDC-1971 (an inhibitor of Src homology region 2- containing protein tyrosine phosphatase-2) and inavolisib (a PI3Kα inhibitor) (Sacher et al., 2023). Clinical studies with several other covalent *KRAS* inhibitors are ongoing (Xie et al., 2023) (See Table 1).

Table 1
Clinical trials with KRAS inhibitors as single agent or in combinatorial regimens *(accessed on clinicaltrials.gov)*.

Drug inhibitor	Clinical trial	Phase	Target	Indication	Drug combined	Status	(Partial) Results
Sotorasib (AMG-510)	CodeBreaK100 NCT03600883	I/II	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	-	Active, not recruiting	ORR 37.1%, DCR 80.6%, PFS 6.8 ms, OS 12.5 ms *(Skoulidis, et al. NEJM 2021)*
					-	Active, not recruiting	ORR 41%, DoR 12.3 ms, PFS 6.3 ms, OS 12.5 ms, 2-year OS rate 33% *(Dy, et al. 2023)*
	CodeBreaK101 NCT04185883	II	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	Trametinib, RMC-4630, afatinib, pembrolizumab, panitumumab, carboplatin, pemetrexed, docetaxel, paclitaxel, atezolizumab, palbociclib, bevacizumab-awwb, TNO155, FOLFIRI FOLFOX, BI 1701963 AMG 404 and everolimus	Recruiting	-
	CodeBreak-IGR NCT05631249	II	KRAS G12C	KRAS p.G12C mutant previously treated locally Advanced or Metastatic NSCLC	-	Recruiting	-
	CodeBreak200 NCT04303780	III	KRAS G12C	KRAS p.G12C mutant previously treated advanced NSCLC	-	Active, not recruiting	ORR 28.1% vs 13.2% PFS 5.6 versus 4.5 ms (HR 0.66; p = 0.0017) OS 10.6 vs 11.3 ms *(deLanghen, et al. 2023)*
	CodeBreak201 NCT04933695	II	KRAS G12C	KRAS p.G12C mutant locally advanced or metastatic NSCLC	-	Active, not recruiting	-
	CodeBreak300 NCT05198934	III	KRAS G12C	KRAS p.G12C mutant previously treated metastatic colorectal cancer	Panitumumab	Active, not recruiting	ORR 26.4% PFS 5.6 months *(Fakih, et al. 2023)*
	NCT05815173	I/II	KRAS G12C	KRAS p.G12C mutant advanced NSCLC	Ladarixin	Recruiting	-
	NCT05313009	I/II	KRAS G12C	KRAS p.G12C mutant advanced NSCLC	Tarlox	Active, not recruiting	-
	RAMP203 NCT05074810	I/II	KRAS G12C	KRAS p.G12C mutant advanced NSCLC	Avutometinib (VS-6766)	Recruiting	-
	NCT05054725	II	KRAS G12C	KRAS p.G12C mutant previously treated advanced NSCLC	RMC-4630	Active, not Recruiting	-
	NCT05118854	II	KRAS G12C	Neoadjuvant treatment for surgically resectable (stage IIA-IIIB) KRAS p.G12C mutant NSCLC	Cisplatin or carboplatin and pemetrexed	Recruiting	-
Adagrasib (MRTX-849)	KRYSTAL-1 NCT03785249	I/II	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	Pembrolizumab cetuximab afatinib	Recruiting	ORR 42.9%, DCR 79.5%, DoR 8.5 ms, PFS 6.5 ms, OS 12.6 ms *(Janne, et al. NEJM 2022)* ORR 35.1% DoR 5.3 ms PFS 7.4 ms (*Bekaii,2023)*
	KRYSTAL-12 NCT04685135	III	KRAS G12C	KRAS p.G12C mutant advanced NSCLC	-	Recruiting	-
	KRYSTAL-16 NCT05178888	I	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	Palbociclib	Active, not recruiting	-
	KRYSTAL-14 NCT04975256	I	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	BI 1701963	Completed	-
	KRYSTAL-7 NCT04613596	II/III	KRAS G12C	KRAS p.G12C mutant locally advanced or metastatic NSCLC	Pembrolizumab	Active, not recruiting	-
	KRYSTAL-2 NCT04330664	I/II	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	TNO155	Active, not recruiting	-
	NCT05609578	II	KRAS G12C	KRAS p.G12C mutant metastatic NSCLC and 1% ≤ PD-L1 (TPS) < 50%	Pembrolizumab, pemetrexed, cisplatin or carboplatin	Recruiting	-
	Neo-Kan NCT05472623	II	KRAS G12C	Neoadjuvant treatment for surgically resectable KRAS p.G12C mutant	Nivolumab	Recruiting	-

(*continued on next page*)

Table 1 (*continued*)

Drug inhibitor	Clinical trial	Phase	Target	Indication	Drug combined	Status	(Partial) Results
	RAMP204 NCT05375994	II	KRAS G12C	KRAS p.G12C mutant advanced NSCLC	Avutometinib (VS-6766)	Recruiting	-
	KRYSTAL-19 NCT05840510	II	KRAS G12C	KRAS p.G12C mutant advanced NSCLC	Nab-sirolimus	Recruiting	-
JNJ-74699157 (ARS-3248)	NCT04006301	I	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	-	Completed	Dose-limiting toxicities G3–4 (increased CPK) observed at 100 mg and 200 mg dose *(Wang 2022)*
JAB-21822	NCT05288205	I/II	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	JAB-3312	Recruiting	-
	NCT05276726	I/II	KRAS G12C	KRAS p.G12C and STK11 mutant advanced solid tumors	-	Recruiting	-
	NCT05194995	I/II	KRAS G12C	KRAS p.G12C mutant metastatic colorectal cancer	Cetuximab	Recruiting	-
	NCT05002270	I/II	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	Cetuximab	Recruiting	-
	NCT05009329	I/II	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	-	Recruiting	-
Divarasib (GDC-6036)	NCT04449874	I	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	Atezolizumab, cetuximab, bevacizumab, erlotinib, GDC-1971, inavolisib	Recruiting	ORR 53.4% and PFS 13.1 ms (NSCLC); ORR 29.1% and PFS 5.6 ms (CRC) *(Sacher, 2023)*
D-1553	NCT05383898	I/II	KRAS G12C	KRAS p.G12C mutant advanced NSCLC	-	Active, not recruiting	-
	NCT04585035	I/II	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	Standard treatment for solid tumor	Recruiting	-
	NCT05492045	I/II	KRAS G12C	KRAS p.G12C mutant locally advanced or metastatic NSCLC	Standard treatment for NSCLC	Recruiting	-
	NCT05379946	I/II	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	IN10018	Recruiting	-
JDQ-443	NCT05132075	IIII	KRAS G12C	KRAS p.G12C mutant previously treated metastatic NSCLC	-	Recruiting	-
	NCT05445843	II	KRAS G12C	KRAS p.G12C and STK11 mutant locally advanced or metastatic NSCLC	-	Recruiting	-
	KontRASt-01 NCT04699188	I/II	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	TNO155, tislelizumab	Recruiting	-
	KontRASt-03 NCT05358249	I/II	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	Trametinib, ribociclib, retuximab	Recruiting	-
LY-3537982	NCT04956640	I	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	Abemaciclib, pembrolizumab, LY3295668, cetuximab, pemetrexed, cisplatin or carboplatin	Recruiting	-
BPI-421286	NCT05315180	I	KRAS G12C	KRAS p.G12C Mutant Advanced Solid Tumors	-	Recruiting	-
BI-1823911	NCT04973163	I	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	BI 1701963	Active, not recruiting	-
MRTX-1133	NCT05737706	I/II	KRAS G12D	KRAS p.G12D mutant advanced solid tumors	-	Recruiting	-
RMC-6291	NCT05462717	I	KRAS G12C	KRAS p.G12C mutant advanced solid tumors	-	Recruiting	-
IBI-351 (GFH-925, GF-105)	NCT05497336	I	KRAS G12C	KRAS p.G12C mutant metastatic colorectal cancer	Cetuximab	Recruiting	-
	NCT05504278	I	KRAS G12C	KRAS p.G12C mutant advanced NSCLC	Pemetrexed, cisplatin, sintilimab, carboplatin	Recruiting	-

Abbreviations: ORR: overall response rate: DoR: duration of response; DCR: disease control rate; PFS: progression-free survival; OS: overall survival; ms: months; NSCLC: non-small cell lung cancer; CRC: colorectal cancer.

REFS Table 1.

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4. MRAS activation via signal transducer and activation of transcription (STAT3) and YES associated protein 1 (YAP1)

The clinical shortcomings of single-agent *KRAS* G12C inhibitors are unveiled by bypassing inactive-state selective inhibition with increased resynthesis of drug-insensitive GTP-bound *KRAS* G12C and increased expression of *KRAS* messenger RNA and *KRAS* protein levels (Xue et al., 2020). After receptor tyrosine kinase activation by exposure to epidermal growth factor (EGF) or hepatocyte growth factor (HGF), receptor tyrosine kinases facilitate nucleotide exchange to induce GTP loading of KRAS G12C (Xue et al., 2020). Importantly, in the absence of growth factor stimulation, treatment of KRAS G12C-mutant cell lines with adagrasib or other *KRAS* G12C inhibitors produced initial pathway suppression (extracellular signal-regulated kinase [ERK] inhibition) followed by a rebound over the course of the next 72 h (Xue et al., 2020; Schulze et al., 2023). Therefore, targeting the reactivation state occurring as soon as 72 h after initial treatment with *KRAS* G12C inhibitors could be of utmost clinical significance. Our primary aim is to trace biomarkers of rapid adaptive resistance by liquid biopsy with serial analysis of *KRAS* G12C-mutant NSCLC patients treated with *KRAS* G12C inhibitors. Initially, reports indicated that resistance mechanisms to sotorasib and adagrasib encompass a variety of acquired mutations in *KRAS,* BRAF, and oncogenic fusions, among others (Zhao et al., 2021a; Awad et al., 2021). However, tracking such genetic alterations in blood has revealed their sporadic occurrence at low frequencies, often diminishing during treatment. This suggests that such genetic alterations might possess limited fitness and may not be the clinical cause of resistance. In contrast, the recurrence of *KRAS* G12C amplification emerges as a notable mechanism of resistance to *KRAS* G12C inhibition in colorectal cancer (Yaeger et al., 2023).

