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INVITED REVIEW

Targeting KRAS for cancer therapy

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In recent years, therapeutics targeted against KRAS proto-oncogene GTPase (*KRAS*)-mutant cancers have seen significant progress. Herein we outline the biology and epidemiology of *KRAS* alterations at the lineage and allele levels, reviewing the clinical evidence for $KRAS^{G12C}$ inhibition from the discovery of the recessive switch pocket to sotorasib, adagrasib and other novel molecules, and extending to the non-$KRAS^{G12C}$ era, including RAS (ON)- and $KRAS^{G12D}$-selective strategies and early efficacy signals. We summarize secondary mutations that lead to drug resistance, bypass reconnection, adaptive circuits and reprogramming of lineage-cellular states. We propose a 'three-clock, two-window' framework, which includes half-life exposure, occupation retention and extracellular signal-regulated kinase (ERK) rebound calibration of dosing rhythm; a vascular normalization window and an immune/myeloid plasticity window to achieve longitudinal Src homology 2-containing protein tyrosine phosphatase 2/son of sevenless homologue 1 and transverse epidermal growth factor receptor, phosphoinositide 3-kinase-protein kinase-mammalian target of rapamycin synergy. At the same time, we construct and propose a closed loop of exposure, occupation, pathway inhibition, circulating tumour DNA (ctDNA) and imaging by utilizing ctDNA dynamics, phosphorylated ERK rebound and perfusion imaging, as well as myeloid lineage quantification, to improve durable inhibition and overall survival through time-aligned combined effects.

KEYWORDS
combination therapy, KRAS, KRAS inhibitors, KRAS mutations, therapeutic resistance

1 | INTRODUCTION

The mitogen-activated protein kinase (**MAPK**) pathway is a core cascade involved in cellular proliferation, differentiation and survival (Simanshu et al., 2017). This pathway is regulated by **RAS** guanylate exchange factor (**GEF**) and GTPase-activating protein (GAP) through the molecular switch of RAS GTPase activation (Simanshu et al., 2017). Oncogenic RAS is locked in the guanosine triphosphate (GTP)-bound state, thereby hyperactivating the RAF proto-oncogene serine/threonine-protein kinase (**RAF**)-MAPK (MEK)–extracellular signal-regulated kinase (ERK) pathway (Simanshu et al., 2017). Among the three RAS paralogs (**HRAS**, **KRAS** and **NRAS**), KRAS alterations are the most

Abbreviations: CRC, colorectal cancer; ctDNA, circulating tumour DNA; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; DCR, disease control rate; DOR, duration of response; GAP, GTPase-activating protein; GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; LUAD, lung adenocarcinoma; MDSC, myeloid-derived suppressor cell; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; RTK, receptor tyrosine kinase; SIIP, switch II pocket.

prevalent across tumour lineages (Pylayeva-Gupta et al., 2011). Pan-cancer analysis reveals that *KRAS* mutations are approximately 19% overall prevalent and are unevenly distributed across tumour types, primarily involving codon 12/13 substitutions (Lee et al., 2022; Prior et al., 2020). This lineage specificity is not only epidemiological but also profoundly affects the trajectory of drug sensitivity and resistance.

KRAS alterations have long been considered 'incurable'; however, after the discovery of a cryptic switch II pocket in the G12C-mutant KRAS protein in 2013, KRAS became a drug target for covalent allele selective inhibition (Ostrem et al., 2013). Sotorasib (AMG510) advanced rapidly from preclinical validation to clinical testing (Canon et al., 2019) and, in 2021, received US Food and Drug Administration (FDA) accelerated approval for previously treated $KRAS^{G12C}$-mutant non-small cell lung cancer (NSCLC; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sotorasib-kras-g12c-mutated-nsclc). A second inhibitor, adagrasib, was approved in 2022 (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-adagrasib-kras-g12c-mutated-nsclc). In addition, the non-G12C era of direct KRAS-targeting has begun (Spira et al., 2025). However, the availability of the new drugs does not directly translate into lasting benefits. To this end, primary and acquired drug resistance have been reported, involving secondary point mutations, activation of bypass pathways, adaptive responses and epigenetic remodelling, which hamper the efficacy of the novel medicines (Awad et al., 2021; Ebright et al., 2025; Perurena et al., 2024; Punekar et al., 2022). To date, a combinatorial framework of understanding KRAS inhibition has become central, encompassing the strategies of vertical inhibition, targeting adaptive responses, co-inhibition of parallel pathways and downstream synthetic lethality and collateral dependence (Fedele et al., 2021; Perurena et al., 2024; Punekar et al., 2022). In some settings, these strategies enhance responsiveness to immunotherapy (Fedele et al., 2021; Hofmann et al., 2021; Tang et al., 2022). Importantly, even identical *KRAS* codon substitutions show tissue- and co-mutation-dependent drug susceptibilities (e.g., with Serine/threonine kinase 11 [STK11]/liver kinase B1 [LKB1] and Kelch-like ECH-associated protein 1 [**KEAP1**]) that correlate with immune-microenvironmental features; thus, precise stratification and biomarker-driven trial designs are essential (Ricciuti, Arbour, et al., 2022; Skoulidis et al., 2021). Accumulating experience and recent reviews converge on one theme: sustained benefit requires adding co-targets (e.g., **SHP2**/SOS1, **EGFR** and **ERK**) in addition to direct KRAS inhibition (Perurena et al., 2024). In addition, real-time evaluation and calibration become increasingly feasible, including circulating tumour DNA (ctDNA) dynamics (Paweletz et al., 2023), functional space/perfusion imaging (Andersen et al., 2024; Arevalo-Perez et al., 2024) and immune myeloid compartment resolution, which also provide new insights for real-time monitoring of therapeutic response (Anastasiou et al., 2024; Fedele et al., 2021).

Based on these advances and challenges, we explore the perspective of biological temporal systems pharmacology for effective KRAS inhibition. First, KRAS-related knowledge and cross-ancestry epidemiology are reviewed. Thereafter, the evidence and limitations of $KRAS^{G12C}$ inhibition are explored based on representative clinical studies, the review is extended to non-G12C alleles, and an emergent state/allosteric/complex-centred strategy is described. Finally, we propose a time structure framework centred on pharmacokinetic exposure, target engagement/residence and MAPK adaptive rebound and explore the feasibility and testable hypotheses of time co-targeting within the window of vascular normalization and immune bone marrow plasticity, providing information for future trial design and clinical decision making.

2 | TARGETING THE KRAS PATHWAY

The *KRAS* gene is located on chromosome 12p12.1 (https://www.ncbi.nlm.nih.gov/gtr/genes/3845/) and KRAS protein is a membrane-associated regulatory GTP-binding protein of the GTPase superfamily (Simanshu et al., 2017). However, due to its picomolar affinity for GTP, the high intracellular abundance of GTP (Neal et al., 1988; Traut, 1994) and the lack of a deep ligandable pocket (Lu et al., 2016), KRAS has long been seen as a hard-to-impossible drug target. Hence, the earliest clinical anti-KRAS strategies turned to small-molecule inhibition of downstream kinases in the KRAS pathway.

The KRAS pathway is activated by signals from various growth factors, cytokines, immune receptors and chemokine receptors (Bahar et al., 2023). Canonically, it is engaged by receptor tyrosine kinases (RTK) that couple to this signalling module (Figure 1) (Bahar et al., 2023; Perurena et al., 2024; Punekar et al., 2022). KRAS small GTPases cycle between GTP-bound (active) and guanosine diphosphate (GDP)-bound (inactive) states, driven by KRAS-guanine nucleotide exchange factors (GEFs) and opposed by KRAS- GTPase activating proteins (GAPs) (Simanshu et al., 2017). During this GDP/GTP cycle, Switch I (residues 30–38) and Switch II (residues 60–76) undergo ligand-dependent conformational rearrangements (Matsumoto et al., 2016). Switch I primarily determines the recognition and selectivity of effector molecules (e.g., KRAS binding domain of the RAF family and phosphoinositide 3-kinase [PI3K]) (Pacold et al., 2000). In contrast, Switch II controls the interaction with GEF/GAP and the plasticity of the switch II pocket (SIIP)—a feature directly related to pathway inhibition strategies (Gentile et al., 2017). In GEF, SOS1/SOS2 are the major receptor tyrosine kinases (RTK) and cytokine receptor-responsive KRAS-GEFs. They bind to the adaptor protein growth factor receptor-bound protein 2 (GRB2) via a C-terminal proline-rich motif that binds to the SH3 domain of GRB2 (Punekar et al., 2022). GRB2 recognizes pY-XNX motifs on a variety of proteins through its SH2 domain (Y, tyrosine; X, any amino acid; N, asparagine) to assemble signalling complexes such as RTK, which activate SHP2 and regulate SOS1/SOS2 GEF activity to promote KRAS activation (Punekar et al., 2022; Wang et al., 2024). Collectively, these mechanisms generate several entry points for therapeutic KRAS pathway blockade. SHP2 inhibitors (e.g., TNO155 or batoprotafib) aim to block the RTK–GRB2–SHP2–SOS1 axis and thereby restrain KRAS activation (Brana et al., 2021). SOS1 inhibitors (e.g., BAY3498264) seek to reduce GDP-to-GTP exchange on KRAS (Guthof et al., 2025). In preclinical and early clinical studies, upstream inhibitors are

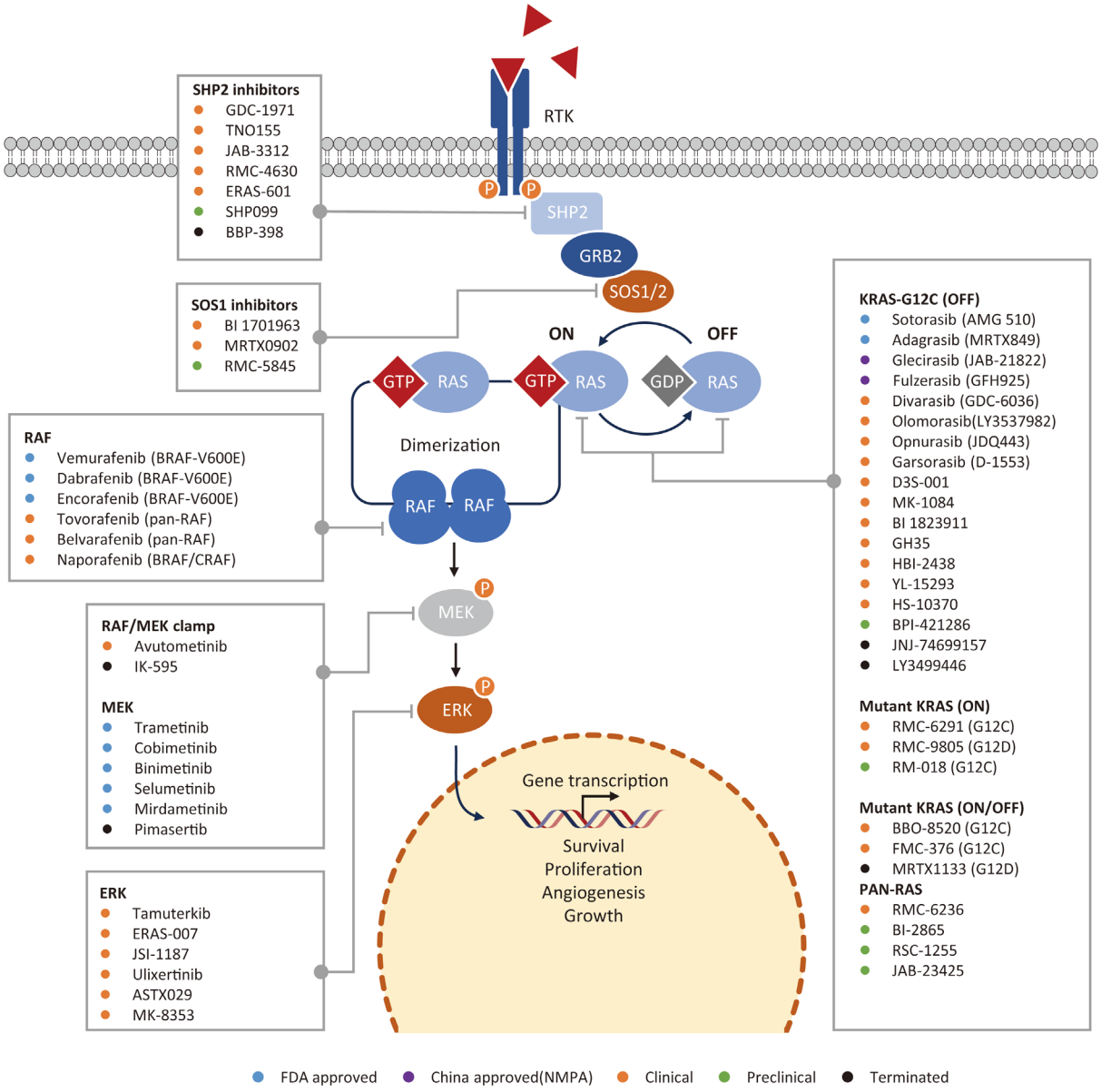

FIGURE 1 Therapeutic entry points across the RTK–KRAS–RAF–MEK–ERK cascade. Ligand-activated receptor tyrosine kinases (RTKs) signal through SHP2–GRB2–SOS1/2 to catalyse the exchange of GDP for GTP on KRAS, converting it from the inactive (OFF) to the active (ON) state. Active KRAS dimerizes and recruits RAF, which sequentially activates MEK and ERK, culminating in transcriptional programs that drive cell survival, proliferation, angiogenesis and growth. Boxes list representative small-molecule inhibitors at each node. Coloured dots indicate development status: blue, FDA approved; purple, China NMPA approved; orange, clinical; green, preclinical; black, terminated. The DNA double helix and the phospholipid bilayer elements were sourced from SciDraw (https://scidraw.io) and lightly adapted for this figure.

combined with RAF/MEK/ERK inhibitors to deepen MAPK suppression and curb adaptive feedback (Hofmann et al., 2021).

After switching onto the GTP-bound state, KRAS binds to the KRAS binding domain of downstream effector proteins and recruits **Raf** serine/threonine-specific protein kinases to the cell membrane, where it interacts with membrane lipids to form dimers and become activated. To this end, B-Raf proto-oncogene, serine/threonine kinase (BRAF)^{V600} targeted inhibitors were the first KRAS pathway inhibitors to receive regulatory approval (Karoulia et al., 2017). Subsequently, pan-RAF inhibitors were developed, such as naporafenib, to better match the wild-type RAF dimer configuration characteristics of *KRAS*-mutant tumours and mitigate the paradoxical activation observed with selective BRAF inhibitors (Janku et al., 2024). Activated RAF phosphorylates and activates MEK1/2, which in turn phosphorylates and activates ERK1/2 (Figure 1). As far as MEK is concerned, five MEK inhibitors have received approval, and mirdametinib was approved as recently as February 2025 (Ram, Singh, et al., 2023). In parallel, RAF/MEK 'clamp' strategies (e.g., avutometinib) aim to inhibit MEK while preventing ERK-dependent MEK reactivation, thereby achieving more profound and durable MAPK suppression (Coma et al., 2023). Downstream, ERK1/2

phosphorylate a broad repertoire of cytoplasmic and nuclear substrates including kinases (e.g., ribosomal S6 kinase [RSK], mitogen- and stress-activated protein kinases [MSK], MAP kinase-interacting serine/threonine-protein kinases [MNK]), transcription factors and cytoskeletal proteins (Bahar et al., 2023). At the ERK tier, ERK inhibitors are in clinical development (primarily Phase II) being tested as monotherapy or in combinations to directly suppress terminal output of the cascade (e.g., LY3214996 and temuterkib) (Taza et al., 2023).

KRAS effects can also be mitigated via targeting PI3K (especially its p110 catalytic subunit), Ral guanine nucleotide dissociation stimulator (Ral-GDS) and the Rho-GEF TIAM Rac1 associated GEF 1 (TIAM1) (Punekar et al., 2022; Simanshu et al., 2017). Due to the extensive crosstalk and compensatory activation between the MAPK and **PI3K-AKT-mTOR** axes, rational combination therapy with PI3K-AKT-mTOR inhibitors can be considered based on the molecular background to counteract bypass signalling and adaptive reprogramming (Mendoza et al., 2011). Intracellularly, the physiological hydrolysis of KRAS-GTP depends on GAPs such as neurofibromatosis type 1 (NF1) and Ras GTPase-activating protein 1 (RASA1)/p120rasGAP (RAS p21 protein activator 1) (Simanshu et al., 2017). These proteins contain SH2/SH3 domains or other docking motifs that can be recruited to activated RTK and scaffold complexes to form a critical negative feedback loop that terminates KRAS signalling (Simanshu et al., 2017).

From a clinical perspective, MEK inhibitors demonstrate a clear benefit in paediatric neurofibromas (Dombi et al., 2016). Downstream inhibitors can reduce the output of ERK; however, their clinical impact is limited by the depth of inhibition and feedback regulation. However, in *KRAS*-mutant lung, pancreatic and colorectal cancers, as well as *NRAS*-mutant melanoma, neither monotherapy nor combinations with chemotherapy have yielded substantial clinical benefits (Jänne et al., 2017). These observations indicate that the inhibition of the KRAS–ERK axis needs to be further strengthened, especially in aggressive malignancies, and strategic combinations with upstream regulators (such as SHP2 and SOS1) and parallel pathway inhibitors are necessary (e.g., PI3K-AKT-mTOR) (Brana et al., 2021; Guthof et al., 2025; Mendoza et al., 2011).

3 | LANDSCAPE OF KRAS MUTATIONS IN CANCER

Comprehensive genomic analyses have shown that about one-fifth of malignant tumours overall display KRAS pathway alterations (Prior et al., 2020). Representative alteration frequencies range from 90% in pancreatic ductal adenocarcinoma (PDAC), to 45% in colorectal carcinoma (CRC), 35% in lung adenocarcinoma (LUAD) and 30% in germ cell tumours (Figure 2a) (Lee et al., 2022; Prior et al., 2020). Among RAS alterations, *KRAS* changes predominate by far, followed by *NRAS*, with *HRAS* being less frequent (Lee et al., 2022; Prior et al., 2020). To add to the complexity, *KRAS* alterations show functional dependence on the specific altered allele, the tissue lineage, the exposure background and the co-existing mutations in determining their biological effects and drug susceptibility profile (Punekar et al., 2022; Sanchez-Vega et al., 2018).

3.1 | Pancreatic ductal adenocarcinoma (PDAC)

PDAC is a tumour with a high incidence of *KRAS* mutations, with an overall mutation rate of approximately 80%–90%, including G12D (43%), G12V (31%) and G12R (16%) mutations, the latter being significantly enriched in the pancreas (Figure 2b) (Chen et al., 2024; Prior et al., 2020). G12R alters the conformation and electrostatic interactions of the P-ring, weakens its interaction with PI3K p110α and promotes the Ral guanine nucleotide dissociation stimulator (RalGDS)/Ras-related C3 botulinum toxin substrate 1 (RAC) signalling pathway and micropinocytosis with metabolic reprogramming (Hobbs et al., 2020). These characteristics are consistent with the adaptation of PDAC to nutrient deprivation and high stromal stress (Hobbs et al., 2020). G12D tends to activate PI3K, and this difference translates into actual signal transduction and biological differences in different co-mutation/RTK backgrounds (Hunter et al., 2015; Rabara et al., 2019). A co-mutation triad also regulates the KRAS signalling pathway: TP53, CDKN2A and SMAD4, which not only drive invasion and metastasis but also modulate the strength of MAPK-PI3K coupling (Murphy et al., 2016; Stefanoudakis et al., 2024).

3.2 | Lung adenocarcinoma (LUAD)

In LUAD, the main RAS alteration is *KRAS*, which accounts for about 35% of all patients (Prior et al., 2020). However, lineage and exposure together determine its distribution pattern. Smoking-related C > A/G > T substitution leads to the dominance of $KRAS^{G12}$ mutations, of which G12C accounts for 40%, followed by G12V (19%), and G12D (14%) (Figure 2b) (Chen et al., 2024). At the allele level, G12C is distinctive for the nucleophilic reactivity of its cysteine side chain and its trappability in the GDP state (Ostrem et al., 2013). The upstream/downstream context can be as determinative as the allele itself: *STK11/LKB1* and *KEAP1* co-mutations rewire the metabolism-stress-immunity hub, reconfiguring MAPK and Nuclear factor erythroid 2-related factor 2 (**NRF2**) axes and influencing responsiveness to inhibition of programmed death-ligand 1 (**PD-L1**)/cluster of differentiation 274 (CD274)/B7 homologue 1 (B7-H1), metabolic plasticity, and even metastatic proclivities; *TP53* co-mutation is more closely linked to augmented genomic instability and phenotypic plasticity (Dziadziuszko, 2022; Skoulidis et al., 2018). Interestingly, in LUAD, *KRAS* is almost mutually exclusive with *EGFR* and ALK driver genes, which reflects the evolutionary selection of pathway occupancy and adaptability. It is not a coincidence that this interaction between genes reveals the vulnerability of tumours and can provide information for new treatment strategies for lung and other cancers (Cancer Genome Atlas Research, N., 2014; Unni et al., 2015).

