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Review

Emerging Strategies for KRAS Inhibition in Cancer: From G12C to Pan-RAS and Beyond

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Abstract

Kirsten RAS oncogene (*KRAS*) is the most frequently mutated oncogene in human cancer and has historically been considered "undruggable". The development of covalent $KRAS^{G12C}$ inhibitors has marked a paradigm shift, leading to the first approved direct Rat Sarcoma Virus (RAS)-targeted therapies in non-small cell lung cancer. However, their clinical benefit is often transient due to intrinsic and acquired resistance, and no targeted therapies are yet approved for other prevalent KRAS variants such as G12D and G12V. This review is intended for clinicians and translational researchers with an interest in precision oncology and early-phase drug development, and summarises recent advances in the field, including next-generation allele-specific inhibitors, pan-KRAS and pan-RAS inhibitors, KRAS degraders, indirect strategies targeting upstream regulators, and emerging immunologic approaches. We also outline rational combination strategies designed to prevent pathway reactivation, overcome tumor heterogeneity, and improve the depth and durability of response. Take together, these developments illustrate both the progress and the persistent challenges in targeting KRAS-mutant cancers. By integrating clinical trial data with mechanistic insights from preclinical studies, this review provides an updated perspective on the opportunities and limitations of KRAS-directed therapies and their broader implications for the future of precision oncology.

Keywords: KRAS; targeted cancer therapy; precision oncology; early-phase clinical trials; RAS signaling

1. Introduction

The Rat Sarcoma Virus (RAS) family of oncogenes plays a central role in regulating cell proliferation, differentiation, and survival, and represents the most frequently mutated oncogene group in human cancer [1]. Activating mutations in three RAS genes, Kirsten RAS oncogene (*KRAS*), Harvey RAS oncogene homolog (*HRAS*), and neuroblastoma RAS oncogene (*NRAS*), are implicated in approximately one-fifth of all cancers [2]. *KRAS* is the predominant isoform, accounting for nearly 75% of RAS-mutant tumours, whereas *NRAS* and *HRAS* mutations account for ~24% and ~1%, respectively [2]. Historically, early experimental work on RAS biology and drug development focused on HRAS, which differs structurally and biochemically from KRAS, a factor that likely contributed to the repeated failure of early RAS-targeted strategies to translate clinically. *KRAS* mutations are especially prevalent in malignancies associated with poor prognosis and high disease burden, including pancreatic ductal adenocarcinoma (PDAC; ~90%), colorectal cancer (CRC; ~50%), and non-small cell lung cancer (NSCLC; ~25%) [1,3].

Despite *KRAS* being identified as a human oncogenic driver as early as 1982 [4,5], efforts to therapeutically target it have long been hindered by significant structural and biochemical challenges. The KRAS protein exhibits picomolar affinity for guanosine triphosphate (GTP) and operates in a cellular environment with high intracellular GTP concentrations, making competitive inhibition at the nucleotide-binding site highly challenging. Additionally, its relatively smooth surface topology lacks the deep hydrophobic pockets required for conventional small-molecule binding, contributing to its long-standing reputation as "undruggable" [6,7,8]. For decades, therapeutic efforts instead centred on indirect strategies, including inhibition of downstream effectors such as the extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K) pathways, or disruption of post-translational modifications essential for membrane localisation [9]. However, these approaches have been largely unsuccessful.

A paradigm shift emerged with the discovery that certain KRAS oncoproteins, particularly $KRAS^{G12C}$, retain partial intrinsic guanosine triphosphatase (GTPase) activity and continue to cycle between active (GTP-bound) and inactive (guanosine diphosphate [GDP]-bound) states [10,11]. This enabled the rational design of covalent $KRAS^{G12C}$ inhibitors, which exploit a unique cysteine

residue within the switch II pocket to achieve direct, irreversible, and selective binding to its inactive conformation [12]. These agents demonstrated meaningful clinical benefit in NSCLC, providing the first proof-of-concept that direct KRAS inhibition is achievable in clinical practice [13,14]. However, responses have been limited by modest durability and applicability only to a small, molecularly-defined subset of KRAS-mutant tumours [15,16].