Barbacid's group has shown that treatment of *KRAS* G12C/Trp53-driven mice lung adenocarcinomas with sotorasib induce rapid onset of resistance, accompanied by amplification of the mutant *KRAS* allele (Salmón et al., 3 2023). Fluorescence in situ hybridization (FISH) analysis on metaphase chromosomes detected *KRAS* amplifications on extrachromosomal DNA (ecDNA, also known as double-minutes) in some sotorasib-resistant cell lines, while others exhibited intrachromosomal amplifications (homogenously staining regions, HSRs) (Salmón et al., 3 2023). Extrachromosomal amplifications on ecDNA were lost upon drug withdrawal, leading to the hypothesis that increasing *KRAS* copy numbers during treatment could be avoided with an intermittent treatment schedule (Salmón et al., 2023). Extrachromosomal DNA is a frequent event that contributes to tumor and extrachromosomal circular DNA is present in both tumor tissue and the bloodstream of patients (Yan et al., 2020; Kumar et al., 2017). In experimental findings in genetically engineered mice by Barbacid's group (Salmón et al., 2023), it was found that resistance and tumor survival occurred through the activation of NF-kB and STAT3-driven pathways. Nuclear localization of STAT3 was detected in a majority of clones (Salmón et al., 2023). Similarly, we observed in the EGFR-mutant cell line that following gefitinib (EGFR TKI) treatment, signal transducer and activator of transcription 3 (STAT3) was activated and translocated into the nucleus (Karachaliou et al., 2018). STAT3 activates many genes, including the concentration of unphosphorylated STAT3 (U-STAT3), which drives a second wave of gene expression, affecting genes such as RANTES, IL6, IL8, MET, and MRAS (Yang et al., 1 2007; Yang et al., 2005). (Fig. 2) MRAS is closely related to the *KRAS* proto-oncogenes (Simanshu et al., 2017). MRAS regulates RAF activity through SHOC2 and protein phosphatase 1 catalytic subunit (PP1C). Dephosphorylation of RAF substrates by PP1C is enhanced in the presence of SHOC2 and MRAS. Different groups have reported the high-resolution structure of the SHOC2:MRAS:PP1C complex, which could pave the way for the discovery of new classes of inhibitors (Liau et al., 2022; Bonsor et al., 2022; Kwon et al., 2022; Hauseman et al., 2022)(Fig. 3). The cell polarity regulator Scribble is often deregulated in human NSCLC, and the loss of Scribble (disrupting apico-basal polarity and junctional integrity) cooperates with KRAS in in vivo models, resulting in more aggressive lung tumors (Elsum et al., 2014). Scribble was earlier reported to antagonize SHOC2-mediated RAF S259 dephosphorylation (Young and Rodriguez-Viciana, 2018).

MRAS can be activated by hepatocyte growth factor (HGF) (Zhang et al., 2004) (Fig. 2) and MRAS, along with MET, is overexpressed in several types of tumors via STAT3 (Young and Rodriguez-Viciana, 2018) (Fig. 2), although also through the transcriptional coactivator yes associated protein 1 (YAP1) (see below). In a rapid-autopsy case of a patient with *KRAS* G12C-mutant lung adenocarcinoma who initially responded to a KRAS G12C inhibitor but promptly developed resistance, deep-RNA and whole-exome sequencing comparing pretreatment and post-treatment tissues revealed reactivation of the MAPK pathway, despite no new mutations in KRAS or downstream mediators being identified (Tsai et al., 2022).

Among other alterations, significant upregulation of pathways involving YAP1 was observed (Tsai et al., 2022). We found that STAT3 and YAP1 activation via Src signaling were activated in EGFR-mutant NSCLC, limiting the response to EGFR TKIs. Cotargeting EGFR, STAT3, and Src was synergistic in two EGFR mutant NSCLC cell lines (PC9 and H1975). In EGFR-mutant NSCLC patients treated with EGFR TKIs, high expression of STAT3 or YAP1 mRNA predicted worse progression-free survival (Chaib et al., 2017). The regulation of YAP1 is commonly governed by the Hippo pathway, which is triggered by a core kinase cascade involving the mammalian sterile-20-like kinases (MST1/2) (Rosell et al., 2021b). Inactivation of MST2 induces the activation of RAF1 (O'Neill et al., 2004). Therefore, RAF1 is a putative therapeutic target in *KRAS*-mutant NSCLC (Blasco et al., 2011; Drosten and Barbacid, 2022). However, previous studies have shown that RAF inhibitors such as MLN2480, GW5074, PLX8394, and LYSN3074753 had no therapeutic effect on RAS-driven tumors. Hence, more potent and selective inhibitors are desired to reproduce the results of RAF1 genetic ablation (Li et al., 2023a).

5. Aquaporin 5 a putative therapeutic co-target?

The epithelium of lung alveoli serves a dual role in both gas exchange and host defense. This alveolar epithelium consists of two main cell

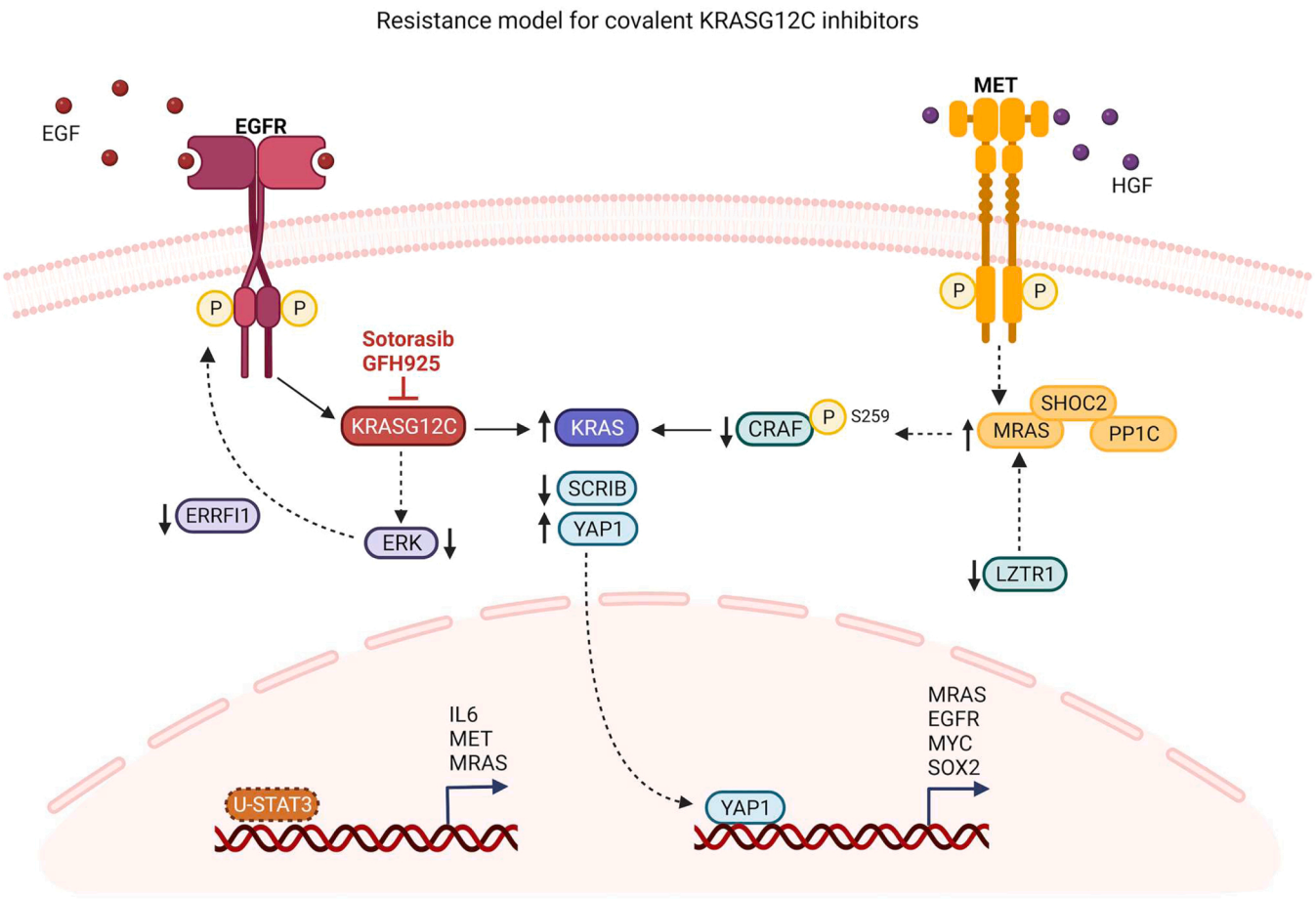

Fig. 2. Depiction model for adaptive resistance to *KRAS* G12C covalent inhibitors. Following K*RAS* G12C inhibition (i.e., sotorasib) there is a mis-localization of Scribble with nuclear translocation of yes-associated protein 1 (YAP1) that can upregulate different genes, among them MRAS. MRAS forms a holoenzyme trimeric complex with SHOC2 and PP1C that dephosphorylates CRAF at serine 259, leading to reactivation of mitogen-activated protein kinase (MAPK) signaling. Several layers of evidence report that MRAS can be activated via Hepatocyte growth factor (HGF), and loss of the tumor suppressor leucine zipper-like transcriptional regulator 1 (LZTR1). Signal transducer and activator of transcription 3 (STAT3), once activated and translocated to the nucleus, leads to augment unphosphorylated STAT3, driving a second wave of activated transcripts, including those of MRAS, interleukin-6 (IL6) and MET). We surmise that rapid feedback activation of epidermal growth factor receptor (EGFR) can occur through downregulation of negative EGFR regulators, for example the expression of ERBB receptor feedback inhibitor 1 (ERFFI1), causing partial reactivation of RAS signaling.

types: AT1 cells, which are thin and quiescent, primarily responsible for facilitating gas exchange, and AT2 cells, cuboidal cells that secrete pulmonary surfactants (Fig. 4). When damage occurs to the alveolar epithelium, AT2 cells play a critical role. They function as stem cells that both self-renew and differentiate to produce AT1 cells, meaning that they can generate new AT1 cells, thus aiding in the repair and regeneration of the damaged alveolar epithelium. Dysregulation of homeostasis can induce chronic inflammatory diseases and lung adenocarcinoma (Rock and Hogan, 2011; Basil et al., 2020; Choi et al., 2020). Barbacid's group identified the cancer-initiating cells as AT2 cells in *KRAS*-driven lung adenocarcinoma, which are a primary component of the alveoli responsible for the production and secretion of surfactant-associated protein C (SPC), effectively replacing AT1 cells (Mainardi et al., 2014). Likewise, all high-grade adenocarcinomas developed in mouse models were also exclusively surfactant protein C positive (Mainardi et al., 2014). Intriguingly, in *KRAS* G12C lung adenocarcinoma patients treated with sotorasib or adagrasib, tissue assessment showed a dramatic induction of AT1 differentiation identified by HOPX protein immunoreactivity, while pre-treatment samples have weak or no HOPX expression (Li et al., 2023b). The phenotype shift towards an AT1 like state was also shown in mouse lung adenocarcinomas (Li et al., 2023b). The results document that suppressing *KRAS* promotes AT1 differentiation of regenerative AT2 cells, suggesting that KRAS signaling is a barrier to AT1 differentiation during the regenerative response (Li et al., 2023b).