3.3 | Colorectal cancer (CRC)

In CRC, the *KRAS* mutation rate is typically 40%–50% (Prior et al., 2020), but the allelic composition differs markedly from pancreas

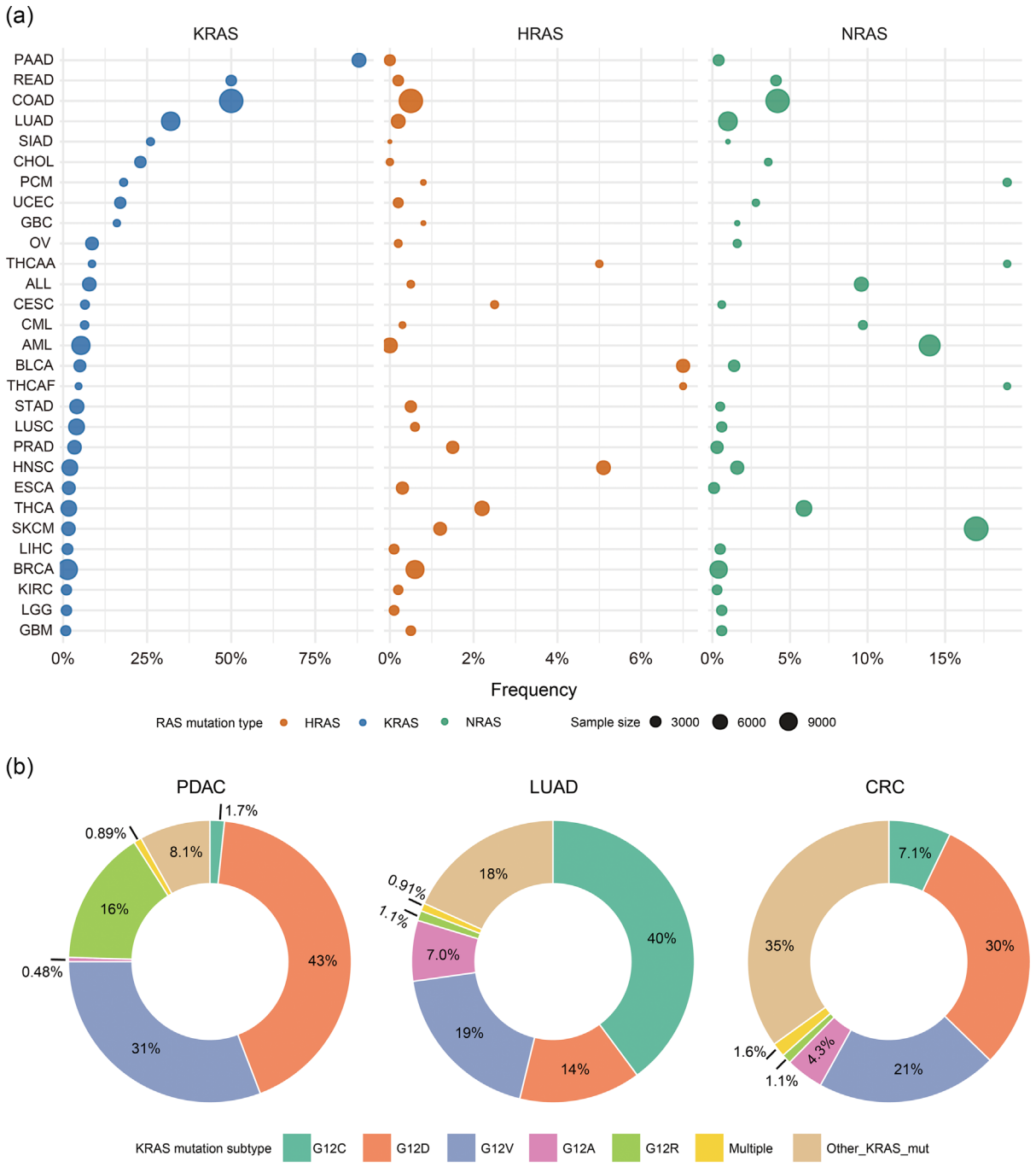

FIGURE 2 Landscape of KRAS mutations across cancers and distribution of KRAS hotspot subtypes. (a) Bubble plots depict the frequency (*x* axis) of somatic HRAS, KRAS and NRAS mutations across tumour types (*y* axis, TCGA abbreviations). Colours denote KRAS family members (orange, HRAS; blue, KRAS; green, NRAS). Bubble area is proportional to the number of tested samples (illustrative sizes: small = 3000; medium = 6000; large = 9000). Data from Prior et al., 2020. (b) Donut charts show the composition of KRAS mutation subtypes in three highly prevalent cancers—pancreatic ductal adenocarcinoma (PDAC), lung adenocarcinoma (LUAD) and colorectal cancer (CRC). Sectors are coloured by hotspot subtype (G12C, G12D, G12V, G12A and G12R) with percentages indicated. 'Multiple' denotes samples harbouring more than one KRAS mutation; 'Other_KRAS_mut' denotes all other KRAS variants. Data from Lee et al., 2022. Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; CML, chronic myeloid leukaemia; COAD, colon adenocarcinoma; ESCA, oesophageal carcinoma; GBC, gallbladder carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KIRC, kidney renal clear cell carcinoma; LGG, lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCM, plasma cell myeloma; PRAD, prostate adenocarcinoma; READ, rectal adenocarcinoma; SIAD, small intestine adenocarcinoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; THCA, papillary thyroid carcinoma; THCAA, anaplastic thyroid carcinoma; THCAF, follicular thyroid carcinoma; UCEC, uterine corpus endometrial carcinoma.

and lung: beyond the high prevalence of G12D (30%) and G12V (21%), G13D (15.7%) is relatively enriched in CRC, whereas G12C (7.1%) is comparatively less common (Figure 2b). This 'gastrointestinal' pattern is partly consistent with tissue specificity as well as selection pressures, such as the higher incidence of inflammatory oxidative/nitrative stress in the colorectal microenvironment (Bardelcikova et al., 2023). *KRAS*^{G13D}-mutant CRC display accelerated intrinsic nucleotide exchange and partial sensitivity to NF1-mediated gap regulation, exhibiting unique feedback dynamics in EGFR-coupled colorectal epithelial cells. Therefore, in the case of EGFR axis intervention and MAPK reprogramming, its pharmacological characteristics may differ from those of G12D/V mutants (Hunter et al., 2015; Rabara et al., 2019). In addition, wild-type *KRAS* amplification occurs in a subset of CRC, upshifting KRAS-ERK flux by quantity rather than quality, yet with comparable functional consequences (Yang et al., 2025).

3.4 | Interim conclusions

Based on the above, tumour alleles, tissue environment, co-mutations and exposure factors, jointly shape dynamic changes in the KRAS signalling pathway, which determine strategies for KRAS-targeting and rational combination drug regimens. The core issue appears not to be 'higher expression of KRAS target genes', but how to accurately stratify patients. First, to define tumour and exposure specificity. Second, to analyse subtypes and hotspot alleles. Third, to integrate co-mutation and RTK/parallel pathway load to ultimately generate a map for clinical trials, treatment and prediction. For translational and clinical relevance, Table S1 provides an overview of the major KRAS hotspot alleles, their lineage-specific enrichment, associated mutational patterns and therapeutic implications.

4 | DIRECT KRAS BLOCKADE FROM KRAS^{G12C} TO PAN-KRAS

4.1 | The KRAS^{G12C} breakthrough

The turning point for direct KRAS inhibitors came in 2013, when Shokat et al. identified a druggable allosteric site in the SIIP of KRAS^{G12C} through disulphide bond-linking screening (Ostrem et al., 2013). By anchoring to Cys12, these ligands locked the protein in the GDP-bound inactive conformation, proving that the once 'undruggable' KRAS could be directly subdued by small molecules (Ostrem et al., 2013). This paradigm rapidly gave rise to sotorasib and adagrasib as covalent inhibitors (Barlesi et al., 2025; Hong et al., 2020). In addition, SIIP plasticity is not unique to KRAS^{G12C}: noncovalent ligands can occupy similar sites of multiple KRAS alleles, laying the foundation for a broader and more flexible drug type (Hitchen et al., 2025).

In recent years, KRAS^{G12C}-targeted therapy has progressed from the feasibility verification stage to the systematic optimization stage. Three of these changes are particularly prominent:

1. The clinical role of OFF-state (GDP-bound) inhibitors is being redefined by more potent agents and better-rationalized combinations.
2. Histologically refined combination therapies, especially as CRCs begin to enter the registration phase.
3. A new generation of ON-state (GTP-bound) mechanisms has shown clinical signals, aiming to delay or overcome resistance to classical Switch-II pocket (SIIP) inhibitors.

We have summarized the data by tumour type, including quantitative endpoints and biological interpretations. Details of clinical trials for *KRAS* mutation inhibitors are shown in Table 1. Tables 1 and 2 summarize clinical trial results only.

4.1.1 | Non-small cell lung cancer (NSCLC)

In clinical settings, Sotorasib was the first KRAS^{G12C} inhibitor to enter the clinic in NSCLC (Hitchen et al., 2025). In the Phase I CodeBreaK 100 study (n = 59), advanced NSCLC patients achieved an objective response rate (ORR) of 32.2%, a disease control rate (DCR) of 88.1%, and median progression-free survival (PFS) of 6.3 months (Hong et al., 2020). In a subsequent Phase II trial (n = 124), ORR was 37.1%, median duration of response (DOR) 11.1 months, PFS 6.8 months, and median overall survival (OS) 12.5 months, prompting accelerated (US Food and Drug Administration) FDA approval in May 2021 for the treatment of *KRAS*^{G12C}-mutant NSCLC (Skoulidis et al., 2021). In the Phase III CodeBreaK 200 trial (n = 345), sotorasib significantly improved PFS over docetaxel (5.6 vs. 4.5 months), but OS was not improved, prompting scrutiny of design and follow-up differences (de Langen et al., 2023). A detailed results record of the clinical trial overview of the *KRAS* mutation inhibitor is shown in Table 1. The FDA subsequently issued a complete response letter for the conversion to regular approval, requesting new confirmatory evidence.

From a clinical perspective, by comparison, in the Phase III KRYSTAL-12 study (n = 453) for previously treated NSCLC, adagrasib improved PFS from 3.8 to 5.5 months versus docetaxel, with ORR 32% versus 9% and a manageable safety profile, with consistent trends across subgroups; OS remained unchanged but displayed a favourable trend (Barlesi et al., 2025). These signals emphasize that optimizing internal mechanisms, including the intrinsic potency and pharmacokinetics of a drug, can translate into clinically meaningful benefits. Divarasib has broken through the efficacy ceiling of monotherapy. Phase I clinical trial data showed that divarasib was well-tolerated and demonstrated significant anti-tumour efficacy (NSCLC, n = 60: ORR, 53.4%; median PFS, 13.1 months), while also showing a decrease in ctDNA levels (Sacher et al., 2023). With ≥1-year follow-up in NSCLC, activity appeared durable with consistent safety (ORR 55.6%, DOR 18.0 months and PFS 13.8–15.3 months) (Sacher et al., 2025). A head-to-head Phase III trial will compare the efficacy and safety of divarasib with those of sotorasib or adagrasib in previously treated patients with KRAS^{G12C}-mutant advanced or metastatic NSCLC (NCT06497556).

Clinical studies have shown that controlling brain metastases is pivotal in the treatment of NSCLC. For patients with a central nervous

TABLE 1 Selected KRAS-targeted agents: Mechanisms, key trials and clinical outcomes.

KRAS mutation types	Mechanism	Agent	Trial name/ NCT number	Phase	Tumour type	No. of patients	Result	Reference
KRAS G12C	Off	Sotorasib (AMG510)	Codebreak100 NCT03600883	I	NSCLC	59	ORR 32.2%, DCR 88.1%, mPFS 6.3 months	PMID: 32955176
					CRC	38	ORR 7%, DCR 73.8%, mPFS 4 months	PMID: 32955176
				I/II	PDAC	38	ORR 21%, mPFS 4.0, mOS 6.9 months	PMID: 36546651
				II	NSCLC	124	ORR 37.1%; mDoR 11.1, mPFS 6.8, mOS 12.5 months	PMID:34096690
			CodeBreaK 200 NCT04303780	III	NSCLC	345	Sotorasib versus docetaxel mPFS: 5.6 versus 4.5 months (HR 0.66; $P = 0.0017$)	PMID:36764316
		Adagrasib (MRTX849)	KRYSTAL-1 NCT03785249	I/II	NSCLC	116	ORR42.9%, mDoR 8.5, mPFS6.5, OS12. 6 months	PMID: 35658005
					CRC	43	ORR19%, mDoR 4.3, mPFS 5.6 months	PMID: 36546659
					PDAC	21	ORR 33.3%, mPFS 5.4, mOS 8.0 months	PMID:37099736
			KRYSTAL-12 NCT04685135	III	NSCLC	453	Adagrasib versus docetaxel mPFS: 5.4 versus 3.8 months (HR 0.58; $P = 0.0001$)	PMID: 40783289
		Divarasib (GDC-6036)	NCT04449874	I	NSCLC	60	ORR 53.4%, mPFS13. 1 month	PMID: 37611121
				I	CRC	55	ORR 29.1%, mPFS5.6 1 months	PMID:37611121
		Olomorasib (LY3537982)	NCT04956640	I	NSCLC	14	KRAS G12Ci naive (n = 5): ORR 60%, DCR 80% KRAS G12Ci treated (n = 9): ORR 0%, DCR 67%	https://doi.org/10.1158/1538-7445.AM2023-CT028
				I	CRC	32	ORR 13%, DCR 84%	https://doi.org/10.1200/JCO.2024.42.3_suppl.94
				I	PANC	24	ORR 33%, DCR 92%	https://doi.org/10.1200/JCO.2024.42.3_suppl.94
		Opnurasib (JDQ443)	KontRASt-01 NCT04699188	I/II	NSCLC	22	ORR 41.7%	https://doi.org/10.1200/JCO.2023.41.16_suppl.9007
		Glecirasib (JAB-21822)	NCT05009329 NCT05002270	I/II	PDAC	28	ORR 46.4%, DCR 96.4%; mDOR 4.1, mPFS 5.5 months	https://doi.org/10.1200/JCO.2024.42.3_suppl.604
		Garsorasib (D-1553)	NCT05383898	II	NSCLC	123	ORR52.0%, DCR 88.6%, mDOR12.5, mPFS 9.1, Estimated mOS 14.1 months	DOI: 10.1016/j.jtho.2024.09.072
			NCT04585035	I/II	CRC	24	ORR20.8%, DCR 95.8%, mPFS 7.62 months	https://doi.org/10.1200/JCO.2023.41.16_suppl.3563
		Fulzerasib (IBI531)	NCT05005234	II	NSCLC	116	ORR 46.6%, DCR 90.5%, mDoR 8.3, mPFS8. 3 months	DOI: 10.1016/j.annonc.2023.10.584

(Continues)

TABLE 1 (Continued)

KRAS mutation types	Mechanism	Agent	Trial name/ NCT number	Phase	Tumour type	No. of patients	Result	Reference
			NCT05005234 NCT05497336	I	CRC	56	ORR44.6%, DCR 87.5%, mPFS 8.1, mOS 17.0 months	PMID: 40715048
		D3S-001	NCT05410145	I	NSCLC	21	ORR71.4%, DCR 100%	PMID: 40301557
					CRC	9	ORR 88.9%, DCR 88.9%	PMID: 40301557
					PDAC	4	ORR 100%, DCR 100%	PMID: 40301557
	On	RMC-6291	NCT05410145	I/II	NSCLC	7	ORR 57%	https://doi.org/10.1158/1535-7163.TARG-23-PR014
					CRC	9	ORR 44%	https://doi.org/10.1158/1535-7163.TARG-23-PR014
	On/off	BBO-8520	NCT06343402	I/II	NSCLC	In progress		
		FMC-376	NCT06244771	I/II	Solid Tumours	In progress		
KRAS G12D	Off	MRTX-1133	NCT05737706	I/II	Solid Tumours	Terminated on the registry platform due to 'formulation issues'		
	On	Zoldonrasib RMC-9805	NCT06040541	I	PDAC	104	ORR (confirmed or awaiting confirmation) 30%, DCR 80%	https://doi.org/10.1200/JCO.2025.43.4_suppl.724
pan-KRAS RAS	On	Daraxonrasib RMC-6236	NCT05379985	I	PDAC	99	KRAS G12X (n = 42): ORR 29%, mPFS 8.5, mOS 14.5 months RAS-mutant (n = 57): ORR 25%; mPFS 7.6, mOS 14.5 months	https://doi.org/10.1200/JCO.2025.43.4_suppl.722

Note: Response metrics: ORR, objective response rate; DCR, disease control rate; mPFS, median progression-free survival; mOS, median overall survival; mDoR, median duration of response. Unless otherwise stated, time-to-event endpoints are reported in months. Tumour types: NSCLC, non–small-cell lung cancer; CRC, colorectal cancer; PDAC, pancreatic ductal adenocarcinoma; PANC, pancreatic cancer (not otherwise specified); solid tumours, basket or multi-tumour cohorts. Mechanism shorthand: OFF-state inhibitors covalently or allosterically trap KRAS in the GDP-bound (inactive) state; ON-state inhibitors target the GTP-bound (active) state; ON/OFF indicates compounds reported to engage both states; pan-RAS denotes agents with activity across multiple RAS isoforms/mutations. 'In progress' indicates ongoing enrollment or immature efficacy readouts at the time of data extraction. 'Terminated' refers to administrative or formulation-related discontinuation of the trial as indicated in the registry. Where multiple NCT numbers are listed for one agent, data reflect the specified cohort(s) within those trials.

system tumour burden, pharmacokinetic and pharmacodynamic properties, as well as blood–brain barrier penetration, are decisive factors. In a prospective KRYSTAL-1 cohort, adagrasib demonstrated apparent intracranial activity without prior radiotherapy or surgery (ORR 42%, DCR 90%, PFS 5.4 months) (Negrao, Spira, et al., 2023). Intracranial activity evidence for sotorasib comes from an exploratory post-hoc analysis of CodeBreaK 200, which showed that it prolonged PFS of patients with central nervous system involvement and delayed intracranial progression compared to docetaxel. However, early clinical trials excluded active brain metastases, which limited direct comparisons (Dingemans et al., 2025).

4.1.2 | Colorectal cancer (CRC)

In clinical settings, in CRC, monotherapy has limited efficacy. In a Phase I trial (n = 38), sotorasib achieved ORR of 7%, DCR of 73.8% and PFS of 4 months (Hong et al., 2020). In another single-arm, Phase II trial (n = 62), sotorasib showed an ORR of 9.7%, a DCR of 82% and a PFS of 4 months (Fakih et al., 2022). These outcomes are primarily attributed to the adaptive rebound of upstream EGFR signalling and the broad expression of baseline RTKs (Desai et al., 2024). The solution coined was to block this feedback directly. By 2024–2025, two regulatory combinations established a '$KRAS^{G12C}$ + EGFR inhibition' combined approach. First, adagrasib in combination with cetuximab received accelerated FDA approval. In KRYSTAL-1 (pooled n = 94; blinded independent central review), the combination yielded an ORR of 34.0%, a DCR of 85.1%, a median DOR of 5.8 months, a median PFS of 6.9 months and an OS of 15.9 months (Yaeger et al., 2024). Another open-label, Phase 1/2 non-randomized study of sotorasib plus cetuximab (n = 32) reported an ORR of 46%, a DOR of 7.6 months and a PFS of 6.9 months (Yaeger et al., 2023). Second, in January 2025, the FDA approved sotorasib in combination with panitumumab for $KRAS^{G12C}$-mutated metastatic CRC. In the Phase III

TABLE 2 Selected combination strategies with KRAS inhibitors: key trials and outcomes.