This review summarises recent advances in KRAS-targeted therapy, with a focus on breakthroughs in direct pharmacologic inhibition. We discuss the molecular landscape and functional consequences of *KRAS* mutations, advances in allele-specific and pan-RAS inhibitors, and emerging mechanisms of resistance. Finally, we outline future directions, including rational combination strategies and immunologic approaches, to more fully realise the therapeutic potential of targeting KRAS-mutant cancers.

2. KRAS Structure and Signalling

The classical RAS subfamily comprises approximately 36 genes encoding 39 GTPase proteins that regulate diverse cellular functions [17,18]. Among these, three well-characterised proto-oncogenes, *KRAS*, *NRAS*, and *HRAS*, encode four highly homologous canonical RAS proteins: H-Ras, N-Ras, K-Ras4A, and K-Ras4B [19]. These membrane-associated GTPases function as molecular switches, cycling between inactive GDP-bound and active GTP-bound conformations, to regulate key intracellular signalling pathways involving cell proliferation, survival, differentiation, and metabolism [20].

This cycle is tightly regulated by guanine nucleotide exchange factors (GEFs), including Son of Sevenless 1 and 2 (SOS1/SOS2) and growth factor receptor-bound protein (GRB2), which promote GTP loading onto RAS in response to extracellular signals, primarily downstream of receptor tyrosine kinase (RTK) activation. In contrast, GTPase-activating proteins (GAPs), such as neurofibromin (NF1), accelerate GTP hydrolysis and RAS inactivation [19,21]. Src homology-2 domain-containing phosphatase (SHP2) serves as an additional upstream regulator by facilitating recruitment of the GRB2/SOS1 complex to the plasma membrane, enhancing signal-dependent RAS activation [22]. Under normal physiological conditions, a tight equilibrium is maintained between these active and inactive states. However, oncogenic *RAS* mutations disrupt this balance by impairing intrinsic GTPase activity or GAP-mediated hydrolysis, resulting in sustained signalling from the active GTP-bound state [23].

Structurally, RAS proteins comprise a highly conserved catalytic G-domain and a hypervariable C-terminal region (see Fig. 1) [24]. The G-domain contains the P-loop and switch I and II regions, which mediate nucleotide binding, hydrolysis, and effector engagement [25]. The C-terminal region contains the CAAX motif (cysteine, two aliphatic amino acids, and a terminal residue) that undergoes post-translational modifications essential for membrane anchoring and the spatial organisation of signalling [20,26]. Despite high sequence homology, the four canonical RAS proteins differ primarily within their hypervariable regions which dictate distinct post-translational modifications, such as farnesylation and palmitoylation, that influence membrane localisation [27]. Alternative splicing is unique to *KRAS*, giving rise to two isoforms, K-Ras4A and K-Ras4B, whereas *HRAS* and *NRAS* do not undergo alternative splicing. K-Ras4B relies primarily on a polybasic domain for plasma membrane association, whereas H-Ras, N-Ras, and K-Ras4A undergo additional palmitoylation cycles that regulate membrane trafficking and localisation [27,28]. As K-Ras4B is the predominant splice variant in adult tissues, it will be the primary focus of this review and is hereafter referred to as KRAS.

3. Molecular Landscape of KRAS Mutations

KRAS is the most commonly mutated isoform within the RAS family, accounting for approximately 75% of RAS-driven cancers [2]. Oncogenic activation results from single-nucleotide substitutions, with ~95% of mutations occurring at hotspot codons 12, 13, and 61. Codon 12 mutations predominate, typically involving substitutions of glycine with aspartic acid (G12D), valine (G12V), cysteine (G12C), or arginine (G12R) [20]. While these variants dominate the mutational landscape, their distribution varies markedly across cancer types [2]. For example, G12D is most frequent in PDAC and CRC, while G12C, which is strongly associated with tobacco exposure, is enriched in NSCLC [2].