Paradoxically, recent reports indicate that p53 suppresses lung adenocarcinoma by regulating alveolar differentiation, specifically by promoting AT1 differentiation (Kaiser et al., 2023).

As a personal hypothesis, it is conceivable that *KRAS* G12C cell lines with wild-type p53 might exhibit greater resistance. This resistance could be attributed to the role of p53 in promoting the transition to AT1 cancer cells following *KRAS* G12C inhibition. In this regard, SW1573 stands out as a de novo resistant cell line to sotorasib (AMG-510) (Canon et al., 2019), as previously explained. It was found that isolated AT1-like cancer cells exhibit significantly higher growth potential than the remining pool of lung adenocarcinoma cells in residual disease, primarily composed of AT2-like cancer cells (Li et al., 2023b). The study suggests the development of therapeutic approaches targeting the AT1-like lung adenocarcinoma cells (Li et al., 2023b). Aquaporin 5 (AQP5) serves as a marker of AT1 cells (Rock and Hogan, 2011; Mainardi et al., 2014) (Fig. 4). AQP5 is a water channel protein that is notably expressed at the apical membrane of AT1 cells, conferring high osmotic permeability, and it is upregulated in lung cancer (Zhang et al., 2010). AQP5 protein and mRNA expression are elevated in lung adenocarcinoma cell lines, with higher expression levels observed in the A549 cells. Notably, AQP5 downregulation has been shown to inhibit A549 cell

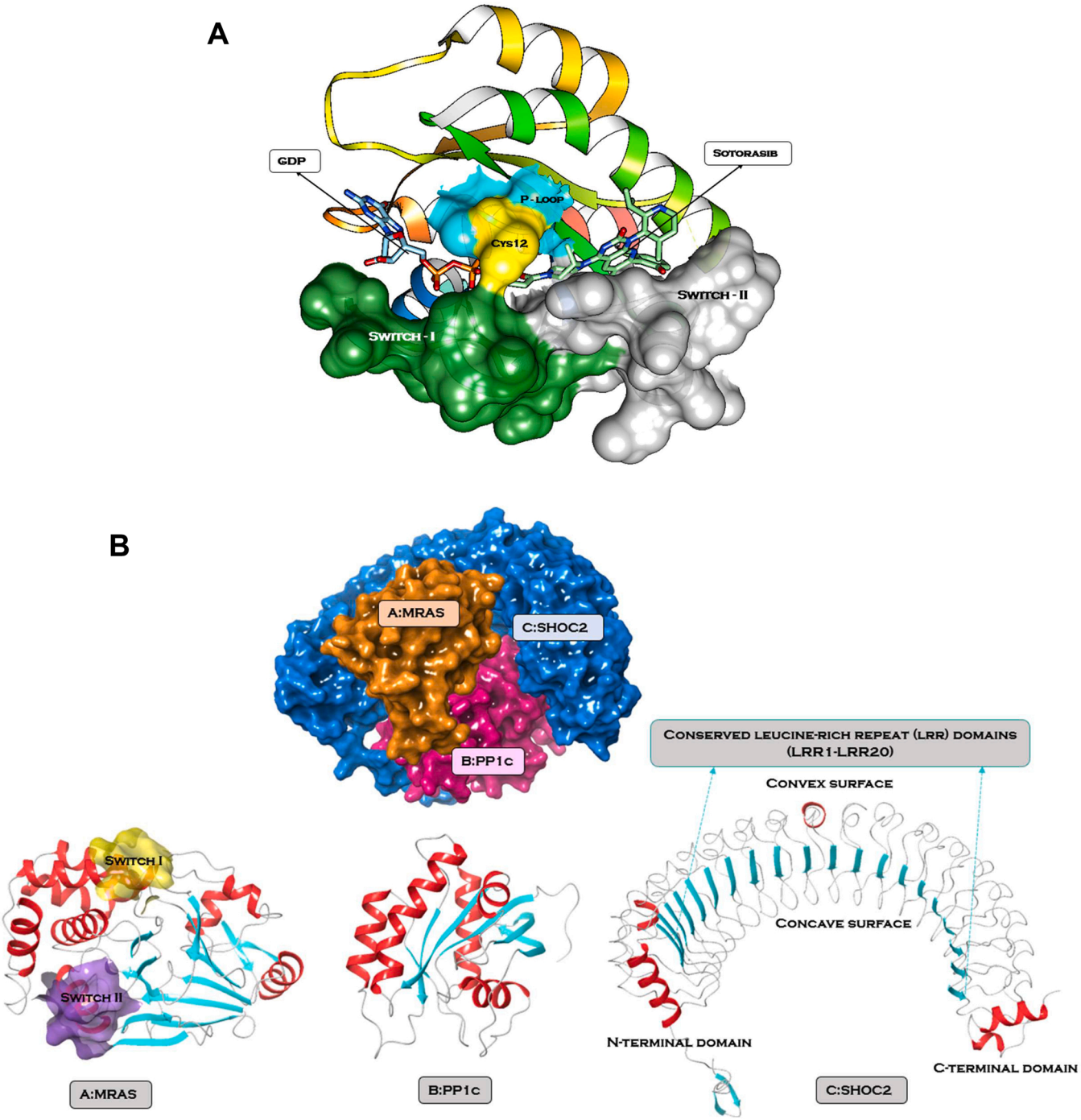

Fig. 3. A. A co-crystalized structure of GDP-bound **KRAS G12C** (PDB ID:6OIM) highlighting the mutant CYS 12 residue (yellow surface), P-loop (cyan surface), switch I (dark green surface) and switch II (gray surface) to which sotorasib is covalently docked. **B.** (**Upper**) Hydrophobicity surface of the cryo-electron microscopy structure of **SHOC2:MRAS:PP1C** holophosphatase complex. (PDB ID: 7UPI). (**Below**) The ribbon structures of chain **A:MRAS** highlighting its two contact regions of SHOC2, switch I (yellow surface) and switch II (Purple surface) that change conformation upon the exchange of GDP–GTP. The secondary structure of chain **B:PP1C** which binds to SHOC2 through complementary electrostatic interactions. The crescent-shaped structure of chain **C:SHOC2 is** comprised of 20 tandem leucine-rich-repeat (LRR) domains that act as a cradle to bind the other two proteins to form a complex. Each LRR has 22–24 amino acids and is made up of a β-strand, a descending loop, an α-helix, and an ascending loop. The solenoid's concave surface is produced by the parallel assembly of LRR β-strands, while the majority of the convex surface is made up of α-helices.

proliferation (Zhang et al., 2018). Interestingly, AQP5 has been found to activate EGFR, ERK1/2, and p38 mitogen-activated protein kinase (p38 MAPK) signaling in lung cancer (Zhang et al., 2010; Jaskiewicz et al., 2023). The role of AQP5 in lung cells is noteworthy. Both pathways are relevant as potential resistance mechanisms to *KRAS* G12C inhibitors. Acetazolamide is recognized as an AQP5 inhibitor (Rosell et al., 2023). In silico analysis has identified chemotypes that can be considered for testing in preclinical assays (Fig. 5 displays the crystallographic structure of AQP5). To summarize, AQP5 inhibitors could hold significant promise in the context of co-targeting in *KRAS* G12C-driven lung adenocarcinomas.

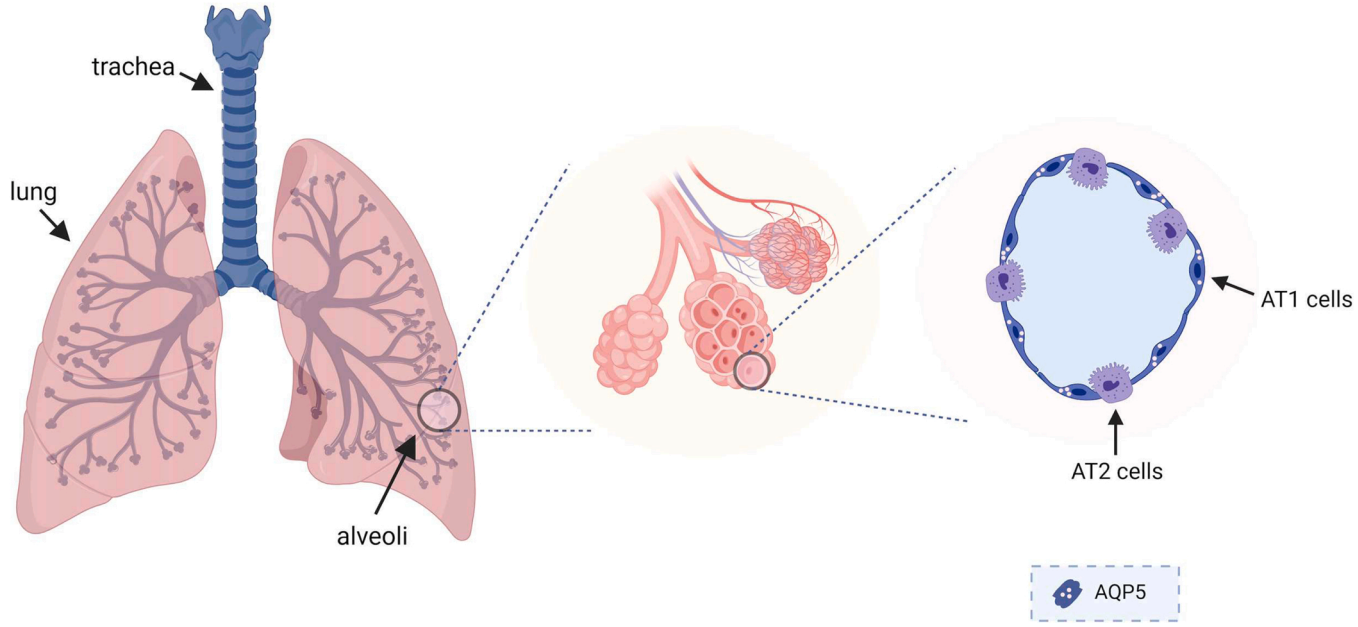

Fig. 4. Epithelium of lung alveoli. Schematic diagram showing the subcellular pattern of aquaporin 5 (AQP5) expressed in apical membrane of type 1 pneumocytes (AT1). This figure was designed using BioRender.