Combination strategy	KRAS inhibitor	Combination agent	Trial name/NCT number	Phase	Tumour type	No. of patients	Result	References
EGFR inhibitor	Sotorasib	Cetuximab	NCT03785249	I/II	CRC	76	Monotherapy (n = 43): ORR 19%, mDOR 4.3, mPFS 5.6 months. Combination (n = 28): ORR 46%,mDOR 7.6, mPFS 6.9 months.	PMID: 36546659
		Panitumumab	CodeBreakK 300 NCT05198934	III	CRC	160	Sotorasib 960 mg + panitumumab (n = 53): ORR 30.2% Sotorasib 240 mg + panitumumab (n = 53): ORR 7.5% only trifluridine/ tipiracil or regorafenib (n = 54): ORR 1.9%	PMID: 40215429
		Panitumumab	CodeBreaK 101 NCT04185883	I	CRC	40	ORR30.0%,mPFS 5.7, mOS15.2 months	PMID: 38177853
	Adagrasib	Cetuximab	KRYSTAL-1	1	CRC	94	ORR 34.0%, DCR 85.1%, mDOR 5.8, mPFS 6.9, mOS 15.9 months	PMID: 38587856
	Divarasib	Cetuximab	NCT04449874	I	CRC	24	ORR 62.5%, mDOR 6.9, mPFS 8.1 months	PMID: 38052910
	Garsorasib	Cetuximab	NCT04585035	II	CRC	29	ORR 51.7% DCR 93.1%, mPFS 7.56 months	10.1016/j.annonc.2023.09.1741
SHP2 inhibitor	Divarasib	Migoprotafib GDC-1971	NCT04449874	I	NSCLC	48	ORR 43.8%, mPFS 15.2 months	https://doi.org/10.1158/1538-7445.AM2025-CT022
	Opnurasib JDQ443	TNO155	NCT04699188	I/II	NSCLC	12	KRAS G12Ci treated: ORR 33.3%,DCR 66.7%	10.1016/j.jtho.2023.09.151
	Glecirasib JAB-21822	JAB-3312	NCT05288205	I/II	NSCLC	80	Overall: ORR 72.5%, DCR6.3%. Glecirasib 800 mg qd + JAB-3312 2 mg (1w on/1w off): ORR 77.8%; DCR 92.6%.	https://doi.org/10.1200/JCO.2024.42.16_suppl.3008
	Sotorasib	RMC-4630	CodeBreaK101 NCT05054725	I	NSCLC	11	Partial response 27%	https://doi.org/10.1016/j.jtho.2022.07.022
		TNO155	NCT04185883	I/II	Solid tumours	In progress		
	Adagrasib	TNO155	NCT04330664	I/II	Solid tumours	In progress		

(Continues)

TABLE 2 (Continued)

Combination strategy	KRAS inhibitor	Combination agent	Trial name/NCT number	Phase	Tumour type	No. of patients	Result	References
SOS1 inhibitor	Sotorasib	BI-1701963	NCT04185883	I/II	Solid tumours	In progress		
	Adagrasib	MRTX0902	NCT05578092	I/II	Solid tumours	In progress		
anti-VEGF	Sotorasib	Chemotherapy and Bevacizumab	ACTRN12622000973718	II	NSCLC	In progress		
CXCR1/2 inhibitor	Sotorasib	Ladarixin	NCT05815173	I	NSCLC	In progress		
Immune Checkpoint Inhibitor	Sotorasib	Pembrolizumab or Atezolizumab	CodeBreaK 100/101	I/II	NSCLC	58	ORR 29%, mDOR 17.9 months, mOS15.7 months	10.1016/j.jtho.2022.07.025
	Adagrasib	Pembrolizumab	KRYSTAL-7 NCT04613596	II	NSCLC	149	Overall: ORR 44.3%, mDOR 26.3, mPFS 11 months PD-L1 ≥ 50% (n = 54): ORR 59.3%, mPFS 27.7 months PD-L1 < 50% (n = 95): ORR 35.8%, mPFS 6.9 months	https://doi.org/10.1200/JCO.2025.43.16_suppl.8500
	Divarasib	Atezolizumab	NCT04449874	I	NSCLC	27	ORR 55.6%	10.1016/j.jtho.2024.09.075
	Divarasib	Pembrolizumab	NCT06793215	III	NSCLC	In progress		
	Divarasib	Pembrolizumab	NCT05789082	I/II	NSCLC	In progress		
	Opnurasib	Tislelizumab	NCT04699188	I/II	Solid tumours	In progress		
	Olomorasib (LY3537982)	Pembrolizumab	NCT04956640	I/II	NSCLC	30	Overall: ORR 63%, DCR 93%. PD-L1 ≥ 50% (n = 12): ORR 75%. PD-L1 < 50% (n = 18): ORR 56%.	https://doi.org/10.1200/JCO.2024.42.16_suppl.8510
	MK-1084	Pembrolizumab	KANDLELIT-001 NCT05067283	I/II	NSCLC	34	ORR 74%, DCR91%, mPFS 25 months	https://doi.org/10.1200/JCO.2025.43.16_suppl.8605
RAS-pathway targeted	Sotorasib	Trametinib	NCT04185883	1	Solid tumours	In progress		
		Avutometinib (VS-6766)	NCT05074810	I/II	NSCLC	In progress		
		ERAS-007	NCT04959981	I	NSCLC	In progress		
	Adagrasib	Svutometinib	NCT05375994	I/II	NSCLC	In progress		

Note: ORR, objective response rate; DCR, disease control rate; mPFS, median progression-free survival; mOS, median overall survival; mDoR, median duration of response; PD-L1, programmed death-ligand 1. Tumour types: NSCLC, non–small-cell lung cancer; CRC, colorectal cancer; PDAC, pancreatic ductal adenocarcinoma; Solid tumours, multi-tumour/basket cohorts. Targets: EGFR, epidermal growth factor receptor; SHP2, Src-homology-2–containing protein tyrosine phosphatase 2; SOS1, Son of Sevenless 1; VEGF, vascular endothelial growth factor; ICI, immune checkpoint inhibitor. Time units are months unless stated. 'In progress' indicates ongoing enrollment or immature efficacy readouts at the time of data extraction.

CodeBreaK 300 trial (n = 160), daily sotorasib 960-mg plus panitumumab achieved a PFS of 5.6 months and an ORR of 30.2%, significantly outperforming regorafenib or trifluridine/tipiracil; the 240-mg dose was less effective, directly supporting a dose–occupancy–efficacy relationship (Fakih et al., 2023; Pietrantonio et al., 2025). Patient-reported outcomes from the same trial showed advantages over standard therapy in terms of fatigue, pain, global health and physical function (Modest et al., 2025). In a Phase I dose-expansion cohort, sotorasib plus panitumumab showed an ORR of 30.0%, a PFS of 5.7 months and an OS of 15.2 months (Kuboki et al., 2024). Notably, more potent KRAS^{G12C} inhibitors employing the same strategy can raise the efficacy ceiling: divarasib monotherapy in metastatic CRC resulted in an ORR of 29% and a PFS of 5.6 months (Sacher et al., 2023). Similarly, two additional CRC cohorts evaluating divarasib + cetuximab and garsorasib + cetuximab also showed positive activity, reinforcing the benefit of KRAS^{G12C} inhibition combined with EGFR blockade (Table 2) (Desai et al., 2024; Xu et al., 2023).

4.1.3 | Pancreatic ductal adenocarcinoma (PDAC) and other malignancies

In clinical settings, in PDAC, the low prevalence of KRAS^{G12C} and the highly fibrotic tumour microenvironment have been documented and contribute to treatment resistance (Chen et al., 2024; Prior et al., 2020). Even so, therapeutic effects were observed in heavily pretreated populations with KRAS^{G12C} inhibitors. In the pancreatic cohort of CodeBreaK-100 (n = 38), sotorasib achieved an ORR of 21%, with a PFS of 4.0 months and an OS of 6.9 months (Strickler et al., 2023). Among 21 PDAC patients in the KRYSTAL-1 Phase II cohort, the ORR of adagrasib was 33%, the PFS was 5.4 months and the OS was 8 months (Bekaii-Saab et al., 2023). These results suggest that even among the most challenging tumour types to treat, there are therapeutic opportunities for KRAS targeting. Together with the superior performance of more potent molecules (e.g., divarasib) in other tumour types (Sacher et al., 2023), it is reasonable to hypothesize that increasing target occupancy and combining with upstream blockade (e.g., SOS1) may represent the next steps for KRAS^{G12C}-mutant PDAC (Dilly et al., 2024). Nonetheless, most of the evidence still comes from Phase I/II studies or expansion cohorts with small sample sizes and limited follow-up; durability and overall survival benefit will require larger, confirmatory trials (Bekaii-Saab et al., 2023; Strickler et al., 2023). In other solid tumours, the sample size remains small. However, a consistent trend is emerging, with the KRYSTAL-1 'pan-tumor' expansion cohort showing that subtypes such as cholangiocarcinoma can achieve a reasonably high ORR of approximately 42% (Bekaii-Saab et al., 2023). A prudent strategy is to prioritize enrollment in prospective trials, or to select carefully targeted high-occupancy agents and consider cross-pathway combination therapy (Isermann et al., 2025). Novel selective KRAS^{G12C} inhibitors exert their effects through similar mechanisms, aiming to improve potency and selectivity, and are currently undergoing multiple clinical trials (Hitchen et al., 2025; Perurena et al., 2024; Singhal et al., 2024). Such are JDQ443 (Cassier et al., 2023), Olomorasib (LY3537982) (Hollebecque et al., 2024; Murciano-Goroff et al., 2023), Glecirasib (JAB-21822) (Li, Shen, et al., 2024), Garsorasib (**D-1553**) (Li, Lu, et al., 2024; Ruan et al., 2023), Fulzerasib (IBI351) (Yuan et al., 2025; Zhou et al., 2023) and D3S-001 (Cho et al., 2025) (Table 1).

4.2 | From the 'OFF' state to the 'ON' state

This subsection integrates mechanistic rationale with early clinical translation. A paradigm-shifting advancement in the field of KRAS^{G12C} is shifting from targeting the inactive 'OFF' state to targeting the active 'ON' state, with RMC-6291 being a representative drug for 'ON' state inhibitors. RMC-6291 binds to the KRAS-peptidylprolyl isomerase A (PPIA)/cyclophilin A (CypA)/rotamase A (RotA) complex to form a 'ternary molecular gel' that can directly block the interaction between KRAS-GTP and downstream effector proteins without waiting for KRAS to cycle back to the GDP-binding state (Schulze et al., 2023). Early clinical data indicate that RMC-6291 has produced partial responses in previously treated patients with NSCLC and CRC (Jänne et al., 2023). A related approach is the dual-state (ON/OFF) irreversible inhibitor BBO-8520, which entered Phase I in 2025 (NCT06343402). Its goal is to transcend the nucleotide-state cycle by simultaneously blocking both conformations to delay resistance (Maciag et al., 2025). In parallel, an open-label Phase 1/2 study is evaluating FMC-376 for safety, pharmacokinetics and clinical activity in patients with locally advanced, unresectable or metastatic solid tumours harbouring *KRAS*^{G12C} mutations (NCT06244771).

4.3 | Breakthroughs in KRAS^{G12D}

This subsection distinguishes preclinical findings from early clinical observations. *KRAS*^{G12D} is the most common *KRAS* mutation in PDAC (Chen et al., 2024), and drugs targeting this allele have now entered clinical trials. Unlike KRAS^{G12C}, KRAS^{G12D} lacks a cysteine suitable for covalent locking, which forces drug design to take two paths: first, the non-covalent SIIP 'salt bridge' strategy, represented by MRTX-1133 (Zeissig et al., 2023). Second, the KRAS (ON) ternary complex strategy represented by zoldonrasib (RMC-9805), in which drugs 'glue' KRAS^{12D} to host proteins such as CypA, thus achieving selective inhibition (Zeissig et al., 2023). The former encountered challenges in clinical development: the Phase I/II study of MRTX-1133 was terminated in March 2025 due to 'formulation problems', which highlighted the unresolved problems of physicochemical properties and human exposure (NCT05737706). Preclinically, it confirmed that KRAS^{G12D} can be tightly engaged by highly selective, non-covalent small molecules and demonstrated clear biological synergy with ERBB inhibition in pancreatic/colorectal models (Gulay et al., 2023).

In clinical settings, in PDAC, the latest clinical data (n = 104) provide the strongest early signal for zoldonrasib (RMC-9805). In the second-line PDAC treatment group, the ORR of the 1200 mg once daily dose group was 30%, the DCR was 80%, the ctDNA *KRAS*^{G12D}

variant allele frequency decreased, and the pharmacodynamic "loop" (drug exposure, pathway inhibition, ctDNA decline and imaging response) seemed to be consistent (Spira et al., 2025). Of broader significance, the Phase I update of daraxonrasib (RMC-6236, pan-KRAS KRAS [ON]) in 42 patients with *KRAS*^{G12X} mutations showed an ORR of 29%, a median PFS of 8.5 months and an OS of 14.5 months. The drug is designed to maintain sustained silencing of KRAS (ON) across multiple *KRAS*^{G12X} alleles (Garrido-Laguna et al., 2025). In 2025, RMC-6236 received the FDA breakthrough therapy designation and the Phase III RASOLUTE-302 trial was initiated as second-line treatment for PDAC in comparison to standard chemotherapy (NCT05379985).

4.4 | Toward broad-spectrum targeting of KRAS

This subsection integrates preclinical evidence with selected early clinical observations. In addition to KRAS^{G12C} and KRAS^{G12D}, research on other alleles has made progress. Preclinically, recent work showed that RMC-5127 is a KRAS (ON) inhibitor targeting the active state (e.g., taking KRAS^{G12V}). As monotherapy, it showed significant antitumor effects in a variety of *KRAS*^{G12V} preclinical models (PDAC, NSCLC) and is well tolerated (Edwards, 2025). Notably, the results indicate that the drug has good central nervous system penetration and can be tolerated in relevant intracranial models, exhibiting anti-tumour activity and reducing tumour size (Edwards, 2025). These data suggest that targeting the 'non-G12C/non-G12D' cell population may be achieved via broader inhibition of the ON state. In the 'broad-spectrum KRAS' treatment toolbox, degraders are one approach. Clinically, in a Phase I study (n = 12) of solid tumours, the *KRAS*^{G12D}-selective degrader ASP3082 showed an ORR of 33% and a DCR of 75% with manageable safety in the 300-mg dose group, but dose-limiting toxicities in the 450-mg group (Park et al., 2024). A study by Golan et al. showed that the locally degradable implant siG12D-LODER, combined with chemotherapy, was well tolerated in patients with locally advanced PDAC (n = 15), with a median OS of 15.1 months, which supports the clinical feasibility of KRAS-targeted RNA interventions (Golan et al., 2015). In the Phase I AMPLIFY-201 cohort (20 patients with PDAC and 5 with CRC), the peptide vaccine ELI-002 induced a high rate of mutant KRAS–specific T-cell responses, which were associated with reductions in ctDNA and improved PFS (NCT04853017) (Pant et al., 2024; Wainberg et al., 2025). A recent study treated a patient with advanced metastatic PDAC using T-cell receptor-expressing T cells engineered to clonally express two tumour-targeting T-cell receptor specific for *KRAS*^{G12D} delivered via allogeneic HLA-C*08:02 lentivirus. The results showed objective regression of the patient's visceral metastases (Leidner et al., 2022).

4.5 | Toxicity profiles, adverse effects and patient-centred considerations

Although KRAS G12C inhibitors are generally better tolerated than conventional cytotoxic combinations, their clinical value still depends on whether target suppression can be maintained without cumulative toxicity. Across clinical KRAS G12C programs, the most common adverse effects are gastrointestinal and constitutional, including diarrhoea, nausea, vomiting and fatigue, as well as transaminase elevations (Barlesi et al., 2025; Bekaii-Saab et al., 2023; de Langen et al., 2023; Fakih et al., 2022; Skoulidis et al., 2021; Strickler et al., 2023). Adagrasib additionally requires attention to QT prolongation and creatinine increases (Bekaii-Saab et al., 2023), whereas transaminase elevations and liver-related toxicity remain clinically relevant considerations with sotorasib (de Langen et al., 2023; Fakih et al., 2022; Skoulidis et al., 2021; Strickler et al., 2023). Accordingly, the practical goal is not merely maximal dose, but durable and tolerable dose intensity. Combination therapy changes the toxicity landscape in a mechanism-specific manner. In CRC, KRAS G12C inhibitor plus EGFR-antibody regimens add class-consistent toxicities, including rash or acneiform rash, diarrhoea, stomatitis and hypomagnesemia (Fakih et al., 2023; Kuboki et al., 2024; Yaeger et al., 2023; Yaeger et al., 2024). Early dose-escalation studies of next-generation agents also suggest that potency does not eliminate tolerability constraints; for example, dose-limiting toxicities were reported in early clinical evaluation of the KRAS G12D degrader ASP3082 (Park et al., 2024). A patient-centred KRAS strategy therefore requires baseline and on-treatment monitoring tailored to the regimen, including liver function, gastrointestinal symptoms, ECG/QTc when relevant, renal function and electrolytes for EGFR-containing combinations; clear counselling on diarrhoea, rash, fatigue and early hepatotoxicity symptoms; and proactive use of dose interruption, dose reduction and supportive care to preserve adherence. Importantly, symptom burden and patient-reported outcomes should be weighed alongside response metrics. In CodeBreaK 300, sotorasib plus panitumumab improved patient-reported outcomes relative to standard therapy (Modest et al., 2025), underscoring that clinical benefit should be assessed not only by tumour response but also by patient experience.

5 | RESISTANCE TO KRAS INHIBITION

5.1 | Primary resistance

In clinical settings, primary resistance to KRAS inhibitors appears not to be a single-factor phenomenon; rather, it represents the composite effect of multiple factors acting in concert, which vary across tissues. First, the "background noise" of genomic co-mutations determines dependence on pathway suppression. In *KRAS*^{G12C} –mutant NSCLC, a pooled cohort of 424 patients across 21 centres treated with sotorasib or adagrasib monotherapy showed that the KEAP1, SMARCA4, CDKN2A (KSC) triad was significantly enriched among 'early progressors' (PFS < 3 months) and that each gene independently associated with shorter PFS/OS (Negrao, Araujo, et al., 2023). Conversely, patients with low baseline ctDNA burden are more likely to derive prolonged benefit, together defining 'high-risk' versus 'potentially controllable' starting populations (Negrao, Araujo, et al., 2023). Data on the impact of STK11 status on KRAS inhibitor outcomes are limited; however, it is well-documented that *STK11* co-mutation with

KEAP1 is detrimental. In a prospective subgroup analysis of adagrasib-treated patients, patients with versus without *KEAP1* mutations had PFS of 4.1 versus 9.9 months and OS of 5.4 versus 19.0 months, respectively; for patients with versus without *STK11* mutations, PFS was 4.2 months versus 11.0 months, and OS was 9.8 months versus not reached—again indicating a poorer prognosis (Negrao et al., 2025; Negrao, Araujo, et al., 2023). A proposed more pragmatic stratification of a 'long-lasting benefit' patient subset is patients without *KEAP1/STK11* alterations and low *NRF2* expression, which display significantly prolonged PFS/OS (Negrao et al., 2025; Negrao, Araujo, et al., 2023). Second, transcriptome-based 'biological subtypes' help to compensate for the shortcomings of simple genomic stratification. The study by Skoulidis et al., a comprehensive clinical efficacy and biomarker analysis of sotorasib (Skoulidis et al., 2025), grouped *KRAS*-mutant NSCLC into KP, KL and KC subtypes (Skoulidis et al., 2025). The KC subtype is typically characterized by low TTF-1 (NKX2-1) expression, activation of the NRF2 pathway and biallelic deletion of *CDKN2A/B*. (Skoulidis et al., 2025). Mapping this grouping onto sotorasib outcomes yielded an actionable observation: TTF-1–low tumours exhibit ORR 4%, PFS 2.8 months and OS 4.5 months; TTF-1–high tumours show ORR 45%, PFS 8.1 months and OS 16 months (Skoulidis et al., 2025). In addition, TTF-1 immunohistochemistry is the standard pathological diagnostic method for LUAD, and this high-risk subgroup accounts for approximately 15% to 20% of $KRAS^{G12C}$-mutant NSCLC (Skoulidis et al., 2025). This suggests that this subgroup can be identified early in clinical practice, thereby initiating first-line combination therapy or enhancing surveillance. Third, resistance is also affected by tissue-specific RTK dependence. As mentioned earlier, $KRAS^{G12C}$-mutant CRC exhibits tissue-specific dependence on the EGFR axis, and KRAS inhibitor monotherapy is easily offset by EGFR-mediated upstream feedback (Desai et al., 2024).

5.2 | Acquired resistance

Primary resistance sets the framework for first-line treatment; however, acquired resistance dynamically reshapes the treatment landscape. The most common mechanism of acquired resistance is 'pathway reflux' along the KRAS-MAPK axis, which is multifaceted and often polyclonal. Schemes of secondary resistance to KRAS targeting are discussed below. For clinical interpretability, Table S2 summarizes the major resistance mechanisms, representative biomarkers, corresponding therapeutic strategies and the level of supporting evidence (clinical or preclinical).

5.2.1 | On-target (secondary) mutations/amplifications

This subsection draws on translational analyses and preclinical studies. Alterations in the SIIP and its adjacent residues (e.g., R68S, H95D/Q/R and Y96C/D) reshape the pocket geometry and/or hydrogen bond network, preventing stable binding of sotorasib or adagrasib (Awad et al., 2021). Importantly, these alterations exhibit drug-specific cross-resistance. For example, the Q99L mutation confers in vitro resistance to adagrasib but retains sensitivity to sotorasib, indicating that drug switching is not equivalent to equivalence (Koga et al., 2021). The heterogeneity and evolution of drug resistance have yielded consistent findings from large-scale clinical translational cohort studies and deep mutational scanning in Ba/F3 cells. Therefore, molecular-level assessment during disease progression is crucial, rather than switching treatment regimens blindly (Koga et al., 2021).

5.2.2 | By-pass and pathway re-engagement

From a clinical perspective, a study by Awad et al. revealed that among 38 patients (27 with NSCLC, 10 with CRC and one with appendiceal cancer) treated with $KRAS^{G12C}$ inhibitors, 45% developed acquired resistance and 18% exhibited multiple resistance mechanisms (Awad et al., 2021). **MET** amplification, activating alterations in BRAF/MAP 2K1, fusions, involving *ALK*, *RET*, *RAF1* or *FGFR3* and loss-of-function events in *NF1* or *PTEN* all drive the rerouting of signalling to ERK, resulting in ERK reactivation (Awad et al., 2021).

5.2.3 | Nongenetic adaptive circuits

In preclinical studies, in addition to the above, it has been reported that when KRAS is inhibited (KRAS-OFF), the upstream RTK–SOS1/SHP2 pathway, which is regulated by ERK-dependent negative feedback, is rapidly unleashed. Wild-type KRAS regains GTP, and ERK activity recovers within minutes to hours (Ryan et al., 2020). This wild type-KRAS reset does not require new mutations, occurs earliest and broadest among all resistance mechanisms, and largely dictates the time scale of the 'initial benefit followed by loss' seen with anti-$KRAS^{G12C}$ monotherapy (Ryan et al., 2020; Ryan et al., 2022).

5.2.4 | Cell state and lineage reprogramming

In preclinical studies, in LUAD cells, KRAS inhibition appears to induce an alveolar Type I (ATI) cell-like state, which is characterized by low cell proliferation and drug resistance. However, progression can occur again once upstream or downstream pathways are reactivated (Li, Zhuang, et al., 2024). Several studies have reported that alveolar Type 1 cell-like enrichment is a characteristic feature of residual lesions after KRAS-targeted therapy, and targeting alveolar Type 1-like cells may enhance efficacy (Li, Zhuang, et al., 2024). Trans-differentiation from adenocarcinoma to squamous cell carcinoma is one such route. Notably, in the context of *STK11/LKB1* loss, squamous-associated gene programs (e.g., p63 gene generates transactivating and N-terminally truncated transcripts [ΔNp63]/keratin 6A [KRT6A]) are activated, endowing adenocarcinoma with a 'low-proliferative, highly tolerant' squamous phenotype and concomitantly reducing sensitivity to KRAS inhibitors and immunotherapy (Tong et al., 2024). These reasons

explain why some patients' tumours initially shrink and then stagnate, eventually developing functional resistance through lineage bypass.