KRAS mutations were long considered functionally equivalent; however, increasing evidence indicates that specific *KRAS* alleles confer distinct structural and functional consequences that influence tumour behaviour and treatment response. Most variants enhance GTP affinity while reducing GAP sensitivity [29]. Importantly, in contrast with the long-standing dogma, many *KRAS* mutants retain residual intrinsic GTPase activity. For example, G12C and G12D retain partial hydrolytic function, whereas G12V and G12R demonstrate markedly impaired GTP hydrolysis, resulting in a more persistent GTP-bound active state [29].

These biochemical differences translate into clinically relevant phenotypes. For example, G12D, which introduces a negatively charged aspartate that disrupts GAP-mediated hydrolysis, is associated with a poorer prognosis in advanced PDAC compared with other *KRAS* mutations [30]. G12C's partial retention of intrinsic GTPase activity is critical for its susceptibility to inhibitors, which bind the GDP-bound state [6,12]. G13D retains some GAP responsiveness and exhibits a distinct effector interaction profile, potentially explaining its variable sensitivity to anti-epidermal growth factor receptor (EGFR) therapy in CRC [31]. Finally, the rarer codon 61 mutations completely abolish intrinsic GTPase activity and are associated with aggressive

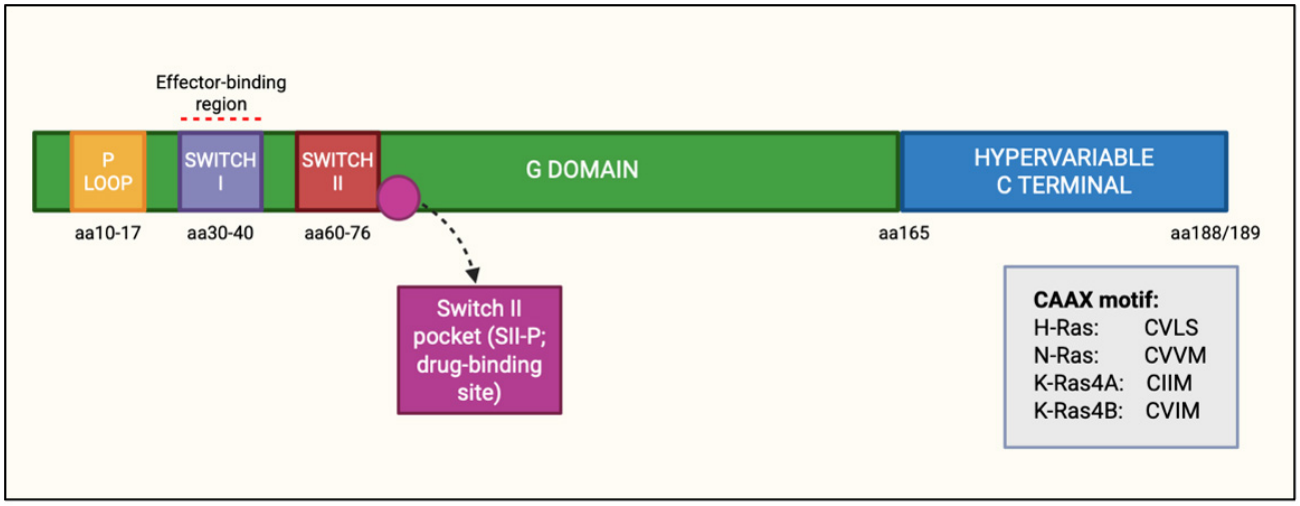

Fig. 1. Domain architecture of the canonical RAS proteins (created with BioRender.com). RAS, Rat Sarcoma Virus.

disease biology [20]. Together, these observations demonstrate that biochemical heterogeneity among *KRAS* alleles drives meaningful differences in tumour phenotype, prognosis, and therapeutic vulnerability.

4. Historical Approaches to Targeting RAS

Although the functional diversity of *KRAS* mutations is now recognised as a major challenge for therapeutic development, this complexity was not appreciated for many years, contributing to the repeated failure of early KRAS-targeted approaches. Consequently, early efforts focused on indirect strategies, as RAS proteins were considered functionally interchangeable and were long regarded as "undruggable" due to their biophysical properties.