6. Scribble and MRAS:SHOC2:PP1C complex in immediate resistance to single *KRAS* G12C inhibitors

The localization of Scribble is controlled by palmitoylation, and the key palmitoyl acyltransferase responsible for regulating Scribble is ZDHHC7. Knockout of ZDHHC7 results in mislocalization of Scribble, leading to YAP activation. Scribble palmitoylation is a dynamic process, and the half-life of palmitoylated Scribble is relatively short. Depalmitoylating enzymes, such as acylprotein thioesterases, are responsible for removing palmitate from proteins. APT1 and APT2 are thioesterases that regulate the acylation cycle of RAS. Rescuing Scribble palmitoylation by upregulating ZDHHC7 or inhibiting APT1/APT2 may also serve as potential therapeutic strategies for cancer cells with dysregulated Scribble (Chen et al., 2016). As previously commented, several studies have demonstrated that SHOC2 directly binds to activate GTP-bound MRAS and serves as a scaffold for the formation of a ternary complex. This complex includes active MRAS, SHOC2, and PP1C (Fig. 2 and Fig. 3). In RTK-mediated signaling, the MRAS:SHOC2:PP1C ternary complex plays a role in dephosphorylating a negative regulatory site that binds 14–3–3 on the RAF kinases. This dephosphorylation process favors the binding of RAF to RAS proteins, thus promoting ERK activation. Furthermore, there is a larger signaling complex that includes active MRAS:SHOC2:PP1C and Scribble, which acts as a tumor suppressor protein (Kaduwal et al., 2015; Kota et al., 2019; Young et al., 2018; Lai et al., 2022) (Fig. 2).

Recently, it has been demonstrated that following a 48-hour treatment with *KRAS* G12C inhibitors, such as sotorasib and adagrasib, E-cadherin undergoes cytoplasmic re-localization (Adachi et al., 2023). E-cadherin is an epithelial marker and loss of E-cadherin expression induces epithelial-mesenchymal transition (EMT) state. Scribble mislocalization also occurred after a few hours of KRAS G12C inhibitor treatment. Scribble is a multidomain scaffolding protein that regulates assembly of tight junction proteins and preserves cell apical-basal polarity (Santoni et al., 2020). Inhibition of mutant KRAS by sotorasib induced re-localization of Scribble from the plasma membrane to the cytosol, which occurred as early as 12 h following sotorasib treatment in NCI-H358, as well as another *KRAS* G12C inhibitor-sensitive cell line LU65 (Adachi et al., 2023). Scribble mis-localization was also seen in the HCC827 EGFR-mutant cell line treated with Osimertinib and the NCI-H2228 ALK-translocated cell line treated with alectinib. Scribble mis-localization was also found following sotorasib treatment in SW837 and SNU1411 *KRAS* G12C mutant colorectal cancer cell lines (Adachi et al., 2023). Localization of Scribble is regulated by its palmitoylation, which is mediated by the zinc finger DHHC-type containing palmitoyl S-acyltransferase ZDHHC7 (Santoni et al., 2020). In NCI-H358 and LU65 cells, ZDHHC7 localizes to Golgi membranes. It was found that ZDHHC7 protein expression was significantly reduced after sotorasib treatment in NCI-H358 and LU65 cells. However, ZDHHC7 messenger RNA levels did not show a constant trend after sotorasib treatment (Adachi et al., 2023). Overexpression of ZDHHC7 prevented Scribble mis-localization following sotorasib treatment in NCI-H358 cells (Adachi et al., 2023).

Mis-localization of Scribble inactivates Hippo-YAP signaling. Gene Set Enrichment Analysis (GSEA) showed that sotorasib induced the upregulation of YAP-related gene signals, as well as EMT in NCI-H358 cells. Scribble is known to positively regulate Hippo pathway kinases and the downregulation of Scribble leads to YAP/TAZ activation (Piccolo, 2012; Chen et al., 2012). Treatment with *KRAS* G12C inhibitors downregulated Hippo pathway signaling, leading to nuclear translocation of YAP protein and its transcriptional activity (Adachi et al., 2023). YAP was previously known to induce mutant *KRAS* independence. Our previous research, along with that of others, has demonstrated that YAP Y357 Hippo-independence is involved in *KRAS* and BRAF-mutant NSCLC, EGFR-mutant NSCLC, and pancreatic cancer, primarily through SRC/YES activation (Rosell et al., 2021). The Hippo effector YAP promotes resistance to RAF and MEK-targeted cancer therapies (Lin et al., 2015; Zhang et al., 2014). *KRAS* and YAP1 converge to regulate EMT and tumor survival (Kapoor et al., 2014; Karachaliou et al., 2018). Of interest is the fact that mislocalization of Scribble interacts with YES, promoting YAP1 phosphorylation (Hippo-independent mechanism) (Zhao et al., 2021b). Importantly, Adachi et al. identified MRAS as a representative YAP downstream gene together with the well-known CYR61 and ANKRD1 (Adachi et al., 2023). qPCR analysis of mRNA levels of MRAS, ANKRD1 and CYR61 were elevated in NCI-H358 cells after 48 h of sotorasib treatment.

MRAS mediates its signal through SHOC2. Activated MRAS binds to SHOC2 and the catalytic subunit of PP1 (PP1C) and recruits them to the plasma membrane where the trimeric complex dephosphorylates CRAF Ser 259 (Kwon et al., 2022). Noteworthy is the fact that leucine

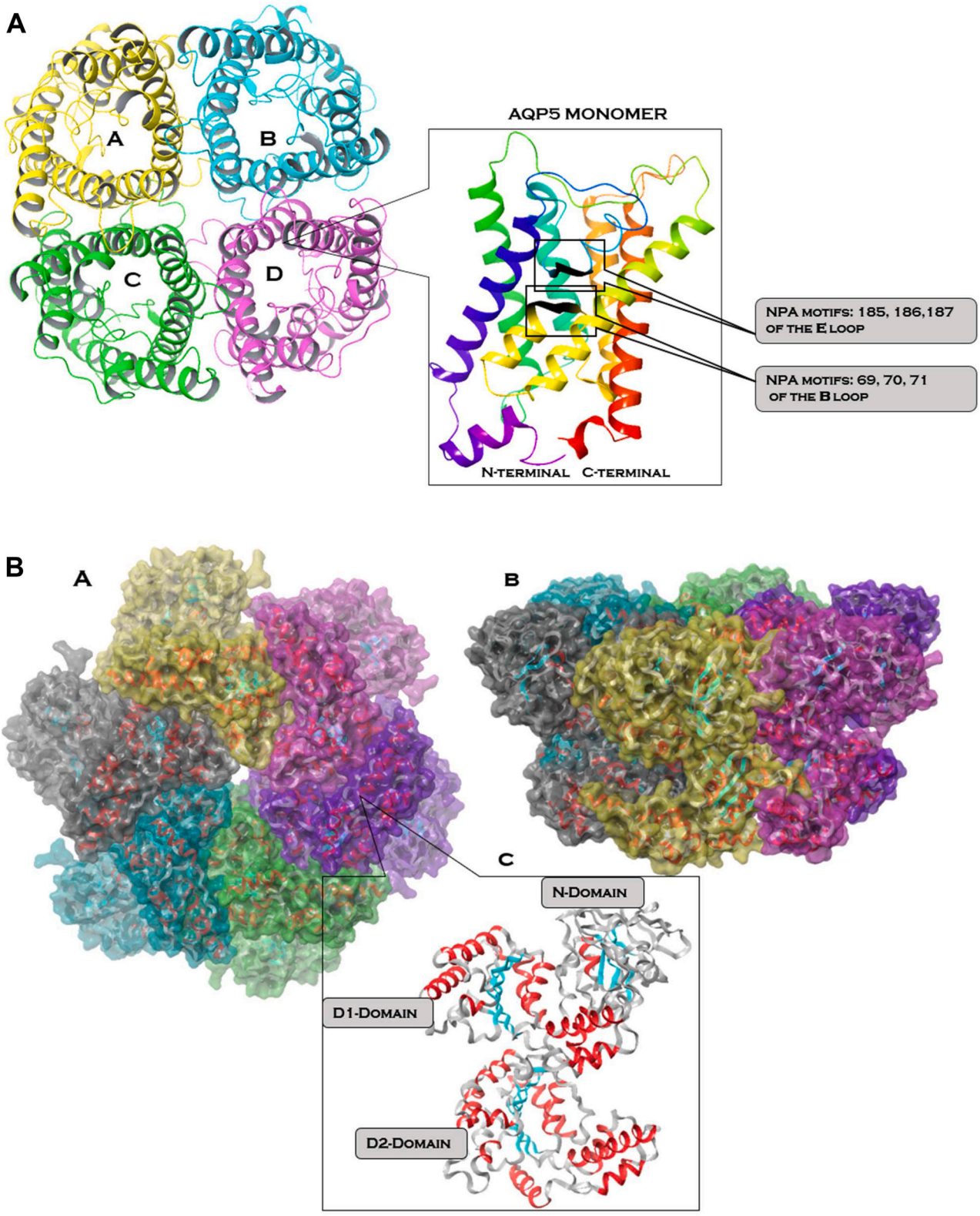

Fig. 5. A. (**Left**) The top view of the tetrameric structure of **aquaporin 5**. (PDB ID:3D9S). (**Right**) The side view of a single monomer highlighting the N- and C-termini of the peptide chain within the cell membrane. It contains six α-helix-rich tandem hydrophobic transmembrane regions which are connected by five loops (A-E loops). The B and D rings are inside the cell, while the A, C, and E rings are on the outside. Aspartyl-proline-alanine (NPA) motifs (highlighted in black) are positioned on the amino acid residues 69, 70, and 71 of the B loop, and 185, 186, and 187 of the E loop. Fig. 5**B.** (**A and B**). Top and Side views of the cryo-electron microscopy structure of human **p97/VCP** (PDB ID: 5FTJ) **C.** Each subunit of this homo-hexamer consists of two tandem AAA+ ATPase domains (D1- and D2-domain) and one N-terminal domain (N-domain). Two linkers connect these domains: the D1-D2 linker connects the D1- and D2-domain, while the N-D1 linker connects the N- and D1-domain.