6 | SPATIOTEMPORAL CO-TARGETING OF KRAS

Having clarified the mechanisms of primary and acquired resistance, the next step is to consider how to combine drugs, when to add them, and which drugs to add, integrating this into a unified framework. To this end, we propose herein a 'three-clock, two-window' model. These three clocks respectively depict pharmacokinetic half-life and exposure levels (Clock 1), target occupancy/residence time (Clock 2) and adaptive rebound of the KRAS-MAPK-ERK axis (Clock 3). The two windows refer to the vascular normalization phase induced by anti-vascular endothelial growth factor (**VEGF**) therapy (Window 1) and the immune/myeloid plasticity phase (Window 2). Aligning the timing and windows of treatment, along with a rational drug combination strategy, is key to overcoming preexisting or incipient resistance. Our proposed strategy includes vertical combinations acting along the KRAS-MAPK axis to limit rebound, lateral combinations blocking compensatory and bypass networks in parallel, and immunotherapy combinations intervening within the immune plasticity window to inhibit immune escape.

6.1 | Clock 1: Aligning half-life and exposure

This subsection is grounded in clinical pharmacology and translational evidence. According to clock 1, pharmacokinetic characteristics (half-life and exposure) are temporally synchronized with clinical effects. Preclinical, Ryan et al. found that inhibition of $KRAS^{G12C}$ may lead to the reactivation of wild-type KRAS through the RTK–SHP2–SOS1 pathway, resulting in phosphorylated extracellular signal-regulated kinase (pERK) rebound (Fedele et al., 2021; Ryan et al., 2022). Hence, during trough exposure between doses, a functional gap of 'occupied yet unstable' is more likely to occur. Rather than simply increasing dose, optimizing dosing cadence ('time in exchange for occupancy') has a stronger mechanistic rationale (Ram, Murphy, et al., 2023; Sahin & Benet, 2008). Clinically, human pharmacokinetic data show that the half-lives of sotorasib and divarasib are 5 to 7 and 17 to 18 h, respectively. Based on human pharmacokinetics, at the same dosing frequency, divarasib could theoretically provide more extended through coverage and a smoother occupancy-time profile, potentially buffering early ERK rebound and upstream reignition (Buchwald, 2019; Finlay et al., 2020; Sahin & Benet, 2008). This may partly explain the differences in the 'peak–trough dynamics' pattern with monotherapy; however, pharmacokinetics is not the sole determinant, and differences in clinical endpoints cannot be attributed solely to half-life. Consistency in pharmacokinetic-pharmacodynamic waveforms may be an area for optimization of this mechanism. However, OS is also influenced by factors such as patient selection, treatment regimen and the quality of trial implementation.

6.2 | Clock 2: Target engagement and residence

This subsection is informed mainly by translational and preclinical evidence. The proposed Clock 2 focuses on 'once occupied, how long can it stay'. Allele biology and the tumour microenvironment together determine the efficiency of transition from 'occupancy' to 'pathway suppression'. Clinical translational/preclinical, secondary mutations (such as R68, H95, Y96 and Q99) that occur after G12C inhibitor treatment can alter the geometry and hydrogen bond network of the SIIP, thereby reducing drug recognition and binding efficiency, and shortening the drug's residence time (Awad et al., 2021; Koga et al., 2021). Enhancing occupancy has little effect on secondary mutations that cause 'pocket remodeling'. Preclinically, the following measures can be taken in order to enhance target engagement and residence. First, to switch to KRAS (ON) inhibition (inducing KRAS-GTP to form a ternary complex with the host protein, thereby directly blocking the binding of KRAS-GTP to the effector protein) (Cregg et al., 2025; Holderfield et al., 2024; Schulze et al., 2023). Second, to clamp the distal pathway by inhibiting ERK or blocking RAF/MEK, thereby inhibiting the downstream output and bypassing the restrictions of SIIP geometry. (Perurena et al., 2024). More importantly, to distinguish 'occupancy-limited' from 'circuit-limited' mismatch. When the target occupancy rate is insufficient, 'deepening occupancy' should be prioritized over 'expanding coverage'. The criteria for ruling in limited target engagement/residence can include 4-([S]-4-acryloyl-2-methylpiperazin-1-yl)-6-fluoro-7-(2-fluoro-6-(2-(2-(2-(2-[fluoro-18F]ethoxy)ethoxy)ethoxy)ethoxy)phenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-d]pyrimidin-2(1H)-one ([18F]PFPMD) positron emission tomography imaging and live cell NanoLuc-based bioluminescence resonance energy transfer assays (sensitive, proximity-based, bioluminescence resonance energy transfer techniques used to monitor protein–protein interactions and drug-target engagement), among other methods (Li et al., 2023; Robers et al., 2015; Vasta et al., 2022). Strategies to overcome target engagement/residence may include optimizing dose density, switching to a similar drug with higher response efficiency, or combining with SHP2/SOS1 inhibitors to stabilize KRAS in the GDP-bound state, thereby extending the target's available time window (Fedele et al., 2021). Note that [18F]PFPMD positron emission tomography is currently used mainly for mutation-state discrimination and pre−/post-treatment changes in standardized uptake value as translational readouts, and should not be directly translated to in vivo occupancy (Li et al., 2023). Clinical translational observation, when receptor occupancy indicators show sufficient levels, but ERK activity remains high and ctDNA levels only briefly decrease before plateauing, this usually indicates that parallel pathways or feedback loops have been activated (Awad et al., 2021; Paweletz et al., 2023). In this case, a combined horizontal strategy should be adopted (circuit restriction): in CRC, EGFR should be preferentially blocked; in NSCLC, precise selection of 'homologous' inhibitors should be made based on molecular characteristics, targeting *MET*/*ERBB2* activation, rare fusion genes (*ALK*, *RET*, *RAF1* and *FGFR3*), PI3K-AKT-mTOR pathway activation or *NF1*/*PTEN* deletion (Awad et al., 2021; Mendoza et al., 2011). The core of this

strategy is to divert signalling pathways, ultimately resulting in convergent inhibition at the downstream ERK node. Preclinically, in PDAC, a neglected clock 2 trap needs to be considered: MAPK inhibition significantly induces protective autophagy. Even if deep target occupancy is achieved, its efficacy may be offset by this cellular state adaptation (Kinsey et al., 2019). In patients with increased autophagy flux (e.g., dynamically elevated LC3-II [a lipidated form of the microtubule-associated protein 1A/1B-light chain 3, serving as a standard membrane-bound marker for autophagosomes, formed by the conjugation of LC3-I to phosphatidylethanolamine] and reduced p62 [sequestosome 1, SQSTM1] levels), the combination of autophagy inhibitors with KRAS/MAPK inhibitors exhibits synergistic effects. This combination can be applied to the 'well-occupied but effect-transmission-limited' scenario (Kinsey et al., 2019).

6.3 | Clock 3: The rebound clock: aligning vertical and horizontal combinations in time

This subsection integrates preclinical, translational and early clinical evidence. Preclinically, as mentioned above, inhibition of $KRAS^{G12C}$ relieves the negative feedback, leading to reactivation of wild-type KRAS via the RTK–SHP2–SOS1 axis. This mechanism has been confirmed in multiple studies, including some at single-cell/subcellular resolution (Ryan et al., 2020; Ryan et al., 2022). The typical clinical pattern of this rebound clock is that the initial response disappears. To combat it, the vertical combination of 'upstream + downstream' is essential to maintaining pathway inhibition (Awad et al., 2021; Fedele et al., 2021; Zhang et al., 2025). Clinical monitoring implication, in practice, timing matters: within hours to ~72 h after starting monotherapy, one should monitor pERK/phosphorylated ribosomal S6 kinase (pRSK) for rapid rebound (Ryan et al., 2022); one should also evaluate early ctDNA decline at ~1–3 weeks (e.g., Cycle 1, Day 8 to Cycle 2, Day 1 [C1D8–C2D1]) to assess the likelihood of sustained suppression (Paweletz et al., 2023; Zhang et al., 2024). Multiple studies indicate that adaptive rebound after KRAS–ERK inhibition is primarily driven by RTK/SHP2/SOS1-mediated reactivation of WT-KRAS (Ryan et al., 2020; Ryan et al., 2022); inhibiting SHP2 or SOS1 attenuates rebound and synergizes with $KRAS^{G12C}$ or downstream MEK/ERK inhibition (Fedele et al., 2021; Thatikonda et al., 2024). Early clinical evidence, a Phase I study of divarasib plus the SHP2 inhibitor GDC-1971 in $KRAS^{G12C}$-mutant and $KRAS^{G12C}$-inhibitor-naïve NSCLC reported a confirmed ORR of 43.8% (48 patients) and a median PFS of 15.2 months (Luo et al., 2025). In a Phase I/IIa study of glecirasib plus the SHP2 inhibitor JAB-3312 in NSCLC (n = 80), ORR was 72.5% and DCR 96.3%; in the glecirasib 800 mg once daily + JAB-3312 2 mg (1-week on/1-week off) group, ORR was 77.8% (21/27) and DCR 92.6% (25/27) (Zhao et al., 2024). Additional Phase 1/2 trials have reported positive results (Falchook et al., 2022; Negrao, Cassier, et al., 2023) or are ongoing (NCT04185883; NCT04330664). Horizontal combination therapy (such as EGFR blockade in CRC) should follow the timing design of the Clock 3 protocol. In order to suppress rebound at peak receptor occupancy, anti-EGFR therapy should be administered at the start of each treatment cycle and continued without interruption in order to maintain a high level of receptor occupancy. In the randomized Phase III CodeBreaK-300 study, the ORR of 960 mg sotorasib in combination with panitumumab was 30.2%, which was higher than that of the 240 mg combination therapy group (7.5%) and the standard therapy group (1.9%), supporting the combined strategy of adequate KRAS inhibition and sustained EGFR blockade (Pietrantonio et al., 2025). With higher potency molecules, the monotherapy baseline is further raised: in CRC, divarasib plus cetuximab achieved ORR 62%, while divarasib monotherapy achieved an ORR of 29%–36% (Desai et al., 2024). When Clock 1 reaches sufficient exposure, occupancy, and duration, EGFR-mediated feedback signals in Clock 3 are more effectively suppressed, and the synergistic effect of horizontal co-operation is amplified.

6.4 | Vascular normalization: A limited, measurable window

This subsection integrates clinical observations with translational biomarker studies. Window 1 (vascular normalization) presents a measurable but time-limited physiological state. In a PDAC Phase III trial, the Phase III CALGB 80303 study showed that gemcitabine combined with bevacizumab failed to improve OS, suggesting that conventional combination therapy alone has limitations (Kindler et al., 2010). However, within a specific dose range, some tumours exhibit physiological microcirculatory remodelling within days of treatment initiation, characterized by increased pericyte coverage and vascular support, decreased vascular permeability and interstitial pressure and more uniform perfusion distribution (Jain, 2005; Kambadakone et al., 2015; Kannan et al., 2018; Sorensen et al., 2009; Tolaney et al., 2015; Willett et al., 2004). This 'vascular normalization' phenomenon was first proposed by Jain et al. and was subsequently validated in human studies (e.g., in vivo imaging of CRC) (Jain, 2005; Kambadakone et al., 2015; Kannan et al., 2018; Sorensen et al., 2009; Tolaney et al., 2015; Willett et al., 2004). Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)-obtained k^{trans}, perfusion computed tomography (CT) and histological markers of pericytes are methods for tracking this change (Jain, 2005; Kambadakone et al., 2015; Kannan et al., 2018; Sorensen et al., 2009; Tolaney et al., 2015; Willett et al., 2004) in order to improve drug delivery and reduce toxicity. Because VEGF promotes a pauci-immune tumour milieu by inhibiting dendritic cell (DC) maturation, by enhancing regulatory T-cell and myeloid-derived suppressor cell (MDSC) infiltration and by damping effector T cell recruitment, the phased combination of anti-angiogenic and immunotherapy has a sound biological basis. Preclinical studies demonstrate that the combination of low-dose anti-**VEGFR2** with anti-**PD-1**/**PD-L1** can enhance $CD8^+$ T cell-dependent anti-tumour activity (Li, Amaladas, et al., 2022; Yang et al., 2018; Yang et al., 2022). A multicentre Phase II trial (SHERLOCK, ACTRN12622000973718) is evaluating sotorasib + carboplatin/pemetrexed + bevacizumab in $KRAS^{G12C}$-mutant advanced

NSCLC (Table 2) (Lee et al., 2023). Hence vascular normalization requires precise drug timing and dosage in order to create more favourable conditions for other combination therapies and not to increase OS per se. Future prospective studies with well-designed timelines are still needed to validate this strategy, especially in densely matrixed PDACs. From an operational perspective, the vascular-normalization window should be treated as approximate and regimen-dependent rather than fixed. Across anti-VEGF/VEGFR studies, normalization-related changes have been documented as early as 1 day after exposure and have also been assessed at approximately 12–14 days or after 2 weeks of therapy; thus, baseline assessment with early on-treatment repeat perfusion imaging may be a practical strategy, although an exact schedule is likely regimen-specific rather than universal (Jain, 2005; Kambadakone et al., 2015; Sorensen et al., 2009; Tolaney et al., 2015; Willett et al., 2004). Candidate biomarkers include DCE-MRI Ktrans, computed tomography (CT) perfusion-derived parameters, interstitial-fluid-pressure or oedema-related readouts and histologic vascular-maturation indices such as increased pericyte coverage where tissue is available (Jain, 2005; Kambadakone et al., 2015; Kannan et al., 2018; Sorensen et al., 2009; Tolaney et al., 2015; Willett et al., 2004).

6.5 | KRAS-driven immune remodelling: Seizing the immune–myeloid window

In this subsection, preclinical and animal-model observations are described first, followed by available clinical findings and early clinical signals. Like other oncogenic drivers, mutant KRAS not only reprograms the cancer cell's intrinsic behaviour but also the microenvironment (Figure 3). Via a Ras-related protein B (RALB)/tank binding kinase 1 (TBK1)/inhibitor of κB kinase (IKK) α and ε/nuclear factor (NF)-κB relay, it amplifies the transcription of pro-inflammatory/chemotactic genes, establishing strong myeloid chemokine gradients and driving the infiltration of neutrophils and MDSCs (Marazioti et al., 2018; Sparmann & Bar-Sagi, 2004; Spella et al., 2023). In

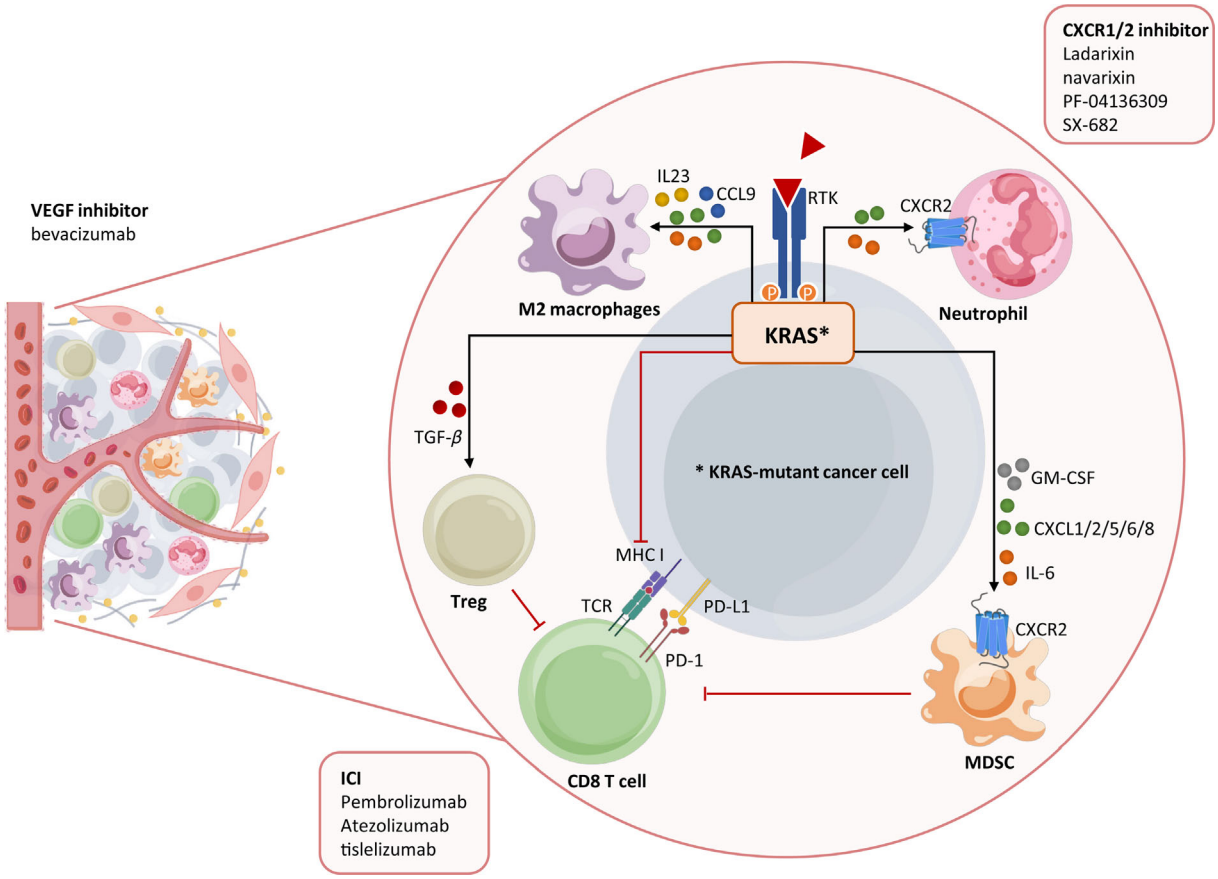

FIGURE 3 KRAS-driven immune evasion and therapeutic entry points in the tumour microenvironment. Schematic of a KRAS-mutant cancer cell and surrounding immune milieu. Oncogenic KRAS (KRAS*) is constitutively active. KRAS* drives an immunosuppressive program: it induces chemokines CXCL1/2/5/6/8 and cytokines (e.g., GM-CSF, IL-6), recruiting and activating neutrophils and MDSCs via CXCR2; alternatively activated (M2) macrophages provide protumor cues (e.g., IL-23and CCL9). KRAS* upregulates PD-L1 and downregulates major histocompatibility complex Class I, reducing $CD8^+$ T-cell recognition, while TGF-β promotes regulatory T-mediated suppression. Black arrows denote stimulatory/paracrine interactions; red bars indicate inhibitory effects; 'P' marks phosphorylation; KRAS* indicates an activating. ICI denotes immune checkpoint inhibitor. All elements were sourced from https://biogdp.com/workspace and adapted for this figure.