4.1 Targeting Membrane Localisation

RAS proteins must localise to the plasma membrane for signalling, a process requiring a series of post-translational modifications, including prenylation of the CAAX motif by farnesyltransferase, proteolytic cleavage by RAS-converting enzyme (RCE1), and methylation of the terminal isoprenylcysteine by isoprenylcysteine carboxyl methyltransferase (ICMT). Early studies established that farnesylation is essential for the membrane localisation of RAS proteins, enabling their association with the plasma membrane and facilitating interaction with downstream effector pathways. Farnesyltransferase inhibitors (FTIs), such as tipifarnib and lonafarnib, were developed to block this step and showed early promise, particularly in HRAS-driven tumours [32,33]. However, clinical trials performed in the late 1990s in unselected populations failed to demonstrate a survival benefit [34]. Subsequent experiments revealed that KRAS and NRAS can bypass farnesylation through alternative prenylation by geranylgeranyltransferase, rendering FTIs ineffective in these cancers [35]. In contrast, HRAS is uniquely dependent on farnesylation, making it more susceptible to FTI therapy. This mechanistic insight led to the premature abandonment of FTIs as a class, although subsequent recognition of isoform-specific differences has prompted renewed clinical interest in this strategy for HRAS-driven tumours. In a phase II study, tipifarnib demonstrated encouraging efficacy in patients with HRAS-mutant advanced head and neck squamous cell carcinoma, with an overall response rate (ORR) of 55%, a median progression-free survival (PFS) of 5.6 months, and a median overall survival (OS) of 15.4 months [36].

Building on these observations, other strategies to disrupt RAS membrane binding were developed in an effort to more selectively target KRAS-driven oncogenesis. Salirasib, a farnesylthiosalicylic acid derivative that competes with farnesylated RAS for membrane binding, showed no objective responses in a phase II trial in KRAS-mutant NSCLC, limiting further development [37]. Phosphodiesterase-δ (PDEδ), a chaperone that facilitates diffusion of farnesylated RAS to the plasma membrane, has also been targeted; however, PDEδ inhibition with deltarasin has been limited by poor bioavailability and toxicity despite preclinical activity [38]. Inhibition of ICMT represents another membrane-targeting strategy that remains under preclinical investigation [39]. Furthermore, RAS signalling is now recognised to occur not only at the plasma membrane but also at intracellular organelles such as the Golgi and endoplasmic reticulum, thereby potentially limiting the impact of therapies that exclusively target membrane localisation [40].

4.2 Inhibiting Downstream Effector Pathways

Due to the challenges of directly targeting KRAS and the failure of FTIs, considerable efforts shifted toward inhibiting downstream signalling cascades. The rationale was that oncogenic RAS signalling could be attenuated by blocking key effector pathways. This strategy was initially considered highly promising, and multiple agents targeting

these pathways have since entered clinical practice for other indications. MAPK/ERK kinase (MEK) inhibitors, such as trametinib and selumetinib, demonstrated promising preclinical efficacy in KRAS-mutant models but yielded only modest clinical benefit. This limited efficacy reflects feedback reactivation of the ERK pathway, pathway redundancy, compensatory activation of parallel RAS effector networks, and rapid adaptive resistance [9,41].

These findings highlight the critical importance of pathway architecture and protein-protein interactions in determining therapeutic response to targeted agents. This principle is further illustrated by rapidly accelerated fibrosarcoma (RAF) inhibitors such as vemurafenib and dabrafenib, which are highly effective in BRAF-mutant cancers but ineffective in KRAS-mutant tumours due to paradoxical ERK pathway activation driven by RAF dimerisation and engagement of parallel effector pathways [42,43]. Next-generation pan-RAF inhibitors and RAF dimer disruptors (e.g., belvarafenib, naporafenib) have been developed to overcome this limitation [44,45]. Computational modelling studies have provided mechanistic insight into this phenomenon, demonstrating that structural asymmetry within RAF dimers and the thermodynamics of drug binding allow RAF inhibitors to bind only one protomer. This allosterically activates the unbound protomer, resulting in paradoxical ERK pathway activation [46]. This form of resistance can be overcome by combining structurally distinct RAF inhibitors that bind different protomer conformations, an approach that has demonstrated activity in both BRAF- and RAS-mutant preclinical models [46,47]. Combining RAF or MEK inhibitors with autophagy inhibition (e.g., hydroxychloroquine) has shown preclinical synergy in KRAS-mutant PDAC models, although clinical translation remains challenging and an area of active investigation [48,49,50].