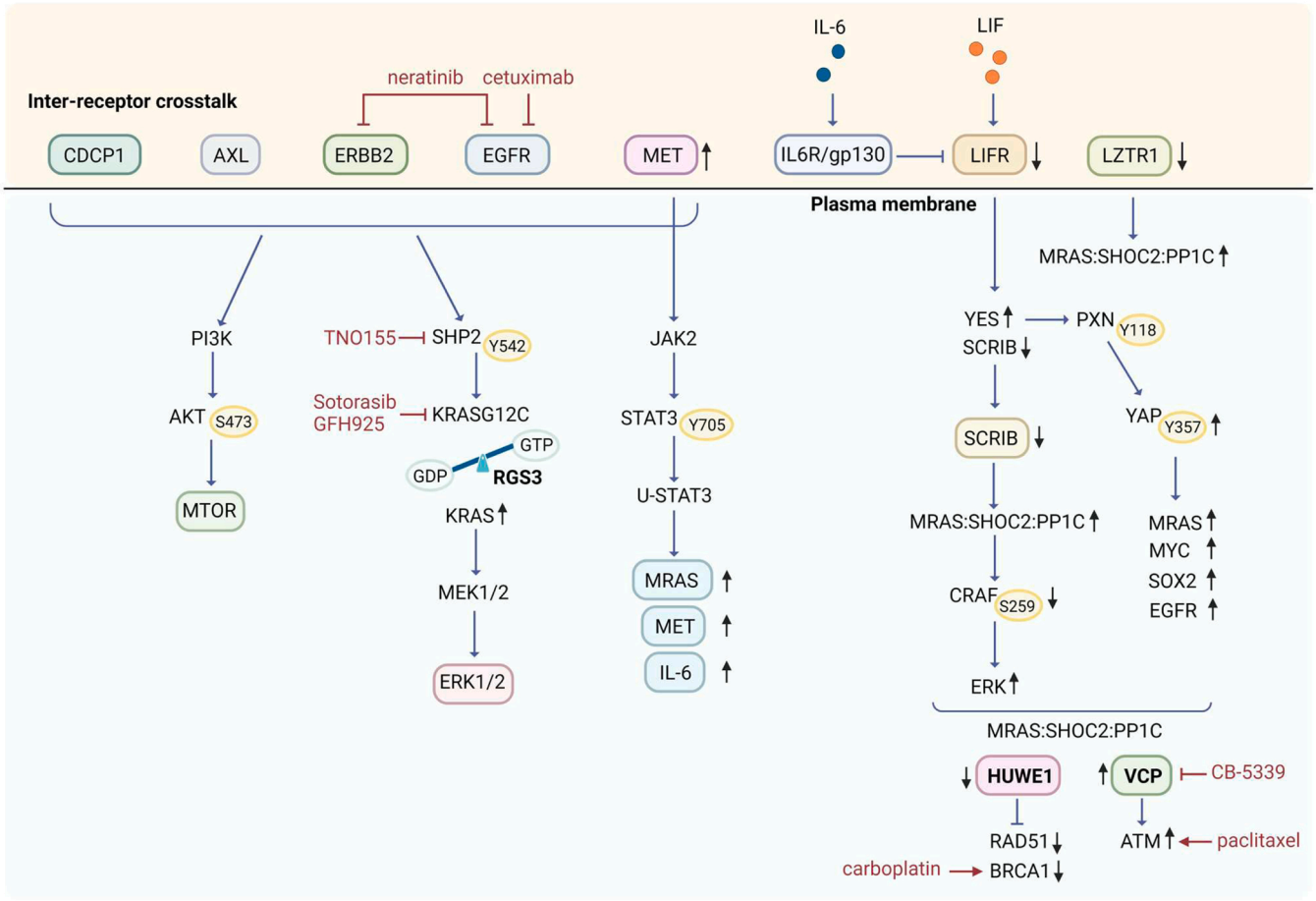

Fig. 6. Depiction of potential signaling pathways that lead to MRAS up-regulation in K*RAS*-mutant lung cancer. Several receptor tyrosine kinases (RTKs) such as cub-domain containing protein 1 (CDCP1), AXL, ERBB2, EGFR and MET could influence the response to *KRAS* G12C inhibitors in native *KRAS*-mutant G12C cell lines or after treatment with sotorasib (in the figure another covalent inhibitor, GFH925, is also represented). Adaptive resistance to sotorasib occurs after 48–72 h of treatment with Scribble (SCRIB) destabilization. Through Hippo-dependent pathway dysregulation, YAP is activated with MRAS up-regulation. Notwithstanding, YAP could be translocated into the nucleus by tyrosine phosphorylation at 357, which is a result of YES-paxillin (PXN) activation (PAX tyrosine phosphorylation at 118). We hypothesize that MRAS activation could occur through YAP via either Hippo-dependent or Hippo-independent mechanisms. Additionally, the loss of leukemia inhibitory factor receptors (LIFR) leads to alterations in SCRIB localization on the plasma membrane, as reported in breast cancer. Loss of LIFR has also been described in KRAS-mutant lung adenocarcinoma (refer to the text for more details). Leucine zipper transcriptional regulator 1 (LZTR1) has been identified as a negative regulator of MRAS. It is plausible that the signaling of MRAS through the MET-Janus kinase 2 (JAK2)-STAT3-U-STAT3 pathway should also be investigated. Co-treatment with EGFR inhibitors (cetuximab or neratinib) could abrogate the activation of MRAS and reactivation of ERK phosphorylation. Also, an SHP2 phosphatase inhibitor (i.e., TNO155) could suppress the elevation of MRAS. RGS3 can potentially serve as a marker of the activity of covalent *KRAS* G12C inhibitors. HUWE1 and valosin-containing protein (VCP) may serve as predictive markers of response to *KRAS* G12C inhibitors for HUWE1 feedback inhibition of the SHOC2: MRAS:PP1C holoenzyme, and VCP plays a contrasting role in resetting the holoenzyme complex, facilitating further MAPK reactivation. Additionally, we posit that HUWE1 and VCP may also predict response to different chemotherapy treatments, such as carboplatin and paclitaxel. See details in text.

zipper-like transcriptional regulator 1 (LZTR1) is a regulator of different canonical and non-canonical RAS GTPases proteins mediating proteasomal degradation of a variety of RAS proteins, including NRAS, KRAS, HRAS, MRAS and RIT1 (Chen et al., 2022). Therefore, loss of LZTR1 is a mechanistic explanation of feedback reactivation of RAS signaling through wild-type NRAS and HRAS following *KRAS* G12C inhibition (Ryan et al., 2022) (Fig. 2).

In the Adachi et al. study it was noted that MRAS displayed low expression at baseline, however, treatment with sotorasib induced an increase in its expression while also causing the downregulation of CRAF Ser 259 (Adachi et al., 2023). At the basal level, SHOC2 is bound to Scribble, but when Scribble is mis-localized, the interaction between SHOC2 and Scribble, downregulated by sotorasib, is disrupted. Meanwhile, MRAS, which is prompted by YAP signaling, forms a bond with SHOC2. The results from Adachi et al. demonstrate that *KRAS* inhibition induces a molecular switch from Scribble:SHOC2 to MRAS:SHOC2, leading to reactivation of MPK signaling by dephosphorylating CRAF Ser 259. In addition, MRAS-knockout cells become more sensitive to sotorasib (Adachi et al., 2023) (Fig. 2).

The research conducted by Adachi et al. provides further evidence on the crucial role of the formation of a membranous complex involving MRAS, SHOC2, and PP1C in the context of adaptive resistance to *KRAS* G12C inhibitors (Adachi et al., 2023). It has been demonstrated that receptor tyrosine kinase ligands like EGF and HGF can activate GTP-bound MRAS (Kwon et al., 2022) (Fig. 2). Additionally, the combined use of afatinib and sotorasib effectively counters MRAS activation and prevents the reactivation of ERK phosphorylation (Adachi et al., 2023). Moreover, the combination of sotorasib with BI-3406 (SOS1 nucleotide exchange factor inhibitor) also suppressed the elevation of MRAS-GTP. The study by Adachi et al. emphasizes that MRAS may play a role in the transformation of adaptive resistant cells into fully resistant phenotypes, possibly by acquiring stemness and/or a more mesenchymal character. Furthermore, it has been observed that RTK-activated MRAS can form a complex with SHOC2:PP1C, and this complex formation can be induced by HGF (Zhang et al., 2004) (Fig. 2). Intriguingly, MRAS along with MET is overexpressed in multiple types of cancer

(Young and Rodriguez-Viciana, 2018).

We posit that leukemia inhibitory factor receptor (LIFR) (Fig. 5) could be an important biomarker since it was seen, first, that mutant *KRAS* represses LIFR and, second, that survival data derived from TCGA showed worse survival for *KRAS*-mutant lung adenocarcinomas with low LIFR expression (Liu et al., 2021). Previously it was found that LIFR is an upstream regulator of the Hippo-Scribble pathway (Piccolo, 2012) and the loss of LIFR alters Scribble localization and activates YAP (Chen et al., 2012) (Fig. 5). As a matter of interest, histone deacetylase inhibitors (HDACi), such as vorinostat and entinostat, restored and increased LIFR levels in breast cancer cell lines (Clements et al., 2021). YAP1 could be a biomarker of ferroptosis and therefore could be targeted with ferroptosis inducers (Rosell et al., 2023).