tumour models, genetic or pharmacological blockade of **CXCR2** can significantly inhibit neutrophil/MDSC infiltration, thereby enhancing $CD8^+$ T cell infiltration (Steele et al., 2016). However, a randomized Phase II study evaluating the efficacy of the CXCR2 antagonist navarixin in combination with pembrolizumab in an unselected patient population with castration-resistant prostate cancer, Microsatellite Stable Colorectal Cancer and NSCLC showed extremely low ORRs (5.0%, 2.5% and 0%, respectively), leading to the study's premature termination at the pre-specified interim analysis due to insufficient efficacy. Notably, absolute neutrophil counts decreased by approximately 40%–48% 6–12 h post-dose (Armstrong et al., 2024). *KRAS*^{G12D}-mutant cancer cells can also induce tumour-derived granulocyte-macrophage colony-stimulating factor (GM-CSF), which expands $Gr1^+CD11b^+$ myeloid cells and suppresses $CD8^+$ T-cells, thereby promoting early pancreatic intraepithelial neoplasia and immune evasion (Figure 3) (Bayne et al., 2012). Animal models have shown that blocking tumour-derived GM-CSF can inhibit MDSC recruitment and restore $CD8^+$ T-cell-mediated anti-tumour activity (Bayne et al., 2012). However, selective inhibition of monocyte/macrophage migration did not yield benefits in patients. The **CCR2** inhibitor PF-04136309 in combination with chemotherapy failed to outperform standard chemotherapy in metastatic PDAC and raised concerns about potential lung toxicity; randomized clinical trials of the colony-stimulating factor 1 receptor (**CSF1R**) inhibitor cabiralizumab in combination with nivolumab (± chemotherapy) also failed to improve survival (Ju et al., 2024; Noel et al., 2020). The reasons for this clinical failure are, possibly, compensatory redundancy with parallel activation of chemokine pathways, inclusion of advanced stage patients with extensive prior treatment and weakened immune response, and non selective study design leading to signal dilution (Armstrong et al., 2024; Ju et al., 2024; Noel et al., 2020; Tang et al., 2022). Future research directions include biomarker stratification, multi-axis blockade and optimized treatment sequencing. Furthermore, when the KRAS-ERK pathway is inhibited, tumour cells induce the infiltration of MDSCs with high S100A8/9 expression by upregulating C-C-motif and C-X-C-motif chemokine ligands via NF-κB, thereby offsetting the number of T cells gained due to enhanced antigen presentation. This has been validated in various NSCLC models (Molina-Arcas & Downward, 2024; Tang et al., 2022). Mechanism-aligned combinations close the loop in animals: SHP2 inhibition, combined with CXCR1/2 inhibition (e.g., SX-682), blocks MDSC trafficking, promotes Th1 polarization and induces more cytotoxic killer cell lectin-like receptor G1 $(KLRG1)^+$ $CD8^+$ T cells, significantly prolonging survival (Tang et al., 2022). Early clinical exploration supports this finding: SX-682 combined with pembrolizumab demonstrated acceptable safety, with dose-related signals of objective response/disease control in a Phase I trial for PD-1-refractory metastatic melanoma (NCT03161431) (Patel et al., 2024). Based on the same pathway logic, a Phase II NSCLC study is evaluating SX-682 in combination with anti-PD-1 in first-line or relapsed settings, with enhanced biomarker stratification (NCT05570825). In line with this axis, a Phase I trial of sotorasib plus ladarixin (NCT05815173) is enrolling patients with *KRAS*^{G12C}-mutant NSCLC (Table 2). The KRAS oncogene can inhibit the type I/II interferon response and downregulate major histocompatibility complex class I and T cell chemokines, such as CXCL9/10, with *MYC* being a key node. (Figure 3) (Molina-Arcas & Downward, 2024; Mugarza et al., 2022). In mouse LUAD models, KRAS and MYC remodel the immune microenvironment via the CCL9/IL-23 axis, leading to rejection of T cells, B cells and NK cells, while enriching M2-like macrophages (Kortlever et al., 2017). Direct inhibition of $KRAS^{G12C}$ alleviated these inhibitory effects in various immunogenicity models, upregulating interferon signalling and antigen presentation, and thereby increasing $CD8^+$ T cell infiltration (Anastasiou et al., 2024; Canon et al., 2019; Cole et al., 2024; Mugarza et al., 2022). These immune shifts provide the biological rationale for KRAS inhibition (adagrasib) + immune checkpoint inhibitor combinations (Table 2). Clinically, sotorasib combined with pembrolizumab or atezolizumab in 58 patients with NSCLC yielded an ORR 29% and an OS of 15.7 months (Li, Falchook, et al., 2022). The Phase I/II study KRYSTAL-7 demonstrated an ORR of 63% and a DCR of 84% in the PD-L1 expression ≥50% cohort among previously untreated first-line NSCLC patients, with overall favourable safety (Garassino et al., 2023). Follow-up in 2025 showed: PD-L1 expression ≥50% arm (n = 54): ORR 59.3%, median PFS 27.7 months and PD-L1 expression <50% arm (n = 95): ORR 34%, median mPFS 6.9 months, while the study is ongoing (Jänne et al., 2025). Divarasib + atezolizumab (Phase I) showed a confirmed ORR 55.6% in 27 $KRAS^{G12C}$ inhibitor-naïve NSCLC patients with measurable baseline disease (Sacher et al., 2024). Olomorasib + pembrolizumab (Phase I/II) reported, among 30 evaluable $KRAS^{G12C}$ inhibitor-naïve NSCLC patients (60% with prior therapy), ORR 63% and DCR 93% [ORR 75% (9/12) in PD-L1 ≥ 50% expressors and 56% (10/18) in PD-L1 < 50% expressors] (Burns et al., 2024). That said, within the context of KRAS + immune checkpoint inhibition, the specific agents and sequencing have a profound impact on hepatotoxicity risk, which occurs in parallel with microenvironment activation and immune synergy. Real-world and multicentre retrospective data indicate that initiating sotorasib within 30 days after PD-(L)1 therapy substantially increases the incidence of grade ≥3 hepatotoxicity (Chour et al., 2023; Desai et al., 2023). Early CodeBreaK 101 data also suggest higher liver toxicity with concurrent starts, whereas a short sotorasib lead-in may partially mitigate adverse events (Li, Falchook, et al., 2022). These observations, now reported across multiple studies, are a key safety premise when designing first-line immunotherapy combinations or sequencing strategies. Alleles and lineage jointly shape the tumour's immune baseline, which in turn sets the breadth of the immune-plastic window achievable by subsequent therapy. In large multicentre NSCLC cohorts, *KRAS*^{G12D}—versus other KRAS subtypes—shows lower PD-L1 expression and tumour mutational burden with reduced $CD8^+PD\text{-}1^+$ T-cell infiltration, indicating an intrinsically 'colder' ecosystem (Ricciuti, Alessi, et al., 2022; Zeissig et al., 2023). In an analysis of 850 *KRAS*-mutant NSCLC patients, the $KRAS^{G12D}$ subgroup had inferior outcomes versus $KRAS^{non\text{-}G12D}$ with PD-(L)1 monotherapy (ORR 15.8% vs. 28.4%) (Fucikova et al., 2020; Ricciuti, Alessi, et al., 2022). By contrast, in first-line chemo-immunotherapy, this disadvantage was attenuated relative to $KRAS^{non\text{-}G12D}$ (ORR 30.6% vs. 35.7%), and PFS/OS gaps were not

statistically significant, consistent with chemotherapy-enhanced immunogenicity partially offsetting the allele's lower antigenicity (Fucikova et al., 2020; Ricciuti, Alessi, et al., 2022). PDAC, real-world data from resectable cases indicate a worse prognosis for $KRAS^{G12D}$ and lower $CD8^+$ T-cell activation after PD-1 + GVAX vaccination, suggesting a colder immune phenotype and a narrower plastic window (Christenson et al., 2024). In CRC, KRAS mutations—predominantly G12D/G12V—are common; most cases are MSS and generally insensitive to PD-1 monotherapy (Hanggi & Ruffell, 2019). Only the microsatellite instability-high/dMMR subgroup derives substantial benefit from immune checkpoint inhibitors, surpassing chemotherapy (André et al., 2020). The immune/myeloid plasticity window is likewise dynamic and multi-layered. Adaptive MAPK rebound can emerge within hours to ~72 h after KRAS inhibition (Ryan et al., 2020; Ryan et al., 2022; Zhang et al., 2025), and pharmacodynamic neutrophil suppression after CXCR1/2 blockade has been documented within 6–12 h (Armstrong et al., 2024). Early on-treatment ctDNA changes may be observed within approximately 3 weeks after treatment initiation, before the first radiographic assessment (Paweletz et al., 2023). Accordingly, on-treatment evaluation may include pERK/pRSK, serial ctDNA KRAS variant allele frequency, complete blood counts with differential, biomarkers of myeloid activity related to CXCR2 ligands and GM-CSF and profiling of $CD8^+$ T-cells and suppressive myeloid populations (Anastasiou et al., 2024; Armstrong et al., 2024; Bayne et al., 2012; Molina-Arcas & Downward, 2024; Mugarza et al., 2022; Paweletz et al., 2023; Tang et al., 2022).

7 | CONCLUSION

Taken together, KRAS-directed therapy has moved on from the question of 'can we inhibit it?' to 'how do we sustain inhibition over time?' Breakthrough advancements in $KRAS^{G12C}$ have established the feasibility of directly targeting KRAS. Furthermore, the rise of G12 and KRAS (ON) strategies has expanded the eligible patient population; however, actual efficacy is ultimately constrained by factors such as tissue lineage, allele background, co-mutation networks and limitations in the microenvironment and drug delivery. Primary and acquired resistance are not rare or accidental events, but rather a common phenomenon encountered after KRAS inhibitor treatment. They are shaped by targeted secondary mutations, bypass/reactivation, adaptive rebound and cell state/lineage reprogramming. Therefore, pharmacology and time must be incorporated into a unified decision-making framework, including practical considerations. In colorectal cancer, EGFR feedback should be blocked from the outset, pairing adequate-occupancy KRAS inhibition with sustained upstream blockade. In NSCLC, stratification by co-mutations (e.g., KEAP1/STK11) and TTF-1 phenotype can help delineate who may traverse a monotherapy bridge versus those who require early combination therapy and standardized monitoring. In PDAC, the primary constraint is 'arrival' rather than 'drug', so leveraging the transient perfusion improvement from vascular normalization and optimizing dose density could effective for amplifying meaningful exposure than simply escalating the dose. Our 'three clocks + two windows' framework provides an operational timing grammar: calibrate dosing cadence by half-life and trough coverage (Clock 1); use occupancy/residence efficiency to distinguish 'occupancy-limited' from 'circuit-limited' failure (Clock 2); and tune the entry point for vertical combinations by the magnitude and time constant of MAPK rebound (Clock 3). Within the anti-VEGF–induced vascular-normalization window and the immune/myeloid plasticity window between KRAS inhibition onset and ERK rebound, deploy mechanism-matched co-targets—shifting from 'adding drugs' to 'time-aligned dosing'. When pocket-remodelling second-site mutations or clear distal reflux emerge, pivot decisively to KRAS (ON) inhibition or downstream ERK/RAF–MEK 'clamps'. When early monitoring reveals rapid pERK rebound or only a transient drop in ctDNA, introduce SHP2/SOS1 or distal capping promptly, rather than merely increasing the dose. Combined immunotherapy has significantly improved treatment outcomes; however, managing hepatotoxicity requires close monitoring of the treatment regimen and pharmacokinetic clearance. Sequential dosing regimens or extended dosing intervals are generally preferred, with continuous monitoring of liver function and immunological parameters to assess efficacy and toxicity. Future drug development should advance simultaneously in terms of both 'state-based inhibition' and 'broad accessibility', exploring bistate/ternary mechanisms and their complementarity with degrading agents, RNA and immune strategies. Regarding biomarkers, indicators such as ctDNA dynamics, pERK rebound, functional perfusion and immune/myeloid quantification should be integrated into a closed loop and prospectively used as stratification and trigger thresholds to validate the causal chain of exposure, occupation, pathway inhibition, ctDNA and imaging. Only by unifying the 'molecular network clock' into a measurable and reproducible tool and administering combined targeted therapy at the appropriate times can KRAS-targeted therapy reliably translate into more profound therapeutic effects and prolonged survival.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2025/26 (Alexander, Davenport et al., 2025; Alexander, Fabbro, Gibb, et al., 2025 Alexander, Fabbro, Peach, et al., 2025; Alexander, Gibb et al., 2025).

AUTHOR CONTRIBUTIONS

Jianlong Jia: Conceptualization (lead); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); visualization (supporting); writing—original draft (lead). **Ruonan Liu:** Conceptualization (supporting); data curation (lead); formal analysis (equal); investigation (supporting); methodology (equal); visualization (lead). **Tonia A. Adamide:** Validation (equal); writing—review and editing (equal). **Isis E. Fernandez:** Supervision (equal); writing—review and

editing (equal). **Georgios T. Stathopoulos:** Conceptualization (equal); investigation (equal); project administration (equal); resources (lead); supervision (lead); writing—review and editing (equal).

CONFLICT OF INTEREST STATEMENT

The authors have declared that no conflict of interest exists.

REFERENCES

Alexander, S. P. H., Davenport, A. P., Kelly, E., Gibb, A. J., Mathie, A. A., Peach, C. J., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Southan, C., Davies, J. A., Abbracchio, M. P., Abraham, G. R., Agoulnik, A., Alexander, W., Al-hosaini, K., Bäck, M., Baker, J. G., … Zaidman, N. (2025). The Concise Guide to PHARMACOLOGY 2025/26: G protein-coupled receptors. *British Journal of Pharmacology*, *182*(Suppl 1), S24–S151. https://doi.org/10.1111/bph.70230

Alexander, S. P. H., Fabbro, D., Peach, C. J., Gibb, A. J., Kelly, E., Mathie, A. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Southan, C., Davies, J. A., Beuve, A., Brouckaert, P., Bryant, C., Burnett, J. C., Farndale, R. W., Friebe, A., Garthwaite, J., … Waldman, S. A. (2025). The Concise Guide to PHARMACOLOGY 2025/26: Catalytic receptors. *British Journal of Pharmacology*, *182*-(Suppl 1), S259–S306. https://doi.org/10.1111/bph.70233

Alexander, S. P. H., Fabbro, D., Gibb, A. J., Kelly, E., Mathie, A. A., Peach, C. J., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Southan, C., Davies, J. A., Annett, S., Boison, D., Burns, K. E., Dessauer, C., Gertsch, J., Helsby, N. A., Izzo, A. A., … Wong, S. S. (2025). The Concise Guide to PHARMACOLOGY 2025/26: Enzymes. *British Journal of Pharmacology*, *182*(Suppl 1), S307–S403. https://doi.org/10.1111/bph.70234

Alexander, S. P. H., Gibb, A. J., Kelly, E., Mathie, A. A., Peach, C. J., Veale, E. L., Cidlowski, J. A., Davenport, A. P., Fabbro, D., Spedding, M., Striessnig, J., Armstrong, J. F., Buneman, O. P., Faccenda, E., Harding, S. D., Southan, C., Davies, J. A., Ahlers-Dannen, K. E., Alqinyah, M., … Zolghadri, Y. (2025). The Concise Guide to PHARMACOLOGY 2025/26: Introduction and Other Protein Targets. *British Journal of Pharmacology*, *182*(Suppl 1), S1–S23. https://doi.org/10.1111/bph.70229

Anastasiou, P., Moore, C., Rana, S., Tomaschko, M., Pillsbury, C. E., de Castro, A., Boumelha, J., Mugarza, E., de Carné Trécesson, S., Mikolajczak, A., Blaj, C., Goldstone, R., Smith, J. A. M., Quintana, E., Molina-Arcas, M., & Downward, J. (2024). Combining KRAS (ON) G12C-selective inhibitor with SHP2 inhibition sensitises lung tumours to immune checkpoint blockade. *Nature Communications*, *15*(1), 8146. https://doi.org/10.1038/s41467-024-52324-3

Andersen, M. B., Drljevic-Nielsen, A., Ehlers, J. H., Thorup, K. S., Baandrup, A. O., Palne, M., & Rasmussen, F. (2024). DCE-CT parameters as new functional imaging biomarkers at baseline and during immune checkpoint inhibitor therapy in patients with lung cancer - a feasibility study. *Cancer Imaging*, *24*(1), 105. https://doi.org/10.1186/s40644-024-00745-0

André, T., Shiu, K. K., Kim, T. W., Jensen, B. V., Jensen, L. H., Punt, C., Smith, D., Garcia-Carbonero, R., Benavides, M., Gibbs, P., & de la Fouchardiere, C. (2020). Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *The New England Journal of Medicine*, *383*(23), 2207–2218. https://doi.org/10.1056/NEJMoa2017699

Arevalo-Perez, J., Trang, A., Yllera-Contreras, E., Yildirim, O., Saha, A., Young, R., Lyo, J., Peck, K. K., & Holodny, A. I. (2024). Longitudinal Evaluation of DCE-MRI as an Early Indicator of Progression after Standard Therapy in Glioblastoma. *Cancers (Basel)*, *16*(10), 1839. https://doi.org/10.3390/cancers16101839

Armstrong, A. J., Geva, R., Chung, H. C., Lemech, C., Miller, W. H., Hansen, A. R., Lee, J. S., Tsai, F., Solomon, B. J., Kim, T. M., Rolfo, C., Giranda, V., Ren, Y., Liu, F., Kandala, B., Freshwater, T., & Wang, J. S. (2024). CXCR2 antagonist navarixin in combination with pembrolizumab in select advanced solid tumors: A phase 2 randomized trial. *Investigational New Drugs*, *42*(1), 145–159. https://doi.org/10.1007/s10637-023-01410-2

Awad, M. M., Liu, S., Rybkin, I. I., Arbour, K. C., Dilly, J., Zhu, V. W., Johnson, M. L., Heist, R. S., Patil, T., Riely, G. J., Jacobson, J. O., Yang, X., Persky, N. S., Root, D. E., Lowder, K. E., Feng, H., Zhang, S. S., Haigis, K. M., Hung, Y. P., … Aguirre, A. J. (2021). Acquired Resistance to KRAS(G12C) Inhibition in Cancer. *The New England Journal of Medicine*, *384*(25), 2382–2393. https://doi.org/10.1056/NEJMoa2105281

Bahar, M. E., Kim, H. J., & Kim, D. R. (2023). Targeting the KRAS/RAF/-MAPK pathway for cancer therapy: From mechanism to clinical studies. *Signal Transduction and Targeted Therapy*, *8*(1), 455.

Bardelcikova, A., Soltys, J., & Mojzis, J. (2023). Oxidative Stress, Inflammation and Colorectal Cancer: An Overview. *Antioxidants (Basel)*, *12*(4), 901. https://doi.org/10.3390/antiox12040901

Barlesi, F., Yao, W., Duruisseaux, M., Doucet, L., Martínez, A. A., Gregorc, V., Juan-Vidal, O., Lu, S., De Bondt, C., de Marinis, F., Linardou, H., Kim, Y. C., Jotte, R., Felip, E., Lo Russo, G., Reck, M., Michenzie, M. F., Yang, W., Meade, J. N., … Mok, T. S. K. (2025). Adagrasib versus docetaxel in KRAS(G12C)-mutated non-small-cell lung cancer (KRYSTAL-12): A randomised, open-label, phase 3 trial. *Lancet*, *406*(10503), 615–626. https://doi.org/10.1016/S0140-6736(25)00866-9

Bayne, L. J., Beatty, G. L., Jhala, N., Clark, C. E., Rhim, A. D., Stanger, B. Z., & Vonderheide, R. H. (2012). Tumor-derived granulocyte-macrophage colony-stimulating factor regulates myeloid inflammation and T cell immunity in pancreatic cancer. *Cancer Cell*, *21*(6), 822–835. https://doi.org/10.1016/j.ccr.2012.04.025

Bekaii-Saab, T. S., Yaeger, R., Spira, A. I., Pelster, M. S., Sabari, J. K., Hafez, N., Barve, M., Velastegui, K., Yan, X., Shetty, A., der-Torossian, H., & Pant, S. (2023). Adagrasib in Advanced Solid Tumors Harboring a KRAS(G12C) Mutation. *Journal of Clinical Oncology*, *41*(25), 4097–4106. https://doi.org/10.1200/JCO.23.00434

Brana, I., Shapiro, G., Johnson, M. L., Yu, H. A., Robbrecht, D., Tan, D. S.-W., Siu, L. L., Minami, H., Steeghs, N., Hengelage, T., Tan, E., Biette, K., Xu, K., Moody, S. E., & Jove, M. (2021). Initial results from a dose finding study of TNO155, a SHP2 inhibitor, in adults with advanced solid tumors. *Journal of Clinical Oncology*, *39*(15_suppl), 3005. https://doi.org/10.1200/JCO.2021.39.15_suppl.3005

Buchwald, P. (2019). A Receptor Model With Binding Affinity, Activation Efficacy, and Signal Amplification Parameters for Complex Fractional Response Versus Occupancy Data. *Frontiers in Pharmacology*, *10*, 605. https://doi.org/10.3389/fphar.2019.00605

Burns, T. F., Dragnev, K. H., Fujiwara, Y., Murciano-Goroff, Y. R., Lee, D. H., Hollebecque, A., Koyama, T., Cassier, P. A., Italiano, A., Heist, R. S., Han, J.-Y., Deming, D. A., Spira, A. I., Sabari, J. K., Chisamore, M. J., Fink, A. A., Chen, A., Willard, M. D., Oxnard, G. R., & Ammakkanavar, N. R. (2024). Efficacy and safety of Olomorasib (LY3537982), a second-generation KRAS G12C inhibitor (G12Ci), in combination with Pembrolizumab in patients with KRAS G12C-mutant advanced NSCLC. *Journal of Clinical Oncology*, *42*(16_suppl), 8510. https://doi.org/10.1200/JCO.2024.42.16_suppl.8510

Cancer Genome Atlas Research, N. (2014). Comprehensive molecular profiling of lung adenocarcinoma. *Nature*, *511*(7511), 543–550.