ERK inhibitors have also been explored as a means of targeting downstream RAS signalling. In a phase I trial of the ERK inhibitor MK-8353, no radiological responses were observed among 26 patients with RAS-mutated cancers [51]. Ulixertinib has demonstrated clinical activity in NRAS-mutant melanoma, and trials are ongoing in other RAS-driven malignancies [52]. However, responses in KRAS-mutant cancers have been limited, with clinical development constrained by dose-limiting toxicity and a narrow therapeutic window. Nonetheless, rational combination strategies involving ERK inhibitors remain under active investigation.

The PI3K pathway represents another major canonical RAS effector cascade that has been extensively explored. Inhibitors of the PI3K-protein kinase B (AKT)-mechanistic target of rapamycin (mTOR) pathway have demonstrated limited efficacy as monotherapy in RAS-mutant malignancies, in part due to pathway redundancy and compensatory ERK reactivation following PI3K or AKT inhibition [53]. Although dual PI3K and MEK inhibition has demonstrated preclinical synergy, clinical translation has been hampered by narrow therapeutic windows and dose-limiting toxicities [54]. While AKT inhibition has achieved clinical validation in biomarker-selected breast cancer [55], its role in RAS-mutant tumours remains unproven, with combination approaches continuing to be limited by toxicity [56].

4.3 Synthetic Lethality and Contextual Vulnerabilities

Another avenue of investigation has been the pursuit of synthetic lethal interactions with RAS mutations, whereby genes non-essential in normal cells become critical for the survival of RAS-mutant cancers. Early screens highlighted several promising targets, including TANK-binding kinase 1 (*TBK1*), serine/threonine kinase 33 (*STK33*), and cyclin-dependent kinase 4 (*CDK4*) [57]. However, many of these findings failed to translate reproducibly in subsequent studies or clinical settings due to cell line-specific effects, off-target toxicity, or context-dependent dependencies [58]. Despite these limitations, the synthetic lethality concept has remained influential, underpinning current combination strategies involving KRAS inhibition with agents targeting autophagy, DNA damage response, or tumour metabolism [12,17].

Collectively, these efforts established key biological principles that paved the way for the success of direct KRAS inhibitors, highlighting the need to move beyond linear models of RAS signalling toward precision strategies informed by allele specificity, isoform biology, and tumour context, insights that ultimately enabled the development of $KRAS^{G12C}$ inhibitors.

5. Direct RAS Inhibitors

5.1 First-Generation $KRAS^{G12C}$ Inhibitors

The long-standing dogma that RAS proteins, particularly KRAS, were undruggable was overturned over the past decade. In 2013, the laboratory of Kevan Shokat identified a previously unrecognised allosteric binding site in $KRAS^{G12C}$, subsequently termed the switch II pocket. This pocket is transiently exposed only when KRAS is in its inactive, GDP-bound conformation, enabling the covalent engagement of small molecules with the mutant cysteine residue at position 12. Exploitation of this vulnerability facilitated the development of the first direct KRAS inhibitors. By irreversibly locking KRAS in its inactive state, these inhibitors block effector interactions and downstream signalling, thereby disrupting oncogenic signalling cascades – a mechanism now referred to as KRAS(OFF) inhibition [59].