7. HUWE1 and valosin containing protein, regulators of MRAS: SHOC2:PP1C

Moreover, in addition to Scribble, HUWE1 also regulates the MRAS: SHOC2:PP1C holoenzyme trimeric complex. Shortly after SHOC2 is activated, it undergoes ubiquitination by HUWE1, subsequently, the MRAS:SHOC2:PP1C complex is repositioned by valosin containing protein (VCP) which detects and binds to the polyubiquitinated SHOC2, resulting in HUWE1 disassociation from the complex. The displacement of HUWE1 enables the restoration of MRAS:SHOC2:PP1C activity (Kwon and Hahn, 2021). In addition to PP1C, several SHOC2 interacting proteins are found in the leucine-rich repeat regions, including HUWE1, the AAA+ATPases, VCP/p97 and PSMC5. These proteins collectively regulate the ubiquitination of MRAS:SHOC2:PP1C by HUWE1 (Jang et al., 2021). PSMC5 and VCP trigger redistribution of the SHOC2 complex to late endosomes and/or multivesicular bodies reactivating the signaling complex and the amplitude of the ERK1/2 activity (Jang et al., 2015; Meyer et al., 2012; Jang et al., 2019). VCP inhibitors suppress inositol-requiring enzyme 1a-X-box binding protein 1 (XBP1) pathway and induce irreversible endoplasmic reticulum stress (Zhang et al., 2017; Lee et al., 2018).

Recent findings have demonstrated that sotorasib-resistant tumors exhibit both reactivated ERK and hyperactivated AKT. This reactivation is attributed to the restoration of inositol-requiring enzyme 1α and the suppression of inositol-requiring enzyme 1α, which is one of the three pathways involved in endoplasmic reticulum stress (Mielczarek-Lewandowska et al., 2019). This restoration and suppression together overcome resistance to *KRAS* G12C inhibitors (Lv et al., 2023). Therefore, the assessment of VCP in *KRAS* G12C-driven lung adenocarcinoma seems to be of utmost importance, as well the assessment of VCP inhibitors to disrupt proteostasis (Anderson et al., 2015; Banerjee et al., 2016; Roux et al., 2021). A novel moonlight function of VCP has been identified in colorectal cancer, where it facilitates fatty acid oxidation. In this role, nuclear VCP binds to histone deacetylase 1 (HDAC1), which promotes its degradation. This, in turn, leads to the increased transcription of genes associated with fatty acid oxidation, including the critical rate-limiting enzyme carnitine palmitoyltransferase 1 A (CPT1A) (Huang et al., 2023). As a matter of additional interest, CPT1A confers resistance to immunotherapy (Liu et al., 2023).

8. Regulator of G protein signaling 3 and enolase 1

Regulator of G protein signaling 3 (RGS3) is a GTPase-activating protein (GAP) that accelerates the conversion of active GTP-bound RAS to inactive, GDP-bound RAS. RGS3 expression correlates with sensitivity to *KRAS* G12C inhibitors in patient-derived NSCLC xenograft models (Li et al., 2021a) (Fig. 1). The discovery of RGS3 GAP activity could contribute to predict response to sotorasib, adagrasib and other K*RAS* G12C inhibitors under evaluation (Rosell et al., 2021a). Overexpression of enolase1 mRNA has been observed in lung cancer with high expression of enolase 1 associated with poor survival of patients with NSCLC. The role of the glycolytic enzyme enolase 1 involved upregulation of mesenchymal markers such as vimentin along with concurrent downregulation of E-cadherin. Mechanistically, enolase 1 interacts with MET (Li et al., 2021b) (Fig. 7). Therefore, gauging the expression of enolase 1 in serial blood samples of *KRAS* G12C-mutant NSCLC patients could provide additional valuable insights in the ongoing study. Finally, nuclear factor erythroid 2-related factor 2 (NRF2) signaling pathway has been observed to play a critical role in ferroptosis. Genetic inhibition of the NRF2 pathway hampers *KRAS* G12C-mutant induced tumor growth in pancreatic cancer models, effectively antagonizing ferroptosis in vivo. Moreover, resistance to ferroptosis inducers, such as erastin or sulfasalazine, activates the transsulfuration pathway through NRF2 transcriptional upregulation of cystathionine β-synthase (Rosell et al., 2023). Mutations with loss of Kelch-like ECH-associated protein (KEAP1) increase NRF2 expression (Fig. 1). NRF2 reprograms cell metabolism by regulating the expression of genes and enzymes involved in various metabolic pathways. These pathways include glycolysis (e.g., enolase 1), the pentose phosphate pathway, one-carbon metabolism, nucleotide biosynthesis, glutaminolysis, fatty acid synthesis, and glutathione synthesis (e.g., SLC7A11) (He et al., 2020). Furthermore, TRIM 25, a tripartite motif-containing (TRIM) family member, causes ubiquitination of KEAP1 in distinct tumors, mediating tumor growth in colon cancer and gliomas. Elevated TRIM25 mRNA expression has been associated with poor prognosis (Huang et al., 2023; Wei et al., 2023).

In *KRAS*-mutant NSCLC with loss of heterozygosity for any RAS (Gkrania-Klotsas et al., 2010)(wild-type RAS), there are elevated levels of fatty acid synthase (FASN) associated with shorter overall survival. *KRAS*-mutant lung cancer cells with LAKR showed higher levels of FASN with sensitivity to FASN inhibitors and synergistic effects with MRTX849 (adagrasib) (Liu et al., 2021).

9. STK11/LKB1 co-mutations and resistance to immune checkpoint therapy

The combination of pembrolizumab with pemetrexed and platinum in the first-line treatment of metastatic non-squamous NSCLC, predominantly lung adenocarcinoma (KEYNOTE-189), demonstrated improved progression-free survival with a duration of 9 months. This contrasts with the pemetrexed-platinum group, which had a progression-free survival of 4.9 months (hazard ratio, 0.49). Additionally, the objective response rate was 48.3% for the pembrolizumab combination group, while it was 19.9% for the pemetrexed-platinum group. Median overall survival was 22 months in the pembrolizumab plus pemetrexed-platinum group and 10.6 months in the pemetrexed-platinum group (hazard ratio, 0.569) (Rodríguez-Abreu et al., 2021). However, unresponsiveness or reduced sensitivity to immune checkpoint therapy (e.g., pembrolizumab) can result from a number of tumor-intrinsic or extrinsic factors that collectively favor the immune escape of cancer cells. These factors include lack of tumor antigens, impaired major histocompatibility complex (MHC)-restricted antigen presentation, mutational landscape (such as STK11 mutations coexisting with KRAS mutations) and oncogenic signaling, deregulation in interferon signaling, overexpression of inhibitory checkpoint molecules, immunosuppressive cells (e.g., myeloid derived suppressor cells, M2-like macrophages, and regulatory T cells), or cytokines in the tumor microenvironment (Kirchhammer et al., 2022).

STK11/LKB1 alterations were identified as a major driver of primary resistance to immune checkpoint therapy (to PD-1 or PD-L1 inhibitors) with median progression-free survival of 1.7 months and median overall survival of 11.1 months versus 19.3 months and 26.5 months in STK11 wild-type groups in *KRAS*-mutant lung adenocarcinoma (Skoulidis et al., 2018). Several other studies have reported the negative impact of comutations involving STK11, as well as those of KEAP1 (Ricciuti et al., 2022; Pavan et al., 2021). Another report confirms that somatic STK11 mutations correlate with a poor objective response rate and reduced survival with durvalumab (anti-PD-L1 inhibitor) or durvalumab plus

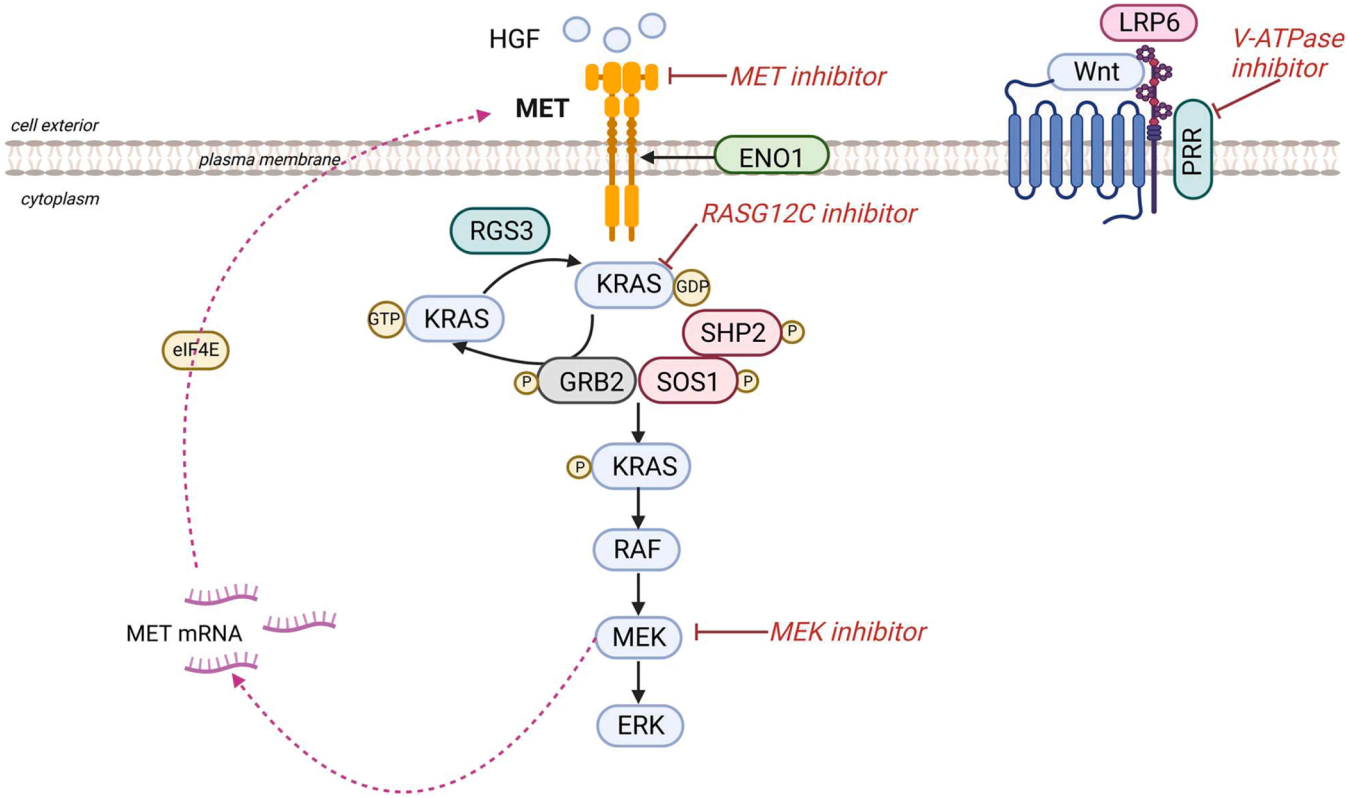

Fig. 7. Enolase involvement in KRAS mutant lung cancer via MET and WNT co-receptor signaling. Enhanced MET translation and signaling is observed in *KRAS*-mutant cancer cells for anchorage independent tumor growth. Enolase 1 (ENO1) interacts and activates MET and Wnt signaling via increased phosphorylation of MET and the Wnt coreceptor low density lipoprotein receptor-related protein 5/6 (LRP5/6). Wnt signaling requires V-ATPase function. LRP6 and Frizzled are bound to the prorenin receptor (PRR), which acts as an adapter between the receptor complex and the V-ATPase. We surmise that the combination *KRAS* G12C inhibitors with V-ATPase inhibitors could be a promising combinatory strategy that merits attention.