Canon, J., Rex, K., Saiki, A. Y., Mohr, C., Cooke, K., Bagal, D., Gaida, K., Holt, T., Knutson, C. G., Koppada, N., Lanman, B. A., Werner, J., Rapaport, A. S., San Miguel, T., Ortiz, R., Osgood, T., Sun, J. R., Zhu, X., McCarter, J. D., … Lipford, J. R. (2019). The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature*, *575*(7781), 217–223. https://doi.org/10.1038/s41586-019-1694-1

Cassier, P. A., Dooms, C. A., Gazzah, A., Felip, E., Steeghs, N., Rohrberg, K. S., De Braud, F. G., Solomon, B. J., Schuler, M. H., Tan, D. S.-W., Yamamoto, N., Loong, H. H. F., Cho, B. C., Wolf, J., Lin, C.-C., Negrao, M. V., Werner, L., Cui, X., Farago, A. F., & de

Miguel, M. J. (2023). Kontrast-01 update: Safety and efficacy of JDQ443 in KRAS G12C-mutated solid tumors including non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology*, *41*(16_suppl), 9007. https://doi.org/10.1200/JCO.2023.41.16_suppl.9007

Chen, Y., Liu, Q. P., Xie, H., & Ding, J. (2024). From bench to bedside: current development and emerging trend of KRAS-targeted therapy. *Acta Pharmacologica Sinica*, *45*(4), 686–703. https://doi.org/10.1038/s41401-023-01194-4

Cho, B. C., Lu, S., Lee, M. A., Song, Z., Park, J. J., Lim, S. M., Li, Z., Zhao, J., Richardson, G., Zhang, Y., Zhang, J., Liu, A., Loong, H. H., Chen, C., Wang, J., Shen, Y., Fan, Z., Chen, Q., Wang, H., … Mok, T. (2025). D3S-001 in advanced solid tumors with KRAS(G12C) mutations: a phase 1 trial. *Nature Medicine*, *31*(8), 2768–2777. https://doi.org/10.1038/s41591-025-03688-6

Chour, A., Denis, J., Mascaux, C., Zysman, M., Bigay-Game, L., Swalduz, A., Gounant, V., Cortot, A., Darrason, M., Fallet, V., Auclin, E., Basse, C., Tissot, C., Decroisette, C., Bombaron, P., Giroux-Leprieur, E., Odier, L., Brosseau, S., Creusot, Q., … Duruisseaux, M. (2023). Brief Report: Severe Sotorasib-Related Hepatotoxicity and Non-Liver Adverse Events Associated With Sequential Anti-Programmed Cell Death (Ligand)1 and Sotorasib Therapy in KRAS(G12C)-Mutant Lung Cancer. *Journal of Thoracic Oncology*, *18*(10), 1408–1415. https://doi.org/10.1016/j.jtho.2023.05.013

Christenson, E. S., Yu, R., Gai, J., Wang, H., Lei, M., & Zheng, L. (2024). The impact of KRAS mutations on the clinical outcome and immune response following immunotherapy for pancreatic cancer. *Annals Pancreat Cancer*, *7*, 6. https://doi.org/10.21037/apc-24-2

Cole, M., Anastasiou, P., Lee, C., Yu, X., de Castro, A., Roelink, J., Moore, C., Mugarza, E., Jones, M., Valand, K., Rana, S., Colliver, E., Angelova, M., Enfield, K. S. S., Magness, A., Mullokandov, A., Kelly, G., de Gruijl, T. D., Molina-Arcas, M., … van Maldegem, F. (2024). Spatial multiplex analysis of lung cancer reveals that regulatory T cells attenuate KRAS-G12C inhibitor-induced immune responses. *Science Advances*, *10*(44), eadl6464. https://doi.org/10.1126/sciadv.adl6464

Coma, S., Musteanu, M., Caffarra, C., Mira, A., Patrucco, E., Dilly, J., Aguirre, A. J., Barbacid, M., Ambrogio, C., & Pachter, J. A. (2023). Abstract B025: The RAF/MEK clamp avutometinib (VS-6766) enhances antitumor efficacy of KRAS G12C and G12D inhibitors through vertical inhibition of KRAS, RAF and MEK. *Molecular Cancer Research*, *21*(5_Supplement), B025. https://doi.org/10.1158/1557-3125.RAS23-B025

Cregg, J., Pota, K., Tomlinson, A. C., Yano, J., Marquez, A., Liu, Y., Schulze, C. J., Seamon, K. J., Holderfield, M., Wei, X., & Zhuang, Y. (2025). Discovery of Elironrasib (RMC-6291), a potent and orally bioavailable, KRAS (ON) G12C-selective, covalent tricomplex inhibitor for the treatment of patients with KRAS G12C-addicted cancers. *Journal of Medicinal Chemistry*, *68*(6), 6041–6063.

de Langen, A. J., Johnson, M. L., Mazieres, J., Dingemans, A. C., Mountzios, G., Pless, M., Wolf, J., Schuler, M., Lena, H., Skoulidis, F., Yoneshima, Y., Kim, S. W., Linardou, H., Novello, S., van der Wekken, A., Chen, Y., Peters, S., Felip, E., Solomon, B. J., … CodeBreaK 200 Investigators. (2023). Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRAS(G12C) mutation: a randomised, open-label, phase 3 trial. *Lancet*, *401*(10378), 733–746. https://doi.org/10.1016/S0140-6736(23)00221-0

Desai, A., Rakshit, S., Bansal, R., Ashara, Y., Potter, A., Manochakian, R., Lou, Y., Zhao, Y., Ernani, V., Savvides, P., Schwecke, A., Moffett, N., Hocum, C., Leventakos, K., Adjei, A., Marks, R., Molina, J., Mansfield, A. S., Chen, Z. M., & Dimou, A. (2023). Time from immune checkpoint inhibitor to sotorasib use correlates with risk of hepatotoxicity in non-small cell lung cancer: A brief report. *Cancer Treatment and Research Communications*, *36*, 100743. https://doi.org/10.1016/j.ctarc.2023.100743

Desai, J., Alonso, G., Kim, S. H., Cervantes, A., Karasic, T., Medina, L., Shacham-Shmueli, E., Cosman, R., Falcon, A., Gort, E., Guren, T., Massarelli, E., Miller, W. H. Jr., Paz-Ares, L., Prenen, H., Amatu, A., Cremolini, C., Kim, T. W., Moreno, V., … Han, S. W. (2024). Divarasib plus cetuximab in KRAS G12C-positive colorectal cancer: a phase 1b trial. *Nature Medicine*, *30*(1), 271–278. https://doi.org/10.1038/s41591-023-02696-8

Dilly, J., Hoffman, M. T., Abbassi, L., Li, Z., Paradiso, F., Parent, B. D., Hennessey, C. J., Jordan, A. C., Morgado, M., Dasgupta, S., Uribe, G. A., Yang, A., Kapner, K. S., Hambitzer, F. P., Qiang, L., Feng, H., Geisberg, J., Wang, J., Evans, K. E., … Aguirre, A. J. (2024). Mechanisms of Resistance to Oncogenic KRAS Inhibition in Pancreatic Cancer. *Cancer Discovery*, *14*(11), 2135–2161. https://doi.org/10.1158/2159-8290.CD-24-0177

Dingemans, A. C., Syrigos, K., Livi, L., Paulus, A., Kim, S. W., Chen, Y., Felip, E., Griesinger, F., Ohashi, K., Zalcman, G., Hughes, B. G. M., Sørensen, J. B., Blais, N., Ferreira, C. G. M., Lindsay, C. R., Dziadziuszko, R., Ward, P. J., Obiozor, C. C., Wang, Y., & Peters, S. (2025). Intracranial activity of sotorasib vs docetaxel in pretreated KRAS G12C-mutated advanced non-small cell lung cancer from a global, phase 3, randomized controlled trial. *Lung Cancer*, *207*, 108683. https://doi.org/10.1016/j.lungcan.2025.108683

Dombi, E., Baldwin, A., Marcus, L. J., Fisher, M. J., Weiss, B., Kim, A. R., Whitcomb, P., Martin, S., Aschbacher-Smith, L. E., Rizvi, T. A., Wu, J., Ershler, R., Wolters, P., Therrien, J., Glod, J., Belasco, J. B., Schorry, E., Brofferio, A., Starosta, A. J., … Widemann, B. C. (2016). Activity of Selumetinib in Neurofibromatosis Type 1-Related Plexiform Neurofibromas. *The New England Journal of Medicine*, *375*(26), 2550–2560. https://doi.org/10.1056/NEJMoa1605943

Dziadziuszko, R. (2022). STK11 and KEAP1 Mutations in Lung Adenocarcinoma: Solving the Puzzle Continues. *Journal of Thoracic Oncology*, *17*(3), 351–352. https://doi.org/10.1016/j.jtho.2022.01.004

Ebright, R. Y., Dilly, J., Shaw, A. T., & Aguirre, A. J. (2025). Response and resistance to KRAS inhibition in cancer. *Cancer Discovery*, *15*(7), 1325–1349.

Edwards, A. (2025). Abstract ND06: Discovery of RMC-5127, an oral, KRAS (ON) G12V-selective, noncovalent, tri-complex inhibitor. *Cancer Research*, *85*(8_Supplement_2), ND06. https://doi.org/10.1158/1538-7445.AM2025-ND06

Fakih, M. G., Kopetz, S., Kuboki, Y., Kim, T. W., Munster, P. N., Krauss, J. C., Falchook, G. S., Han, S. W., Heinemann, V., Muro, K., Strickler, J. H., Hong, D. S., Denlinger, C. S., Girotto, G., Lee, M. A., Henary, H., Tran, Q., Park, J. K., Ngarmchamnanrith, G., … Price, T. J. (2022). Sotorasib for previously treated colorectal cancers with KRAS(G12C) mutation (CodeBreaK100): a prespecified analysis of a single-arm, phase 2 trial. *The Lancet Oncology*, *23*(1), 115–124. https://doi.org/10.1016/S1470-2045(21)00605-7

Fakih, M. G., Salvatore, L., Esaki, T., Modest, D. P., Lopez-Bravo, D. P., Taieb, J., Karamouzis, M. V., Ruiz-Garcia, E., Kim, T. W., Kuboki, Y., Meriggi, F., Cunningham, D., Yeh, K. H., Chan, E., Chao, J., Saportas, Y., Tran, Q., Cremolini, C., & Pietrantonio, F. (2023). Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated KRAS G12C. *The New England Journal of Medicine*, *389*(23), 2125–2139. https://doi.org/10.1056/NEJMoa2308795

Falchook, G., Li, B. T., Marrone, K. A., Bestvina, C. M., Langer, C. J., Krauss, J. C., Strickler, J. H., Meloni, A., Dai, T., Varrieur, T., & Hong, D. S. (2022). OA03.03 Sotorasib in combination with RMC-4630, a SHP2 inhibitor, in KRAS p.G12C-mutated NSCLC and other solid tumors. *Journal of Thoracic Oncology*, *17*(9), S8. https://doi.org/10.1016/j.jtho.2022.07.022

Fedele, C., Li, S., Teng, K. W., Foster, C. J. R., Peng, D., Ran, H., Mita, P., Geer, M. J., Hattori, T., Koide, A., Wang, Y., Tang, K. H., Leinwand, J., Wang, W., Diskin, B., Deng, J., Chen, T., Dolgalev, I., Ozerdem, U., … Neel, B. G. (2021). SHP2 inhibition diminishes KRASG12C cycling and promotes tumor microenvironment remodeling. *The Journal of Experimental Medicine*, *218*(1), e20201414. https://doi.org/10.1084/jem.20201414

Finlay, D. B., Duffull, S. B., & Glass, M. (2020). 100 years of modelling ligand-receptor binding and response: A focus on GPCRs. *British Journal of Pharmacology*, *177*(7), 1472–1484. https://doi.org/10.1111/bph.14988

Fucikova, J., Kepp, O., Kasikova, L., Petroni, G., Yamazaki, T., Liu, P., Zhao, L., Spisek, R., Kroemer, G., & Galluzzi, L. (2020). Detection of immunogenic cell death and its relevance for cancer therapy. *Cell Death & Disease*, *11*(11), 1013. https://doi.org/10.1038/s41419-020-03221-2

Garassino, M. C., Theelen, W. S. M. E., Jotte, R., Laskin, J., de Marinis, F., Aguado, C., Badin, F. B., Chmielewska, I., Hochmair, M. J., Lu, S., Nadal, E., Ostoros, G., Felip, E., Spira, A. I., Lane, C. M., He, J., Chao, R., & Jänne, P. A. (2023). LBA65 KRYSTAL-7: Efficacy and safety of adagrasib with pembrolizumab in patients with treatment-naïve, advanced non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation. *Annals of Oncology*, *34*, S1309–S1310. https://doi.org/10.1016/j.annonc.2023.10.066

Garrido-Laguna, I., Wolpin, B. M., Park, W., Azad, N. S., Spira, A. I., Starodub, A., Sommerhalder, D., Punekar, S. R., Herzberg, B., Barve, M. A., & Pelster, M. (2025). Safety, efficacy, and on-treatment circulating tumor DNA (ctDNA) changes from a phase 1 study of RMC-6236, a KRAS (ON) multi-selective, tri-complex inhibitor, in patients with KRAS mutant pancreatic ductal adenocarcinoma (PDAC). *Journal of Clinical Oncology*, *43*(4_suppl), 722.

Gentile, D. R., Rathinaswamy, M. K., Jenkins, M. L., Moss, S. M., Siempelkamp, B. D., Renslo, A. R., Burke, J. E., & Shokat, K. M. (2017). KRAS binder induces a modified Switch-II pocket in GTP and GDP states. *Cell Chemistry & Biology*, *24*(12), 1455–1466 e14.

Golan, T., Khvalevsky, E. Z., Hubert, A., Gabai, R. M., Hen, N., Segal, A., Domb, A., Harari, G., David, E. B., Raskin, S., Goldes, Y., Goldin, E., Eliakim, R., Lahav, M., Kopleman, Y., Dancour, A., Shemi, A., & Galun, E. (2015). RNAi therapy targeting KRAS in combination with chemotherapy for locally advanced pancreatic cancer patients. *Oncotarget*, *6*(27), 24560–24570. https://doi.org/10.18632/oncotarget.4183

Gulay, K. C. M., Zhang, X., Pantazopoulou, V., Patel, J., Esparza, E., Pran Babu, D. S., Ogawa, S., Weitz, J., Ng, I., Mose, E. S., Pu, M., Engle, D. D., Lowy, A. M., & Tiriac, H. (2023). Dual Inhibition of KRASG12D and Pan-ERBB Is Synergistic in Pancreatic Ductal Adenocarcinoma. *Cancer Research*, *83*(18), 3001–3012. https://doi.org/10.1158/0008-5472.CAN-23-1313

Guthof, N., Xue, H., Jerchel-Furau, I., Hethey, C., Busse, J.-E., Denner, K., Wang, Z., Schulze, V., Jethwa, S., & Cheung, S. (2025). Abstract 4373: Discovery and characterization of BAY 3498264: A small molecule inhibitor targeting the KRAS-SOS1 interaction. *Cancer Research*, *85*-(8_Supplement_1), 4373. https://doi.org/10.1158/1538-7445.AM2025-4373

Hanggi, K., & Ruffell, B. (2019). Oncogenic KRAS Drives Immune Suppression in Colorectal Cancer. *Cancer Cell*, *35*(4), 535–537. https://doi.org/10.1016/j.ccell.2019.03.008

Hitchen, N., Williams, S., & Desai, J. (2025). Recent advances in therapeutic targeting of the KRAS pathway in cancer. *Pharmacology & Therapeutics*, *273*, 108889. https://doi.org/10.1016/j.pharmthera.2025.108889

Hobbs, G. A., Baker, N. M., Miermont, A. M., Thurman, R. D., Pierobon, M., Tran, T. H., Anderson, A. O., Waters, A. M., Diehl, J. N., Papke, B., Hodge, R. G., Klomp, J. E., Goodwin, C. M., DeLiberty, J. M., Wang, J., Ng, R. W. S., Gautam, P., Bryant, K. L., Esposito, D., … der, C. J. (2020). Atypical KRAS(G12R) Mutant Is Impaired in PI3K Signaling and Macropinocytosis in Pancreatic Cancer. *Cancer Discovery*, *10*(1), 104–123. https://doi.org/10.1158/2159-8290.CD-19-1006

Hofmann, M. H., Gmachl, M., Ramharter, J., Savarese, F., Gerlach, D., Marszalek, J. R., Sanderson, M. P., Kessler, D., Trapani, F., Arnhof, H., Rumpel, K., Botesteanu, D. A., Ettmayer, P., Gerstberger, T., Kofink, C., Wunberg, T., Zoephel, A., Fu, S. C., Teh, J. L., … Kraut, N. (2021). BI-3406, a Potent and Selective SOS1-KRAS Interaction Inhibitor, Is Effective in KRAS-Driven Cancers through Combined MEK Inhibition. *Cancer Discovery*, *11*(1), 142–157. https://doi.org/10.1158/2159-8290.CD-20-0142

Holderfield, M., Lee, B. J., Jiang, J., Tomlinson, A., Seamon, K. J., Mira, A., Patrucco, E., Goodhart, G., Dilly, J., Gindin, Y., & Dinglasan, N. (2024). Concurrent inhibition of oncogenic and wild-type KRAS-GTP for cancer therapy. *Nature*, *629*(8013), 919–926.

Hollebecque, A., Kuboki, Y., Murciano-Goroff, Y. R., Yaeger, R., Cassier, P. A., Heist, R. S., Fujiwara, Y., Deming, D. A., Ammakkanavar, N., Patnaik, A., Shimizu, T., Call, J., Han, S. W., Fink, A. A., Chen, A., Willard, M. D., Balar, A. V., & Koyama, T. (2024). Efficacy and safety of LY3537982, a potent and highly selective KRAS G12C inhibitor in KRAS G12C-mutant GI cancers: Results from a phase 1 study. *Journal of Clinical Oncology*, *42*(3_suppl), 94. https://doi.org/10.1200/JCO.2024.42.3_suppl.94

Hong, D. S., Fakih, M. G., Strickler, J. H., Desai, J., Durm, G. A., Shapiro, G. I., Falchook, G. S., Price, T. J., Sacher, A., Denlinger, C. S., Bang, Y. J., Dy, G. K., Krauss, J. C., Kuboki, Y., Kuo, J. C., Coveler, A. L., Park, K., Kim, T. W., Barlesi, F., … Li, B. T. (2020). KRAS(G12C) Inhibition with Sotorasib in Advanced Solid Tumors. *The New England Journal of Medicine*, *383*(13), 1207–1217. https://doi.org/10.1056/NEJMoa1917239

Hunter, J. C., Manandhar, A., Carrasco, M. A., Gurbani, D., Gondi, S., & Westover, K. D. (2015). Biochemical and Structural Analysis of Common Cancer-Associated KRAS Mutations. *Molecular Cancer Research*, *13*(9), 1325–1335. https://doi.org/10.1158/1541-7786.MCR-15-0203

Isermann, T., Sers, C., der, C. J., & Papke, B. (2025). KRAS inhibitors: resistance drivers and combinatorial strategies. *Trends Cancer*, *11*(2), 91–116. https://doi.org/10.1016/j.trecan.2024.11.009

Jain, R. K. (2005). Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science*, *307*(5706), 58–62. https://doi.org/10.1126/science.1104819

Janku, F., Kim, T. M., Iyer, G., Spreafico, A., Elez, E., de Jonge, M., Yamamoto, N., van der Wekken, A. J., Ascierto, P. A., Maur, M., Marmé, F., Kiladjian, J. J., Basu, S., Baffert, F., Buigues, A., Chen, C., Cooke, V., Giorgetti, E., Kim, J., … Dummer, R. (2024). First-in-human study of naporafenib (LXH254) with or without spartalizumab in adult patients with advanced solid tumors harboring MAPK signaling pathway alterations. *European Journal of Cancer*, *196*, 113458. https://doi.org/10.1016/j.ejca.2023.113458

Jänne, P. A., Bigot, F., Papadopoulos, K., Eberst, L., Sommerhalder, D., Lebellec, L., Voon, P. J., Pellini, B., Kalinka, E., Arbour, K., Herzberg, B., Boni, V., Bordenave, S., Lee, H. W., Ou, S. I., Riess, J. W., Beck, J. T., Ponz-Sarvise, M., Ascierto, P. A., … Johnson, M. (2023). Abstract PR014: Preliminary safety and anti-tumor activity of RMC-6291, a first-in-class, tri-complex KRASG12C(ON) inhibitor, in patients with or without prior KRASG12C(OFF) inhibitor treatment. *Molecular Cancer Therapeutics*, *22*(12_Supplement), PR014. https://doi.org/10.1158/1535-7163.TARG-23-PR014

Jänne, P. A., Theelen, W. S. M. E., Garassino, M. C., Spira, A. I., Laskin, J. J., de Marinis, F., Badin, F. B., Boom, L., Aguado de la Rosa, C., Chmielewska, I., Felip, E., Ostoros, G., Jimenez-Kurlander, L., Lane, C. M., Sachdeva, A., Eccles, L., & Lu, S. (2025). First-line adagrasib (ADA) with pembrolizumab (PEMBRO) in patients (pts) with advanced/metastatic KRASG12C-mutated non-small cell lung cancer (NSCLC) from the phase 2 portion of the KRYSTAL-7 study. *Journal of Clinical Oncology*, *43*(16_suppl), 8500–8500. https://doi.org/10.1200/JCO.2025.43.16_suppl.8500

Jänne, P. A., van den Heuvel, M. M., Barlesi, F., Cobo, M., Mazieres, J., Crinò, L., Orlov, S., Blackhall, F., Wolf, J., Garrido, P., & Poltoratskiy, A. (2017). Selumetinib Plus Docetaxel Compared With Docetaxel Alone and Progression-Free Survival in Patients With KRAS-Mutant Advanced Non-Small Cell Lung Cancer: The SELECT-1 Randomized

Clinical Trial. *JAMA*, *317*(18), 1844–1853. https://doi.org/10.1001/jama.2017.3438

Ju, Y., Xu, D., Liao, M. M., Sun, Y., Bao, W. D., Yao, F., & Ma, L. (2024). Barriers and opportunities in pancreatic cancer immunotherapy. *npj Precision Oncology*, *8*(1), 199. https://doi.org/10.1038/s41698-024-00681-z

Kambadakone, A., Yoon, S. S., Kim, T. M., Karl, D. L., Duda, D. G., DeLaney, T. F., & Sahani, D. V. (2015). CT perfusion as an imaging biomarker in monitoring response to neoadjuvant bevacizumab and radiation in soft-tissue sarcomas: comparison with tumor morphology, circulating and tumor biomarkers, and gene expression. *AJR. American Journal of Roentgenology*, *204*(1), W11–W18. https://doi.org/10.2214/AJR.13.12412

Kannan, P., Kretzschmar, W. W., Winter, H., Warren, D., Bates, R., Allen, P. D., Syed, N., Irving, B., Papiez, B. W., Kaeppler, J., Markelc, B., Kinchesh, P., Gilchrist, S., Smart, S., Schnabel, J. A., Maughan, T., Harris, A. L., Muschel, R. J., Partridge, M., … Kersemans, V. (2018). Functional Parameters Derived from Magnetic Resonance Imaging Reflect Vascular Morphology in Preclinical Tumors and in Human Liver Metastases. *Clinical Cancer Research*, *24*(19), 4694–4704. https://doi.org/10.1158/1078-0432.CCR-18-0033

Karoulia, Z., Gavathiotis, E., & Poulikakos, P. I. (2017). New perspectives for targeting RAF kinase in human cancer. *Nature Reviews. Cancer*, *17*(11), 676–691. https://doi.org/10.1038/nrc.2017.79

Kindler, H. L., Niedzwiecki, D., Hollis, D., Sutherland, S., Schrag, D., Hurwitz, H., Innocenti, F., Mulcahy, M. F., O'Reilly, E., Wozniak, T. F., Picus, J., Bhargava, P., Mayer, R. J., Schilsky, R. L., & Goldberg, R. M. (2010). Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *Journal of Clinical Oncology*, *28*(22), 3617–3622. https://doi.org/10.1200/JCO.2010.28.1386

Kinsey, C. G., Camolotto, S. A., Boespflug, A. M., Guillen, K. P., Foth, M., Truong, A., Schuman, S. S., Shea, J. E., Seipp, M. T., Yap, J. T., Burrell, L. D., Lum, D. H., Whisenant, J. R., Gilcrease, G. W. III, Cavalieri, C. C., Rehbein, K. M., Cutler, S. L., Affolter, K. E., Welm, A. L., … McMahon, M. (2019). Protective autophagy elicited by RAF-->MEK-->ERK inhibition suggests a treatment strategy for RAS-driven cancers. *Nature Medicine*, *25*(4), 620–627.