Building on these findings, sotorasib (AMG-510) was the first KRAS inhibitor to gain regulatory approval following evidence of clinical benefit in advanced $KRAS^{G12C}$-mutant NSCLC. In the phase I/II CodeBreaK100 trial, sotorasib achieved an ORR of 37.1% and a median PFS of 6.8 months in previously treated NSCLC patients [60]. These results led to accelerated approval by the United States

(US) Food and Drug Administration (FDA) in 2021 for $KRAS^{G12C}$-mutant NSCLC. More recently, the randomised phase III CodeBreaK200 trial compared sotorasib with docetaxel in previously treated NSCLC, showing a modest improvement in median PFS (5.6 vs. 4.5 months, $p = 0.0017$), but failing to demonstrate an OS benefit [61]. This lack of OS benefit represents a clinically important limitation and raises questions regarding the extent to which $KRAS^{G12C}$(OFF) inhibition, as monotherapy, is sufficient to achieve durable disease control. Potential explanations include rapid emergence of adaptive resistance, incomplete pathway suppression, and limitations with trial design, including imbalanced censoring rates and patient crossover [62]. Interestingly, subsequent real-world analyses have suggested an OS advantage for sotorasib over docetaxel in the second-line and later-line settings [63].

Adagrasib (MRTX849), the second covalent $KRAS^{G12C}$ inhibitor approved for clinical use, similarly targets the inactive, GDP-bound state of the protein. In the phase I/II KRYSTAL-1 trial, adagrasib demonstrated an ORR of 42.9% and a median PFS of 6.5 months in pretreated $KRAS^{G12C}$-mutant NSCLC patients [14]. Importantly, adagrasib exhibits a longer half-life and superior central nervous system (CNS) penetration compared to sotorasib, which may confer clinical advantages in select patient populations [64]. Based on these findings, adagrasib received accelerated FDA approval in 2022. More recently, the phase III KRYSTAL-12 trial comparing adagrasib with docetaxel in pretreated NSCLC demonstrated an improvement in median PFS (5.5 versus 3.8 months, $p < 0.0001$) and ORR (31.9% versus 9.2%, $p < 0.0001$), however, OS data remain immature [65]. While these results support the clinical activity of adagrasib, the absence of mature OS data and the relatively modest PFS benefit observed with first-generation $KRAS^{G12C}$ inhibitors more broadly highlight the need for cautious interpretation of their long-term clinical impact.

Beyond NSCLC, both sotorasib and adagrasib have shown more modest activity in metastatic CRC, with ORRs of 9.7% and 19%, respectively, as monotherapies [66,67]. This limited efficacy contrasts sharply with outcomes in NSCLC and underscores the importance of tumour context in determining response to KRAS inhibition. Consistent with observations from ERK and PI3K pathway inhibition, this limited efficacy is largely attributed to adaptive resistance mechanisms, particularly EGFR-mediated feedback activation. Combining $KRAS^{G12C}$ inhibitors with anti-EGFR therapies has led to improved outcomes, with ORRs of 26.4% for sotorasib combined with panitumumab and 46% for adagrasib with cetuximab in clinical trials [67,68]. These findings provide clinical validation of combination strategies designed to overcome pathway reactivation and highlight the limitations of single-agent KRAS inhibition in tumours with strong upstream signalling dependencies, particularly CRC. In PDAC, data from the CodeBreaK100 cohort reported an ORR of 21.1% and a disease control rate (DCR) of 84.2% among 38 patients. The median PFS in this cohort was 4.0 months, with a median OS of 6.9 months [69]. KRYSTAL-1 included 21 patients with PDAC, with an ORR of 33.3%, DCR of 81%, median PFS of 5.4 months, and median OS of 8.0 months [70].

Numerous ongoing clinical trials are evaluating both sotorasib and adagrasib in alternative NSCLC settings, including first-line treatment of stage IV disease in combination with chemotherapy and/or immunotherapy, unresectable stage III disease, and as neoadjuvant therapy in stage IB-IIIA disease [71]. Additionally, both agents are being investigated across a range of $KRAS^{G12C}$-mutant malignancies, including CRC, PDAC, and other advanced solid tumours, both as monotherapies and in combination with other targeted agents, chemotherapy, and immunotherapy [72].

Collectively, these data suggest that while first-generation $KRAS^{G12C}$ inhibitors represent a major therapeutic advance, their clinical benefit as monotherapy is limited by modest durability and tumour-specific resistance mechanisms, reinforcing the need for rational combination strategies.