tremelimumab (anti-CTLA4 antibody) (Pore et al., 2021). Reduction of STAT3 in the tumor microenvironment using an antisense oligonucleotide reversed immunotherapy resistance in preclinical STK11 knockout models (Pore et al., 2021). Barbie's group (Kitajima et al., 2019) discovered that the impaired response to immune checkpoint therapy was directly linked to the loss of STK11/LKB1, resulting in a marked inhibition of stimulator of interferon genes (STING) expression and insensitivity to cytoplasmic double-strand DNA (dsDNA) sensing (Kitajima et al., 2019; Della Corte and Byers, 2019). In immunoblot analysis, lung cancer cell lines with *KRAS*/LKB1 mutations exhibit a loss of STING expression (e.g., A549, A427, H1994, HCC44, H2122, H358, H23). This contrasts with cell lines that have only *KRAS*/TP53 mutations (e.g., H358, H1792, H441, H2009), which maintain STING expression (Kitajima et al., 2019). Interestingly, it has been observed that STING mRNA levels increase rapidly following MET knockdown in MET-amplified cell lines. STING mRNA stability was decreased by MET activation, which could be avoided with a MET inhibitor (Zhang et al., 2021). Mechanistically, it was seen that MET signaling reduced STING mRNA stability through phosphorylation of UPF1 at Y818 (Zhang et al., 2021). UPF1 is a nonsense-mediated mRNA decay factor (Pastor et al., 2010). The UPF1 phosphorylation promotes its binding to STING mRNA and, hence, decreases STING mRNA levels (Kitajima et al., 2019).

LKB1-mutant lung tumors are also associated with increased autophagy flux and suppressed antigen processing for MHCI presentation. Pharmacological (MRT88921) inhibition of autophagy-inducing kinase ULK1 (unc-51-like autophagy activating kinase 1) restores sensitivity to immune checkpoint therapy with PD-1 inhibitors (Deng et al., 2021). The role of RNA N6-methyladenosine (m^6A) modifications in *KRAS* lung cancer is of interest to be explored. The demethylase fat mass and obesity associated FTO) protein was reported to be a positive regulator of autophagy. FTO targets the ULK1 transcripts and positively regulates the abundance of ULK protein. The decay rate of ULK1 mRNA was lower in FTO-overexpressing cells (Jin et al., 2018) (Fig. 8). Western blot analysis shows that the protein level of FTO was up regulated in lung cancer tissues. The mRNA levels were increased also in lung cancer cell lines (A549, NCI-H1992, NCI-H566 and others (Li et al., 2019). FTO enhances lung squamous proliferation by enhancing myeloid zing finger (MZF1) mRNA transcription by increased mRNA stability (Li et al., 2019; Ding et al., 2020). It is of great interest that STK11/LKB1 loss mediates MZF1 expression in lung adenocarcinoma and MYC expression (Tsai et al., 2015). Patients with low-LKB1 and high MZF1 or low-STK11/LKB1 and high-MYC tumors have shorter overall survival and relapse-free survival than patients with high STK11/LKB1 and low MZF1 or high STK11/LKB1 and low MYC tumors (Tsai et al., 2015) (Fig. 8).

FTO has recently been reported to directly target platelet-derived growth factor C (PDGFC) and stabilize its expression. This, in turn, leads to the activation of the AKT signaling pathway in pancreatic ductal adenocarcinoma (Tan et al., 2022). Fig. 8 compiles these observations and raises the hypothesis that targeting FTO could be relevant in *KRAS*-mutant lung adenocarcinomas with STK11/LKB1 mutations. It is worth noting that omeprazole pretreatment enhances the effect of chemotherapy in gastric cells and inhibits FTO expression (Feng et al., 2021).

The reduction of lactate using a nano-capsule enzyme called lactate oxidase has been found to alleviate tumor immunosuppression and generate hydrogen peroxide (H_2O_2), which in turn promotes the infiltration of T cells and enables immune checkpoint treatment to enhance T cell immunity, as demonstrated in a humanized mouse model of triple-breast cancer. Cancer cell lines including MDA-MB-231, 4T1 and

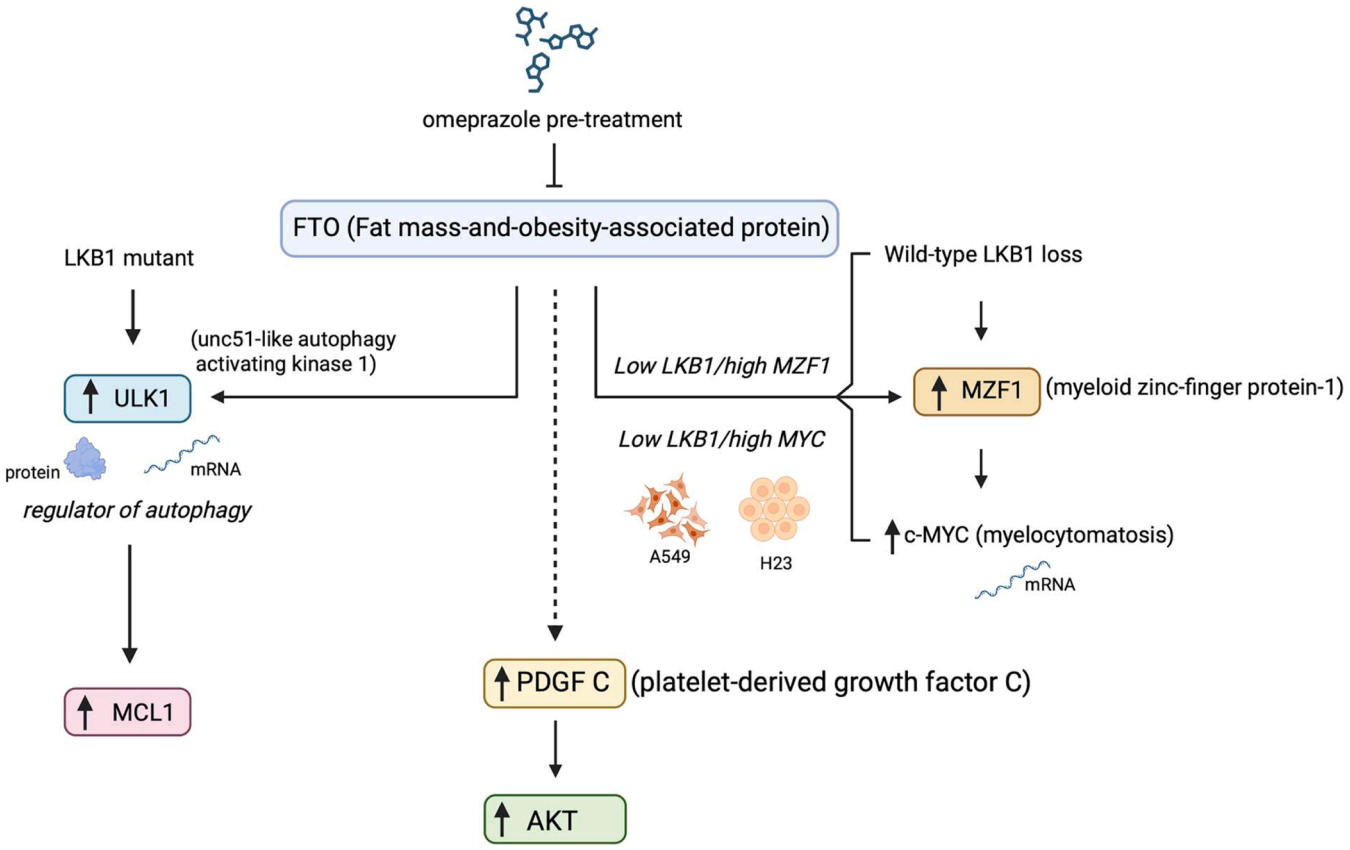

Fig. 8. Fat mass and obesity associated (FTO) protein.FTO is overexpressed in lung cancer cell lines and may play a significant role in *KRAS* mutant lung cancer, either with LKB1 mutations or LKB1 wild-type, by stabilizing the transcript expression of several genes. These genes include unc-51-like autophagy activating kinase 1 (ULK1) and myeloid zinc finger (MZF1), and may potentially activate growth factors, such as platelet-derived growth factor C (PDGFC). Omeprazole (a V-ATPase inhibitor) has been reported to inhibit FTO expression.

B16F10 produce abundant lactate in the culture media. Adding native lactate oxidase or lactate oxidase nano capsules (10 μg/Ml) to MDA-MB-231 cell cultures reduced the lactate concentration in the culture media from 12 to 6 mM in 1 h (Cao et al., 2023).