Koga, T., Suda, K., Fujino, T., Ohara, S., Hamada, A., Nishino, M., Chiba, M., Shimoji, M., Takemoto, T., Arita, T., Gmachl, M., Hofmann, M. H., Soh, J., & Mitsudomi, T. (2021). KRAS Secondary Mutations That Confer Acquired Resistance to KRAS G12C Inhibitors, Sotorasib and Adagrasib, and Overcoming Strategies: Insights From In Vitro Experiments. *Journal of Thoracic Oncology*, *16*(8), 1321–1332. https://doi.org/10.1016/j.jtho.2021.04.015

Kortlever, R. M., Sodir, N. M., Wilson, C. H., Burkhart, D. L., Pellegrinet, L., Swigart, L. B., Littlewood, T. D., & Evan, G. I. (2017). Myc cooperates with KRAS by programming inflammation and immune suppression. *Cell*, *171*(6), 1301–1315.

Kuboki, Y., Fakih, M., Strickler, J., Yaeger, R., Masuishi, T., Kim, E. J., Bestvina, C. M., Kopetz, S., Falchook, G. S., Langer, C., Krauss, J., Puri, S., Cardona, P., Chan, E., Varrieur, T., Mukundan, L., Anderson, A., Tran, Q., & Hong, D. S. (2024). Sotorasib with panitumumab in chemotherapy-refractory KRAS(G12C)-mutated colorectal cancer: a phase 1b trial. *Nature Medicine*, *30*(1), 265–270. https://doi.org/10.1038/s41591-023-02717-6

Lee, C., Pavlakis, N., Zhou, D. D.-X., Brown, C., Hughes, B. G. M., Yip, S., Bray, V. J., Daley, F. T., Roberts-Thomson, R., Cummins, M. M., John, T., Solomon, B. J., & Mitchell, P. (2023). P2.11-05 SHERLOCK: Phase II Trial of upfront Sotorasib with chemotherapy and Bevacizumab for advanced NSCLC with KRASG12C mutation. *Journal of Thoracic Oncology*, *18*(11), S361–S362. https://doi.org/10.1016/j.jtho.2023.09.635

Lee, J. K., Sivakumar, S., Schrock, A. B., Madison, R., Fabrizio, D., Gjoerup, O., Ross, J. S., Frampton, G. M., Napalkov, P., Montesion, M., Schutzman, J. L., Ye, X., Hegde, P. S., Nagasaka, M., Oxnard, G. R., Sokol, E. S., Ou, S. H. I., & Shi, Z. (2022). Comprehensive pan-cancer genomic landscape of KRAS altered cancers and real-world outcomes in solid tumors. *npj Precision Oncology*, *6*(1), 91. https://doi.org/10.1038/s41698-022-00334-z

Leidner, R., Sanjuan Silva, N., Huang, H., Sprott, D., Zheng, C., Shih, Y. P., Leung, A., Payne, R., Sutcliffe, K., Cramer, J., Rosenberg, S. A., Fox, B. A., Urba, W. J., & Tran, E. (2022). Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer. *The New England Journal of Medicine*, *386*(22), 2112–2119. https://doi.org/10.1056/NEJMoa2119662

Li, B. T., Falchook, G. S., Durm, G. A., Burns, T. F., Skoulidis, F., Ramalingam, S. S., Spira, A., Bestvina, C. M., Goldberg, S. B., Veluswamy, R., Iams, W. T., Chiappori, A. A., Lemech, C. R., Meloni, A. R., Ebiana, V., Dai, T., Gauto, D. M., Varrieur, T. L., Snyder, W. J., & Govindan, R. (2022). OA03.06 CodeBreaK 100/101: First report of safety/efficacy of Sotorasib in combination with Pembrolizumab or Atezolizumab in advanced KRAS p.G12C NSCLC. *Journal of Thoracic Oncology*, *17*(9), S10–S11. https://doi.org/10.1016/j.jtho.2022.07.025

Li, J., Shen, L., Gu, Y., Calles, A., Wu, L., Ba, Y., Li, Z. H., Bai, C., Yao, Y., Hubert, A., Perez, J. M., Zugazagoitia, J., Ding, Y., Liu, S., Rao, Z., & He, Z. (2024). Preliminary activity and safety results of KRAS G12C inhibitor glecirasib (JAB-21822) in patients with pancreatic cancer and other solid tumors. *Journal of Clinical Oncology*, *42*(3_suppl), 604. https://doi.org/10.1200/JCO.2024.42.3_suppl.604

Li, X., Ye, J., Wang, J., Quan, Z., Li, G., Ma, W., Zhang, M., Yang, W., Wang, J., Ma, T., Kang, F., & Wang, J. (2023). First-in-Humans PET Imaging of KRAS(G12C) Mutation Status in Non-Small Cell Lung and Colorectal Cancer Patients Using [(18)F]PFPMD. *Journal of Nuclear Medicine*, *64*(12), 1880–1888. https://doi.org/10.2967/jnumed.123.265715

Li, Y., Amaladas, N., O'Mahony, M., Manro, J. R., Inigo, I., Li, Q., Rasmussen, E. R., Brahmachary, M., Doman, T. N., Hall, G., Kalos, M., Novosiadly, R., Puig, O., Pytowski, B., & Schaer, D. A. (2022). Treatment with a VEGFR-2 antibody results in intra-tumor immune modulation and enhances anti-tumor efficacy of PD-L1 blockade in syngeneic murine tumor models. *PLoS ONE*, *17*(7), e0268244. https://doi.org/10.1371/journal.pone.0268244

Li, Z., Lu, S., Dang, X., Huang, D., Jin, S., Li, W., Shi, J., Wang, X., Zhang, Y., Song, Z., Zhang, J., Zhuang, W., Liu, X., Jiang, L., Meng, X., Zhao, M., Zhou, J., Zhang, L., Wang, P., … Shi, Z. (2024). OA14.03 Garsorasib in KRAS G12C-mutated non-small-cell lung cancer: Updated results from a phase 2 study. *Journal of Thoracic Oncology*, *19*(10, Supplement), S40–S41. https://doi.org/10.1016/j.jtho.2024.09.072

Li, Z., Zhuang, X., Pan, C. H., Yan, Y., Thummalapalli, R., Hallin, J., Torborg, S., Singhal, A., Chang, J. C., Manchado, E., Dow, L. E., Yaeger, R., Christensen, J. G., Lowe, S. W., Rudin, C. M., Joost, S., & Tammela, T. (2024). Alveolar Differentiation Drives Resistance to KRAS Inhibition in Lung Adenocarcinoma. *Cancer Discovery*, *14*(2), 308–325. https://doi.org/10.1158/2159-8290.CD-23-0289

Lu, S., Jang, H., Gu, S., Zhang, J., & Nussinov, R. (2016). Drugging KRAS GTPase: A comprehensive mechanistic and signaling structural view. *Chemical Society Reviews*, *45*(18), 4929–4952.

Luo, J., Sacher, A., Santoro, A., Paz-Ares, L., Deva, S., Prennen, H., de Miguel, M., Dziadziuszko, R., Laurie, S. A., Patel, M. R., & Garralda, E. (2025). Abstract CT022: Divarasib plus migoprotafib combination treatment in patients with KRAS G12C-positive non-small cell lung cancer (NSCLC). *Cancer Research*, *85*(8_Supplement_2), CT022–CT022. https://doi.org/10.1158/1538-7445.AM2025-CT022

Maciag, A. E., Stice, J. P., Wang, B., Sharma, A. K., Chan, A. H., Lin, K., Singh, D., Dyba, M., Yang, Y., Setoodeh, S., Smith, B. P., Ju, J. H.,

Jeknic, S., Rabara, D., Zhang, Z., Larsen, E. K., Esposito, D., Denson, J. P., Ranieri, M., … Beltran, P. J. (2025). Discovery of BBO-8520, a First-In-Class Direct and Covalent Dual Inhibitor of GTP-Bound (ON) and GDP-Bound (OFF) KRASG12C. *Cancer Discovery*, *15*(3), 578–594. https://doi.org/10.1158/2159-8290.CD-24-0840

Marazioti, A., Lilis, I., Vreka, M., Apostolopoulou, H., Kalogeropoulou, A., Giopanou, I., Giotopoulou, G. A., Krontira, A. C., Iliopoulou, M., Kanellakis, N. I., & Agalioti, T. (2018). Myeloid-derived interleukin-1beta drives oncogenic KRAS-NF-kappaBeta addiction in malignant pleural effusion. *Nature Communications*, *9*(1), 672.

Matsumoto, S., Miyano, N., Baba, S., Liao, J., Kawamura, T., Tsuda, C., Takeda, A., Yamamoto, M., Kumasaka, T., Kataoka, T., & Shima, F. (2016). Molecular mechanism for conformational dynamics of KRAS. GTP elucidated from in-situ structural transition in crystal. *Scientific Reports*, *6*, 25931. https://doi.org/10.1038/srep25931

Mendoza, M. C., Er, E. E., & Blenis, J. (2011). The KRAS-ERK and PI3K-mTOR pathways: Cross-talk and compensation. *Trends in Biochemical Sciences*, *36*(6), 320–328.

Modest, D. P., Fakih, M., Salvatore, L., Esaki, T., Lopez-Bravo, D. P., Taieb, J., Karamouzis, M., Ruiz-Garcia, E., Kim, T. W., Kuboki, Y., Meriggi, F., Cunningham, D., Yeh, K. H., Cremolini, C., Tran, Q., Chan, E., Chao, J., Majer, I. M., & Pietrantonio, F. (2025). Health-related quality of life in patients with KRAS(G12C)-mutated chemorefractory metastatic colorectal cancer treated with sotorasib plus panitumumab or standard of care (CodeBreaK 300): results from a phase 3, randomised clinical trial. *The Lancet Oncology*, *26*(9), 1240–1251. https://doi.org/10.1016/S1470-2045(25)00352-3

Molina-Arcas, M., & Downward, J. (2024). Exploiting the therapeutic implications of KRAS inhibition on tumor immunity. *Cancer Cell*, *42*(3), 338–357. https://doi.org/10.1016/j.ccell.2024.02.012

Mugarza, E., van Maldegem, F., Boumelha, J., Moore, C., Rana, S., Llorian Sopena, M., East, P., Ambler, R., Anastasiou, P., Romero-Clavijo, P., Valand, K., Cole, M., Molina-Arcas, M., & Downward, J. (2022). Therapeutic KRAS(G12C) inhibition drives effective interferon-mediated antitumor immunity in immunogenic lung cancers. *Science Advances*, *8*(29), eabm8780. https://doi.org/10.1126/sciadv.abm8780

Murciano-Goroff, Y. R., Heist, R. S., Kuboki, Y., Koyama, T., Ammakkanavar, N. R., Hollebecque, A., Patnaik, A., Shimizu, T., Spira, A. I., Nagasaka, M., Han, J. Y., Iams, W. T., Deming, D., Call, J., Cassier, P., Han, S. W., Siu-chung Chu, Q., Cosman, R., Durm, G., … Sabari, J. K. (2023). Abstract CT028: A first-in-human phase 1 study of LY3537982, a highly selective and potent KRAS G12C inhibitor in patients with KRAS G12C-mutant advanced solid tumors. *Cancer Research*, *83*(8_Supplement), CT028. https://doi.org/10.1158/1538-7445.AM2023-CT028

Murphy, S. J., Hart, S. N., Halling, G. C., Johnson, S. H., Smadbeck, J. B., Drucker, T., Lima, J. F., Rohakhtar, F. R., Harris, F. R., Kosari, F., Subramanian, S., Petersen, G. M., Wiltshire, T. D., Kipp, B. R., Truty, M. J., McWilliams, R. R., Couch, F. J., & Vasmatzis, G. (2016). Integrated Genomic Analysis of Pancreatic Ductal Adenocarcinomas Reveals Genomic Rearrangement Events as Significant Drivers of Disease. *Cancer Research*, *76*(3), 749–761. https://doi.org/10.1158/0008-5472.CAN-15-2198

Neal, S. E., Eccleston, J. F., Hall, A., & Webb, M. R. (1988). Kinetic analysis of the hydrolysis of GTP by p21N-KRAS. The basal GTPase mechanism. *The Journal of Biological Chemistry*, *263*(36), 19718–19722.

Negrao, M. V., Araujo, H. A., Lamberti, G., Cooper, A. J., Akhave, N. S., Zhou, T., Delasos, L., Hicks, J. K., Aldea, M., Minuti, G., Hines, J., Aredo, J. V., Dennis, M. J., Chakrabarti, T., Scott, S. C., Bironzo, P., Scheffler, M., Christopoulos, P., Stenzinger, A., … Skoulidis, F. (2023). Comutations and KRASG12C Inhibitor Efficacy in Advanced NSCLC. *Cancer Discovery*, *13*(7), 1556–1571. https://doi.org/10.1158/2159-8290.CD-22-1420

Negrao, M. V., Cassier, P. A., Solomon, B., Schuler, M., Rohrberg, K., Cresta, S., Dooms, C., Tan, D. S. W., Loong, H. H.-f., Amatu, A., Assmann, K. K., Fairchild, L., Sansregret, L., Fan, L., Farago, A. F., & Cho, B. C. (2023). MA06.03 Kontrast-01: Preliminary safety and efficacy of JDQ443 + TNO155 in patients with advanced, KRAS G12C-mutated solid tumors. *Journal of Thoracic Oncology*, *18*(11, Supplement), S117–S118. https://doi.org/10.1016/j.jtho.2023.09.151

Negrao, M. V., Paula, A. G., Molkentine, D., Hover, L., Nilsson, M., Vokes, N., Engstrom, L., Calinisan, A., Briere, D. M., Waters, L., Hallin, J., Diao, L., Altan, M., Blumenschein, G. R., Skoulidis, F., Wang, J., Kopetz, S. E., Hong, D. S., Gibbons, D. L., … Heymach, J. V. (2025). Impact of Co-mutations and Transcriptional Signatures in Non-Small Cell Lung Cancer Patients Treated with Adagrasib in the KRYSTAL-1 Trial. *Clinical Cancer Research*, *31*(6), 1069–1081. https://doi.org/10.1158/1078-0432.CCR-24-2310

Negrao, M. V., Spira, A. I., Heist, R. S., Jänne, P. A., Pacheco, J. M., Weiss, J., Gadgeel, S. M., Velastegui, K., Yang, W., Der-Torossian, H., Christensen, J. G., & Sabari, J. K. (2023). Intracranial efficacy of Adagrasib in patients from the KRYSTAL-1 trial with KRAS(G12C)-mutated non-small-cell lung cancer who have untreated CNS metastases. *Journal of Clinical Oncology*, *41*(28), 4472–4477. https://doi.org/10.1200/JCO.23.00046

Noel, M., O'Reilly, E. M., Wolpin, B. M., Ryan, D. P., Bullock, A. J., Britten, C. D., Linehan, D. C., Belt, B. A., Gamelin, E. C., Ganguly, B., Yin, D., Joh, T., Jacobs, I. A., Taylor, C. T., & Lowery, M. A. (2020). Phase 1b study of a small molecule antagonist of human chemokine (C-C motif) receptor 2 (PF-04136309) in combination with nab-paclitaxel/gemcitabine in first-line treatment of metastatic pancreatic ductal adenocarcinoma. *Investigational New Drugs*, *38*(3), 800–811. https://doi.org/10.1007/s10637-019-00830-3

Ostrem, J. M., Peters, U., Sos, M. L., Wells, J. A., & Shokat, K. M. (2013). K-KRAS(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature*, *503*(7477), 548–551.

Pacold, M. E., Suire, S., Perisic, O., Lara-Gonzalez, S., Davis, C. T., Walker, E. H., Hawkins, P. T., Stephens, L., Eccleston, J. F., & Williams, R. L. (2000). Crystal structure and functional analysis of KRAS binding to its effector phosphoinositide 3-kinase gamma. *Cell*, *103*(6), 931–943.

Pant, S., Wainberg, Z. A., Weekes, C. D., Furqan, M., Kasi, P. M., Devoe, C. E., Leal, A. D., Chung, V., Basturk, O., VanWyk, H., Tavares, A. M., Seenappa, L. M., Perry, J. R., Kheoh, T., McNeil, L. K., Welkowsky, E., DeMuth, P. C., Haqq, C. M., & O'Reilly, E. M. (2024). Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: the phase 1 AMPLIFY-201 trial. *Nature Medicine*, *30*(2), 531–542. https://doi.org/10.1038/s41591-023-02760-3

Park, W., Kasi, A., Spira, A. I., Berlin, J. D., Wang, J. S., Herzberg, B., Kuboki, Y., Kitano, S., Pelster, M., Goldman, J. W., Morgensztern, D., Kondo, S., Jänne, P. A., Fujii, H., Lee, H. J., Gill, S., Saci, A., Lorusso, P., & Tolcher, A. W. (2024). 608O Preliminary safety and clinical activity of ASP3082, a first-in-class, KRAS G12D selective protein degrader in adults with advanced pancreatic (PC), colorectal (CRC), and non-small cell lung cancer (NSCLC). *Annals of Oncology*, *35*, S486–S487. https://doi.org/10.1016/j.annonc.2024.08.675

Patel, S. P., Dimou, A., Victor, A. I., Mooradian, M., Buchbinder, E. I., Hernandez-Aya, L. F., Prieto, P. A., Cohen, J. V., Flaherty, K., Kahn, S., Schuler, A., Maeda, D., & Zebala, J. (2024). Safety and efficacy of first-in-class CXCR1/2 inhibitor SX-682 in combination with pembrolizumab (pem) in patients (pts) with metastatic melanoma (mMEL) with disease progression on anti–PD-1 therapy. *Journal of Clinical Oncology*, *42*(16_suppl), 9508. https://doi.org/10.1200/JCO.2024.42.16_suppl.9508

Paweletz, C. P., Heavey, G. A., Kuang, Y., Durlacher, E., Kheoh, T., Chao, R. C., Spira, A. I., Leventakos, K., Johnson, M. L., Ou, S. H. I., Riely, G. J., Anderes, K., Yang, W., Christensen, J. G., & Jänne, P. A. (2023). Early Changes in Circulating Cell-Free KRAS G12C Predict Response to Adagrasib in KRAS Mutant Non-Small Cell Lung Cancer

Patients. *Clinical Cancer Research*, *29*(16), 3074–3080. https://doi.org/10.1158/1078-0432.CCR-23-0795

Perurena, N., Situ, L., & Cichowski, K. (2024). Combinatorial strategies to target KRAS-driven cancers. *Nature Reviews. Cancer*, *24*(5), 316–337.

Pietrantonio, F., Salvatore, L., Esaki, T., Modest, D. P., Lopez-Bravo, D. P., Taieb, J., Karamouzis, M. V., Ruiz-Garcia, E., Kim, T. W., Kuboki, Y., Meriggi, F., Cunningham, D., Yeh, K. H., Chan, E., Chao, J., Tran, Q., Cremolini, C., & Fakih, M. (2025). Overall Survival Analysis of the Phase III CodeBreaK 300 Study of Sotorasib Plus Panitumumab Versus Investigator's Choice in Chemorefractory KRAS G12C Colorectal Cancer. *Journal of Clinical Oncology*, *43*(19), 2147–2154. https://doi.org/10.1200/JCO-24-02026

Prior, I. A., Hood, F. E., & Hartley, J. L. (2020). The frequency of KRAS mutations in cancer. *Cancer Research*, *80*(14), 2969–2974.

Punekar, S. R., et al. (2022). The current state of the art and future trends in KRAS-targeted cancer therapies. *Nature Reviews. Clinical Oncology*, *19*(10), 637–655.

Pylayeva-Gupta, Y., Grabocka, E., & Bar-Sagi, D. (2011). KRAS oncogenes: Weaving a tumorigenic web. *Nature Reviews. Cancer*, *11*(11), 761–774.

Rabara, D., Tran, T. H., Dharmaiah, S., Stephens, R. M., McCormick, F., Simanshu, D. K., & Holderfield, M. (2019). KRAS G13D sensitivity to neurofibromin-mediated GTP hydrolysis. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(44), 22122–22131. https://doi.org/10.1073/pnas.1908353116

Ram, A., Murphy, D., DeCuzzi, N., Patankar, M., Hu, J., Pargett, M., & Albeck, J. G. (2023). A guide to ERK dynamics, part 2: downstream decoding. *The Biochemical Journal*, *480*(23), 1909–1928. https://doi.org/10.1042/BCJ20230277

Ram, T., Singh, A. K., Kumar, A., Singh, H., Pathak, P., Grishina, M., Khalilullah, H., Jaremko, M., Emwas, A. H., Verma, A., & Kumar, P. (2023). MEK inhibitors in cancer treatment: structural insights, regulation, recent advances and future perspectives. *RSC Medicinal Chemistry*, *14*(10), 1837–1857. https://doi.org/10.1039/D3MD00145H

Ricciuti, B., Alessi, J. V., Elkrief, A., Wang, X., Cortellini, A., Li, Y. Y., Vaz, V. R., Gupta, H., Pecci, F., Barrichello, A., Lamberti, G., Nguyen, T., Lindsay, J., Sharma, B., Felt, K., Rodig, S. J., Nishino, M., Sholl, L. M., Barbie, D. A., … Luo, J. (2022). Dissecting the clinicopathologic, genomic, and immunophenotypic correlates of KRAS(G12D)-mutated non-small-cell lung cancer. *Annals of Oncology*, *33*(10), 1029–1040. https://doi.org/10.1016/j.annonc.2022.07.005

Ricciuti, B., Arbour, K. C., Lin, J. J., Vajdi, A., Vokes, N., Hong, L., Zhang, J., Tolstorukov, M. Y., Li, Y. Y., Spurr, L. F., Cherniack, A. D., Recondo, G., Lamberti, G., Wang, X., Venkatraman, D., Alessi, J. V., Vaz, V. R., Rizvi, H., Egger, J., … Awad, M. M. (2022). Diminished Efficacy of Programmed Death-(Ligand)1 Inhibition in STK11- and KEAP1-Mutant Lung Adenocarcinoma Is Affected by KRAS Mutation Status. *Journal of Thoracic Oncology*, *17*(3), 399–410. https://doi.org/10.1016/j.jtho.2021.10.013

Robers, M. B., Dart, M. L., Woodroofe, C. C., Zimprich, C. A., Kirkland, T. A., Machleidt, T., Kupcho, K. R., Levin, S., Hartnett, J. R., Zimmerman, K., Niles, A. L., Ohana, R. F., Daniels, D. L., Slater, M., Wood, M. G., Cong, M., Cheng, Y. Q., & Wood, K. V. (2015). Target engagement and drug residence time can be observed in living cells with BRET. *Nature Communications*, *6*, 10091. https://doi.org/10.1038/ncomms10091

Ruan, D.-y., Lee, M. A., Deng, Y., Lee, K.-W., Millward, M., Grewal, J. S., Gadgeel, S. M., Sanborn, R. E., Hou, X., Wei, S., Huh, S. J., Liu, F.-R., Xie, X., Xiang, Z., Shi, Z., Wang, Y., Zhang, L., Richardson, G. E., & Xu, R.-H. (2023). Safety and efficacy of D-1553 in KRAS G12C-mutated colorectal cancer: results from a phase I/II study. *Journal of Clinical Oncology*, *41*(16_suppl), 3563–3563. https://doi.org/10.1200/JCO.2023.41.16_suppl.3563

Ryan, M. B., Coker, O., Sorokin, A., Fella, K., Barnes, H., Wong, E., Kanikarla, P., Gao, F., Zhang, Y., Zhou, L., & Kopetz, S. (2022). KRAS (G12C)-independent feedback activation of wild-type KRAS constrains KRAS(G12C) inhibitor efficacy. *Cell Reports*, *39*(12), 110993.