In *KRAS*-mutant lung adenocarcinomas with STK11/LKB1 mutations, an increase in lactate secretion via the monocarboxylate transporter 4 (MCT4) was observed. MCT4 serves as the principal mediator of lactic acid transportation across the plasma membrane and is known to be overexpressed in several types of cancer, including NSCLC (Qian et al., 2023). The increased lactate secretion mediated by MCT4 lactate transporter promotes M2 macrophage polarization and suppresses T cell function. MCT4 depletion reverses the immunosuppressive phenotype mediated by LKB1 and increases the sensitivity to immune checkpoint therapy (Qian et al., 2023). MCT4 upregulation is associated with mitochondrial NADH dehydrogenase mutations, and it was observed that H358 cells, which harbor a NADH dehydrogenase mutation, overexpressed MCT4 (Takenaga et al., 2021). Lactate dehydrogenase (LDH) is the key enzyme that catalyzes the conversion between lactate and pyruvate in the presence of nicotinamide adenine nucleotide (NAD^+)/reduced form of NAD^+ (NADH). LDH plays a function in keeping the energy balance between glycolysis and mitochondrial respiration and in regulating the redox balance of NAD^+/NADH (Cao et al., 2023).

Post-translational modifications influence tumor-associated immune responses with changes in the enzymes in the glycolysis and fatty acid-β-oxidation (FAO) pathways that differentiate immune-cool from immune-hot tumors (Geffen et al., 2023). Carnitine palmitoyltransferase A (CPT1A) is a rate-limiting enzyme of FAO in cancer cells and tumors upon FAO inhibition are more responsive to immunotherapy (Liu et al., 2023). As above mentioned, VCP inhibitor blocks the upregulation of FAO activity and CPT1A expression triggered by metformin in colorectal cancer (Huang et al., 2023).

Immune checkpoint therapy (anti-PD-1) combined with AMG 510 (sotorasib) induced complete responses in CT-26 *KRAS* G12C tumors (a mouse syngeneic tumor model generated by CRISPR technology) (Canon et al., 2019). Also, in the *KRAS* G12C mutant CT26 syngeneic model MRTX849 (adagrasib) decreased intratumoral myeloid-derived suppressor cells and increased M1 polarized macrophages, dendritic cells, $CD4^+$ and $CD8^+$ T cells (Briere et al., 2021). Similarly, although tumors progressed following anti-PD-1 or MRTX849 monotherapy in immune competent mice, combining MRTX849 with anti-PD-1 inhibitor produced durable complete responses (Briere et al., 2021). In addition, MRTX1133 (*KRAS* G12D inhibitor) and MRTX849 (adagrasib) increased the proportion of $CD8^+$ T cells expressing FAS in *KRAS* G1D and in *KRAS* G12C mutant cell lines, respectively. Similar induction of FAS expression in response to MRTX1133 was observed in a pancreatic ductal adenocarcinoma patient-derived organoid supporting the notion of $CD8^+$ T cell-mediated cancer cell clearance through FAS-FASL interaction (Mahadevan et al., 2023).

It has been found that inhibition of Cullin-4B (CUL4B) in alveolar type 2 (AT2) epithelial cells or Lewis lung carcinoma cells (murine lung adenocarcinoma with *KRAS* G12C) promoted tumor progression. Mechanistically, rapid onset of *KRAS*-driven lung tumorigenesis led by the lack of CUL4B is mediated by de-repression of CXCL2 transcription in tumors cells, leading to enhanced myeloid-derived suppressor cells (Liu et al., 2023).

Inhibition of HDACs by mocetinostat leads to an increase in CXCL2 mRNA levels, as well as CXCL2 protein production and secretion, suggesting that HDAC activity inhibits CXCL2 transcription (Liu et al., 2023). Additionally, inhibition of CUL4B results in increased infiltration

of myeloid-derived suppressor cells in *KRAS*-mutant tumors while decreasing the proportion of $CD4^+$ and $CD8^+$ T cells. CXCL2 is responsible for the trafficking of myeloid-derived suppressor cells to CUL4B-deficient tumors. The CXCL2/CXCR2 axis induces myeloid derived suppressor cells chemotaxis and accumulation in tumor tissues (Liu et al., 2023). Continuing along the same lines, it was previously mentioned that *KRAS* repression of interferon regulatory factor 2 (IRF2) leads to an increased expression of CXCL3, which also binds to CXCR2 receptors on myeloid-derived suppressor cells. Inhibition of CXCR2 has been found to overcome resistance to immune checkpoint therapy (anti-PD1 inhibitors) (Liao et al., 2019). Likewise, *KRAS* mutations mediated by ERK1/2 signaling suppress the splicing factor TF1P11, subsequently leading to the upregulation of interleukin-1 receptor antagonist (IL1RN)− 201/203 splicing variants. These variants, in turn, abrogate the aberrant signaling to counterattack excessive inflammatory responses in *KRAS*-mutant intrahepatic cholangiocarcinoma. IL1RN-201 or IL1RN-203 overexpression inhibits ERK1/2 phosphorylation in *KRAS* G12C MIA-PACA-2 cells (pancreatic adenocarcinoma) and *KRAS* G12C NCI-H23 lung adenocarcinoma cells (Zhang et al., 2023). Anakinra treatment enhances anti-PD1 therapy to intratumorally activate granzyme B $CD8^+$ cells in *KRAS*-mutant intrahepatic cholangiocarcinoma, disrupting CXCL3 tumor secretion and preventing its binding to CXCR2 expressed in neutrophils (Zhang et al., 2023).

10. Chemotherapy in *KRAS* G12C NSCLC

The ablation of C-RAF expression induced the regression of lung tumors in *KRAS*/Trp53-mutant mice (Sanclemente et al., 2018). Impressively, SHOC2 depletion prevents xenograft growth in H358 cells (Jones et al., 2019). Not less surprising is the fact that AMG510 (sotrorasib) in combination with carboplatin resulted in almost complete regression of NCI-H358 tumor growth in mice (Canon et al., 2019). Therefore, the synergism between *KRAS* G12C inhibitors and chemotherapy warrants further preclinical analysis. Differential sensitivity to chemotherapy was demonstrated based on BRCA1 expression. Specifically, BRCA1 induces resistance to DNA-damaging agents (e.g., cisplatin, carboplatin). In contrast, BRCA1 induces a >1000-fold increase in sensitivity to anti-microtubule agents, such as paclitaxel or vinorelbine (Quinn et al., 2003). HUWE1, in association with the BRCA1-MERIT40/RAP80 complex, mediates the degradation of BRCA1 (Kao et al., 2018). By contrast, the AAA-ATPase VCP increases DNA repair through homologous recombination in which BRCA1 is an essential component (Roux et al., 2021). It is tempting to posit that the levels of HUWE1 and VCP may serve as predictive factors for the response to single G12C inhibitor treatment, and also for tailoring chemotherapy approaches, potentially favoring carboplatin or paclitaxel (Fig. 6).

EGFR blockade can reverse resistance to *KRAS* G12C inhibition in colorectal cancer. It was strongly suggested that concurrent inhibition of EGFR and *KRAS* G12C should be considered in the treatment of colorectal tumors (Amodio et al., 2020) (Fig. 2). The combination of adagrasib with cetuximab in metastatic colorectal cancer with *KRAS* G12C mutation increased the response rate up to 46% versus 19% with adagrasib alone and augmented the progression-free survival to 6.9 months versus 4.3 months for adagrasib single agent treated patients (Yaeger et al., 2023).

Rapid feedback activation of EGFR was primarily observed in seminal studies of BRAF-mutant colorectal cancer following BRAF inhibition with vemurafenib (Prahallad et al., 2012; Corcoran et al., 2012). Recently, feedback activation of EGFR has been seen with MRTX1123 (*KRAS* G12D inhibitor) in *KRAS* G12D-mutant colorectal cancer. MRTX1133 treatment downregulated the expression of ERBB receptor feedback inhibitor 1 (ERRFI1), a negative regulator of EGFR (Feng et al., 2023) (Fig. 2). Neratinib has been seen to inhibit YAP signaling in addition to its action as an ERBB1/2/4 inhibitor (Dent et al., 2019). The enticing aspect is that the chemotherapeutic drug gemcitabine could potentially be more effective in tumors with YAP activation (nuclear expression) (Gujral and Kirschner, 2017). Further development of YAP inhibitors is warranted. Vysudine is a liposomal formulation of verteporfin that has been tested in glioblastoma (Vigneswaran et al., 2021).

11. Conclusions

KRAS G12C covalent inhibitors are a formidable armamentarium. Despite rapid rewiring mechanisms of cancer activation, they represent an indispensable cornerstone for novel forms of therapies. Accumulated evidence points to the destabilization of Scribble within the MRAS: SHOC2:PP1C complex following treatment with *KRAS* G12C inhibitors. Therefore, the in silico analysis of drugs with binding affinity for this trimeric complex could be of great relevance. In the meantime, the combination of *KRAS* G12C inhibitors with EGFR inhibitors intuitively improves the clinical outcomes of *KRAS* G12C NSCLC patients. Moreover, the preclinical and clinical relevance of disturbances in HUWE1 and PP1C is of utmost importance, as is addressing the inhibition of VCP. The differential modulating effect of carboplatin and paclitaxel according to the levels of HUWE1 and VCP, respectively, warrants exploration. Very promising preclinical evidence indicates that *KRAS* G12C inhibitors modulate the tumor microenvironment, demonstrating a strong synergistic effect with immunotherapy. A multitude of factors deserve examination in both preclinical and clinical settings, including disturbances in glycolysis and fatty acid oxidation. The coexistence of STK11 and LKB1 mutations, which severely impair the effect of immunotherapy in *KRAS* NSCLC patients, offers a great opportunity for developing novel forms of therapy. This may include the restoration of STING function or combating the overexpression of lactate through the overexpression of the monocarboxylate transporter 4 (MCT4).

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CRediT authorship contribution statement

R.R. conceptualized and drafted the manuscript. J.C-S, J. G. A.J., Y. W., M.G-C., C.S., A.G-C. M.M-V., and J.N. revised the manuscript. R.R., A.J., and J. G. drafted the figures. J.C-S, A.J., J. G., revised the figures. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

declare no conflicts of interest.

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Glossary

1: NSCLC: Non-Small Cell Lung Cancer
2: KRAS G12C: Kirsten Rat Sarcoma Viral Oncogene Homolog Glycine 12 to Cysteine
3: SHOC2: Soc-2 suppressor of clear homolog
4: MRAS: Muscle RAS Oncogene Homolog
5: AQP5: Aquaporin 5
6: STK11/LKB1: Serine/Threonine Kinase 11 or Liver Kinase B1
7: HUWE1: HECT, UBA and WWE domain containing E3 ubiquitin protein ligase 1
8: RGS3: Regulator of G protein signaling 3
9: VCP: Valosin-containing protein