Ryan, M. B., Fece de la Cruz, F., Phat, S., Myers, D. T., Wong, E., Shahzade, H. A., Hong, C. B., & Corcoran, R. B. (2020). Vertical Pathway Inhibition Overcomes Adaptive Feedback Resistance to KRAS(G12C) Inhibition. *Clinical Cancer Research*, *26*(7), 1633–1643. https://doi.org/10.1158/1078-0432.CCR-19-3523

Sacher, A., LoRusso, P., Patel, M. R., Miller, W. H., Jr., Garralda, E., Forster, M. D., Santoro, A., Falcon, A., Kim, T. W., Paz-Ares, L., Bowyer, S., de Miguel, M., Han, S.-W., Krebs, M. G., Lee, J.-S., Cheng, M. L., Arbour, K., Massarelli, E., Choi, Y., … for the GO42144 Investigator and Study Group. (2023). Single-Agent Divarasib (GDC-6036) in Solid Tumors with a KRAS G12C Mutation. *The New England Journal of Medicine*, *389*(8), 710–721. https://doi.org/10.1056/NEJMoa2303810

Sacher, A., Miller, W. H. Jr., Paz-Ares, L., Ahn, M.-J., Patel, M., Dziadziuszko, R., Santoro, A., Luo, J., Markman, B., Freres, P., Van Dongen, M., Desai, J., Bowyer, S., Cervantes, A., Mourão Dias, J., Falcon, A., Krebs, M. G., Laurie, S., Prenen, H., … Lorusso, P. (2024). OA14.06 Divarasib single-agent long-term follow-up and Atezolizumab combination treatment in patients with KRAS G12C-positive NSCLC. *Journal of Thoracic Oncology*, *19*(10), S42–S43. https://doi.org/10.1016/j.jtho.2024.09.075

Sacher, A. G., Miller, W. H. Jr., Patel, M. R., Paz-Ares, L., Santoro, A., Ahn, M. J., Dziadziuszko, R., Freres, P., Luo, J., Bowyer, S., & Desai, J. (2025). Single-Agent Divarasib in Patients With KRAS G12C-Positive Non-Small Cell Lung Cancer: Long-Term Follow-Up of a Phase I Study. *Journal of Clinical Oncology*, *43*(30), 3249–3253. https://doi.org/10.1200/JCO-25-00040

Sahin, S., & Benet, L. Z. (2008). The operational multiple dosing half-life: a key to defining drug accumulation in patients and to designing extended release dosage forms. *Pharmaceutical Research*, *25*(12), 2869–2877. https://doi.org/10.1007/s11095-008-9787-9

Sanchez-Vega, F., Mina, M., Armenia, J., Chatila, W. K., Luna, A., La, K. C., Dimitriadoy, S., Liu, D. L., Kantheti, H. S., Saghafinia, S., Chakravarty, D., Daian, F., Gao, Q., Bailey, M. H., Liang, W. W., Foltz, S. M., Shmulevich, I., Ding, L., Heins, Z., … Schultz, N. (2018). Oncogenic signaling pathways in The Cancer Genome Atlas. *Cell*, *173*(2), 321–337 e10. https://doi.org/10.1016/j.cell.2018.03.035

Schulze, C. J., Seamon, K. J., Zhao, Y., Yang, Y. C., Cregg, J., Kim, D., Tomlinson, A., Choy, T. J., Wang, Z., Sang, B., Pourfarjam, Y., Lucas, J., Cuevas-Navarro, A., Ayala-Santos, C., Vides, A., Li, C., Marquez, A., Zhong, M., Vemulapalli, V., … Lito, P. (2023). Chemical remodeling of a cellular chaperone to target the active state of mutant KRAS. *Science*, *381*(6659), 794–799. https://doi.org/10.1126/science.adg9652

Simanshu, D. K., Nissley, D. V., & McCormick, F. (2017). KRAS proteins and their regulators in human disease. *Cell*, *170*(1), 17–33.

Singhal, A., Li, B. T., & O'Reilly, E. M. (2024). Targeting KRAS in cancer. *Nature Medicine*, *30*(4), 969–983. https://doi.org/10.1038/s41591-024-02903-0

Skoulidis, F., Goldberg, M. E., Greenawalt, D. M., Hellmann, M. D., Awad, M. M., Gainor, J. F., Schrock, A. B., Hartmaier, R. J., Trabucco, S. E., Gay, L., Ali, S. M., Elvin, J. A., Singal, G., Ross, J. S., Fabrizio, D., Szabo, P. M., Chang, H., Sasson, A., Srinivasan, S., … Heymach, J. V. (2018). STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. *Cancer Discovery*, *8*(7), 822–835. https://doi.org/10.1158/2159-8290.CD-18-0099

Skoulidis, F., Li, B. T., de Langen, A. J., Hong, D. S., Lena, H., Wolf, J., Dy, G. K., Curioni Fontecedro, A., Tomasini, P., Velcheti, V., van der Wekken, A. J., Dooms, C., Paz-Ares Rodriguez, L., Mountzios, G., Sacher, A., Nadal, E., Couraud, S., Kim, S. W., O'Byrne, K., … Schuler, M. (2025). Molecular determinants of sotorasib clinical efficacy in KRAS(G12C)-mutated non-small-cell lung cancer. *Nature Medicine*, *31*(8), 2755–2767. https://doi.org/10.1038/s41591-025-03732-5

Skoulidis, F., Li, B. T., Dy, G. K., Price, T. J., Falchook, G. S., Wolf, J., Italiano, A., Schuler, M., Borghaei, H., Barlesi, F., Kato, T., Curioni-Fontecedro, A., Sacher, A., Spira, A., Ramalingam, S. S., Takahashi, T., Besse, B., Anderson, A., Ang, A., … Govindan, R. (2021). Sotorasib for Lung Cancers with KRAS p.G12C Mutation. *The New England Journal of Medicine*, *384*(25), 2371–2381. https://doi.org/10.1056/NEJMoa2103695

Sorensen, A. G., Batchelor, T. T., Zhang, W. T., Chen, P. J., Yeo, P., Wang, M., Jennings, D., Wen, P. Y., Lahdenranta, J., Ancukiewicz, M., di Tomaso, E., Duda, D. G., & Jain, R. K. (2009). A "vascular normalization index" as potential mechanistic biomarker to predict survival after a single dose of cediranib in recurrent glioblastoma patients. *Cancer Research*, *69*(13), 5296–5300. https://doi.org/10.1158/0008-5472.CAN-09-0814

Sparmann, A., & Bar-Sagi, D. (2004). KRAS-induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis. *Cancer Cell*, *6*(5), 447–458.

Spella, M., Ntaliarda, G., Skiadas, G., Lamort, A. S., Vreka, M., Marazioti, A., Lilis, I., Bouloukou, E., Giotopoulou, G. A., Pepe, M. A., & Weiss, S. A. (2023). Non-oncogene addiction of *KRAS*-mutant cancers to IL-1β via Versican and mononuclear IKKbeta. *Cancers (Basel)*, *15*(6), 1866. https://doi.org/10.3390/cancers15061866

Spira, A. I., Papadopoulos, K. P., Kim, D. W., Parikh, A. R., Barve, M. A., Powderly, J. D. II, Starodub, A., Strickler, J. H., Li, B. T., Oberstein, P. E., Hassan, F., Yang, M., McCleland, M., Lally, S., Lin, W., Sohoni, S., & Hong, D. S. (2025). Preliminary safety, antitumor activity, and circulating tumor DNA (ctDNA) changes with RMC-9805, an oral, KRAS (ON) G12D-selective tri-complex inhibitor in patients with KRAS G12D pancreatic ductal adenocarcinoma (PDAC) from a phase 1 study in advanced solid tumors. *Journal of Clinical Oncology*, *43*(4_suppl), 724. https://doi.org/10.1200/JCO.2025.43.4_suppl.724

Steele, C. W., Karim, S. A., Leach, J. D. G., Bailey, P., Upstill-Goddard, R., Rishi, L., Foth, M., Bryson, S., McDaid, K., Wilson, Z., Eberlein, C., Candido, J. B., Clarke, M., Nixon, C., Connelly, J., Jamieson, N., Carter, C. R., Balkwill, F., Chang, D. K., … Morton, J. P. (2016). CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma. *Cancer Cell*, *29*(6), 832–845. https://doi.org/10.1016/j.ccell.2016.04.014

Stefanoudakis, D., Frountzas, M., Schizas, D., Michalopoulos, N. V., Drakaki, A., & Toutouzas, K. G. (2024). Significance of TP53, CDKN2A, SMAD4 and KRAS in Pancreatic Cancer. *Current Issues in Molecular Biology*, *46*(4), 2827–2844. https://doi.org/10.3390/cimb46040177

Strickler, J. H., Satake, H., George, T. J., Yaeger, R., Hollebecque, A., Garrido-Laguna, I., Schuler, M., Burns, T. F., Coveler, A. L., Falchook, G. S., Vincent, M., Sunakawa, Y., Dahan, L., Bajor, D., Rha, S. Y., Lemech, C., Juric, D., Rehn, M., Ngarmchamnanrith, G., … Hong, D. S. (2023). Sotorasib in KRAS p.G12C-Mutated Advanced Pancreatic Cancer. *The New England Journal of Medicine*, *388*(1), 33–43. https://doi.org/10.1056/NEJMoa2208470

Tang, K. H., Li, S., Khodadadi-Jamayran, A., Jen, J., Han, H., Guidry, K., Chen, T., Hao, Y., Fedele, C., Zebala, J. A., Maeda, D. Y., Christensen, J. G., Olson, P., Athanas, A., Loomis, C. A., Tsirigos, A., Wong, K. K., & Neel, B. G. (2022). Combined Inhibition of SHP2 and CXCR1/2 Promotes Antitumor T-cell Response in NSCLC. *Cancer Discovery*, *12*(1), 47–61. https://doi.org/10.1158/2159-8290.CD-21-0369

Taza, F., Durm, G. A., Opyrchal, M., Jalal, S. I., Radovich, M., Schneider, B. P., & Turk, A. A. (2023). A phase 2 basket trial of an ERK1/2 inhibitor (LY3214996) in combination with Abemaciclib for patients whose tumors harbor pathogenic alterations in BRAF, RAF1, MAP 2K1/2 ERK1/2, and NF1. *Journal of Clinical Oncology*, *41*-(16_suppl), e15088. https://doi.org/10.1200/JCO.2023.41.16_suppl.e15088

Thatikonda, V., Lyu, H., Jurado, S., Kostyrko, K., Bristow, C. A., Albrecht, C., Alpar, D., Arnhof, H., Bergner, O., Bosch, K., Feng, N., Gao, S., Gerlach, D., Gmachl, M., Hinkel, M., Lieb, S., Jeschko, A., Machado, A. A., Madensky, T., … Hofmann, M. H. (2024). Co-targeting SOS1 enhances the antitumor effects of KRAS(G12C) inhibitors by addressing intrinsic and acquired resistance. *Nature Cancer*, *5*(9), 1352–1370. https://doi.org/10.1038/s43018-024-00800-6

Tolaney, S. M., Boucher, Y., Duda, D. G., Martin, J. D., Seano, G., Ancukiewicz, M., Barry, W. T., Goel, S., Lahdenrata, J., Isakoff, S. J., Yeh, E. D., Jain, S. R., Golshan, M., Brock, J., Snuderl, M., Winer, E. P., Krop, I. E., & Jain, R. K. (2015). Role of vascular density and normalization in response to neoadjuvant bevacizumab and chemotherapy in breast cancer patients. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(46), 14325–14330. https://doi.org/10.1073/pnas.1518808112

Tong, X., Patel, A. S., Kim, E., Li, H., Chen, Y., Li, S., Liu, S., Dilly, J., Kapner, K. S., Zhang, N., Xue, Y., Hover, L., Mukhopadhyay, S., Sherman, F., Myndzar, K., Sahu, P., Gao, Y., Li, F., Fang, Z., … Ji, H. (2024). Adeno-to-squamous transition drives resistance to KRAS inhibition in LKB1 mutant lung cancer. *Cancer Cell*, *42*(3), 413–428 e7. https://doi.org/10.1016/j.ccell.2024.01.012

Traut, T. W. (1994). Physiological concentrations of purines and pyrimidines. *Molecular and Cellular Biochemistry*, *140*(1), 1–22. https://doi.org/10.1007/BF00928361

Unni, A. M., Lockwood, W. W., Zejnullahu, K., Lee-Lin, S. Q., & Varmus, H. (2015). Evidence that synthetic lethality underlies the mutual exclusivity of oncogenic KRAS and EGFR mutations in lung adenocarcinoma. *eLife*, *4*, e06907. https://doi.org/10.7554/eLife.06907

Vasta, J. D., Peacock, D. M., Zheng, Q., Walker, J. A., Zhang, Z., Zimprich, C. A., Thomas, M. R., Beck, M. T., Binkowski, B. F., Corona, C. R., Robers, M. B., & Shokat, K. M. (2022). KRAS is vulnerable to reversible switch-II pocket engagement in cells. *Nature Chemical Biology*, *18*(6), 596–604. https://doi.org/10.1038/s41589-022-00985-w

Wainberg, Z. A., Weekes, C. D., Furqan, M., Kasi, P. M., Devoe, C. E., Leal, A. D., Chung, V., Perry, J. R., Kheoh, T., McNeil, L. K., Welkowsky, E., DeMuth, P. C., Haqq, C. M., Pant, S., & O'Reilly, E. M. (2025). Lymph node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: phase 1 AMPLIFY-201 trial final results. *Nature Medicine*, *31*, 3648–3653. https://doi.org/10.1038/s41591-025-03876-4

Wang, D., Liu, G., Meng, Y., Chen, H., Ye, Z., & Jing, J. (2024). The Configuration of GRB2 in Protein Interaction and Signal Transduction. *Biomolecules*, *14*(3), 259. https://doi.org/10.3390/biom14030259

Willett, C. G., Boucher, Y., di Tomaso, E., Duda, D. G., Munn, L. L., Tong, R. T., Chung, D. C., Sahani, D. V., Kalva, S. P., Kozin, S. V., Mino, M., Cohen, K. S., Scadden, D. T., Hartford, A. C., Fischman, A. J., Clark, J. W., Ryan, D. P., Zhu, A. X., Blaszkowsky, L. S., … Jain, R. K. (2004). Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nature Medicine*, *10*(2), 145–147. https://doi.org/10.1038/nm988

Xu, R. H., Xu, Y., Yan, D., Munster, P., Ruan, D., Deng, Y., Pan, H., Underhill, C. R., Richardson, G., Nordman, I., Lee, K. W., Wei, S., Li, X., Shan, J., Han, G., Henderson, S., Xie, X., Xiang, Z., Shi, Z., & Zhang, L. (2023). 550O Safety and efficacy of D-1553 in combination with cetuximab in KRAS G12C mutated colorectal cancer (CRC): A phase II study. *Annals of Oncology*, *34*, S410–S411. https://doi.org/10.1016/j.annonc.2023.09.1741

Yaeger, R., Uboha, N. V., Pelster, M. S., Bekaii-Saab, T. S., Barve, M., Saltzman, J., Sabari, J. K., Peguero, J. A., Paulson, A. S., Jänne, P. A., Cruz-Correa, M., Anderes, K., Velastegui, K., Yan, X., der-Torossian, H., Klempner, S. J., & Kopetz, S. E. (2024). Efficacy and Safety of Adagrasib plus Cetuximab in Patients with KRASG12C-Mutated Metastatic Colorectal Cancer. *Cancer Discovery*, *14*(6), 982–993. https://doi.org/10.1158/2159-8290.CD-24-0217

Yaeger, R., Weiss, J., Pelster, M. S., Spira, A. I., Barve, M., Ou, S. H. I., Leal, T. A., Bekaii-Saab, T. S., Paweletz, C. P., Heavey, G. A., Christensen, J. G., Velastegui, K., Kheoh, T., der-Torossian, H., & Klempner, S. J. (2023). Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated KRAS G12C. *The New England Journal of Medicine*, *388*(1), 44–54. https://doi.org/10.1056/NEJMoa2212419

Yang, B., Deng, B., Jiao, X. D., Qin, B. D., Lu, Y., Zhang, W., Guo, Y., Chen, S., Li, D., Li, B., & Zang, Y. S. (2022). Low-dose anti-VEGFR2 therapy promotes anti-tumor immunity in lung adenocarcinoma by down-regulating the expression of layilin on tumor-infiltrating CD8(+) T cells. *Cellular Oncology (Dordrecht)*, *45*(6), 1297–1309. https://doi.org/10.1007/s13402-022-00718-0

Yang, J., Yan, J., & Liu, B. (2018). Targeting VEGF/VEGFR to Modulate Antitumor Immunity. *Frontiers in Immunology*, *9*, 978. https://doi.org/10.3389/fimmu.2018.00978

Yang, X., Feng, S., Zhang, Q., Li, W., Li, S., Zhi, M., Lan, P., & Cheng, S. (2025). KRAS amplification in colorectal cancer: correlations with clinicopathological features and prognosis in patients and prediction of response to targeted therapy. *Journal of Translational Medicine*, *23*(1), 824. https://doi.org/10.1186/s12967-025-06864-x

Yuan, Y., Deng, Y., Jin, Y., Guo, Z., Pan, Y., Wang, C., Wang, Z., Hu, Y., Hua, D., Meng, X., Zhang, Z., Zhao, M., Dong, X., Huang, D., Li, X., Liu, L., Sun, M., Wang, H., Wang, X., … Ding, K. (2025). Efficacy and safety of IBI351 (fulzerasib) monotherapy in KRAS(G12C) inhibitor-naive Chinese patients with KRAS(G12C)-mutated metastatic colorectal cancer: A pooled analysis from phase I part of two studies. *Signal Transduction and Targeted Therapy*, *10*(1), 241. https://doi.org/10.1038/s41392-025-02315-7

Zeissig, M. N., Ashwood, L. M., Kondrashova, O., & Sutherland, K. D. (2023). Next batter up! Targeting cancers with KRAS-G12D mutations. *Trends Cancer*, *9*(11), 955–967. https://doi.org/10.1016/j.trecan.2023.07.010

Zhang, J., Lim, S. M., Yu, M. R., Chen, C., Wang, J., Wang, W., Rui, H., Lu, J., Lu, S., Mok, T., Chen, Z. J., & Cho, B. C. (2024). D3S-001, a KRAS G12C Inhibitor with Rapid Target Engagement Kinetics, Overcomes Nucleotide Cycling, and Demonstrates Robust Preclinical and Clinical Activities. *Cancer Discovery*, *14*(9), 1675–1698. https://doi.org/10.1158/2159-8290.CD-24-0006

Zhang, J. Z., Ong, S. E., Baker, D., & Maly, D. J. (2025). Single-cell sensor analyses reveal signaling programs enabling KRAS-G12C drug resistance. *Nature Chemical Biology*, *21*(1), 47–58.

Zhao, J., Fang, J., Yu, Y., Chu, Q., Li, X., Chen, J., Liu, Z., Zhang, L., Wu, L., Zhuang, W., Zhao, Y., Xing, L., Liu, L., Bai, C., Dong, X., Song, Q., Pan, P., Fang, X., & Wang, J. (2024). Updated safety and efficacy data of combined KRAS G12C inhibitor (glecirasib, JAB-21822) and SHP2 inhibitor (JAB-3312) in patients with KRAS p.G12C mutated solid tumors. *Journal of Clinical Oncology*, *42*(16_suppl), 3008. https://doi.org/10.1200/JCO.2024.42.16_suppl.3008

Zhou, Q., Meng, X., Sun, L., Huang, D., Yang, N., Yu, Y., Zhao, M., Zhuang, W., Hu, Y., Pan, Y., Sun, M., Shan, J., Guo, R. H., Chu, Q., Xu, C., Lin, J., Huang, J., Huang, M., Shen, Y., & Wu, Y. L. (2023). LBA12 Efficacy and safety of IBI351 (GFH925), a selective KRASG12C inhibitor, monotherapy in patients (pts) with advanced non-small cell lung cancer (NSCLC): Initial results from a registrational phase II study. *Annals of Oncology*, *34*, S1662. https://doi.org/10.1016/j.annonc.2023.10.584

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