5.2 Resistance to $KRAS^{G12C}$ Inhibition

The limited durability of response observed with first-generation $KRAS^{G12C}$ inhibitors is largely driven by the emergence of resistance mechanisms. Intrinsic resistance can arise from co-occurring mutations that bypass KRAS dependency, leading to primary treatment failure [73]. Acquired resistance mechanisms are diverse and include RTK upregulation, secondary KRAS mutations, KRAS amplification, and activation of bypass signalling pathways [16].

A large genomic profiling study of 143 patients with $KRAS^{G12C}$-mutant NSCLC and CRC treated with first-generation $KRAS^{G12C}$ inhibitors identified secondary KRAS mutations in 25%, KRAS amplifications in 22%, RAF/MEK/ERK mutations or fusions in 21%, switch II pocket mutations in 14%, and NRAS/HRAS alterations in 8% of cases. Notably, ERK pathway reactivation was significantly more frequent in CRC (69%) than in NSCLC (26%) [74], underscoring the influence of tumour context on resistance biology and therapeutic vulnerability. Another study investigating resistance to $KRAS^{G12C}$ inhibition in CRC found that resistance-associated alterations frequently involve RTK signalling, particularly EGFR activation, as well as changes in cell cycle regulation, DNA damage response pathways, and secondary RAS mutations [75]. These findings highlight the importance of upstream signalling in mediating resistance in CRC and provide a strong rationale for combination strategies incorporating EGFR inhibition, which have demonstrated improved clinical activity in $KRAS^{G12C}$-mutant CRC [67,68].

Secondary KRAS mutations, particularly those affecting the switch II pocket (e.g., Y96D/S), directly im-

pair binding of covalent KRAS^{G12C} inhibitors and represent a key mechanism of acquired resistance [76,77]. In preclinical models, up to 87% of KRAS^{G12C} inhibitor-resistant clones harbour secondary KRAS mutations, with A59T/S, Y96D/S, and G13D among the most commonly observed [78]. These alterations have driven the development of next-generation KRAS^{G12C} inhibitors and RAS(ON)-targeted strategies designed to overcome resistance mediated by conformational changes in the target protein [12]. In addition, KRAS amplification and activation of wild-type RAS isoforms can restore downstream signalling despite effective inhibition of the mutant allele, highlighting a key limitation of allele-specific inhibition alone and supporting the development of broader pathway-targeting approaches [78,79], including pan-RAS inhibitors and upstream regulatory targets such as SHP2 and SOS1, as discussed in later sections.

Mesenchymal-epithelial transition (MET) receptor amplification has also emerged as a recurrent mechanism of acquired resistance, representing a potentially actionable target and supporting combination strategies with MET inhibitors in selected patients [80]. Additional resistance mechanisms include histologic transformation from adenocarcinoma to squamous cell carcinoma and constitutive activation of the PI3K pathway [16], further emphasising the role of pathway redundancy and tumour plasticity in limiting the efficacy of KRAS^{G12C} inhibition. These observations provide a rationale for combination strategies targeting parallel signalling pathways, although clinical translation has been constrained by toxicity in some settings [54,56].

Importantly, the mechanisms of resistance observed with KRAS^{G12C}(OFF) inhibitors reflect their dependence on the inactive GDP-bound state and their susceptibility to upstream RTK reactivation and secondary mutations affecting the switch II pocket [16]. In contrast, emerging data from pan-RAS(ON) inhibitors (discussed in Section 5.6) suggest a distinct resistance profile, characterised by increased pathway flux through KRAS amplification and signalling via wild-type RAS isoforms, rather than secondary KRAS mutations [81]. These distinctions have important implications for therapeutic strategy and rational combination design. See Fig. 2 for a summary of resistance mechanisms to KRAS inhibition.

5.3 Next Generation KRAS^{G12C} Inhibitors

Next-generation KRAS^{G12C} inhibitors have been developed to improve inhibitory potency and selectivity and are at various stages of clinical development (see Table 1). Among these, divarasib (GDC-6036) is a next-generation covalent KRAS^{G12C}(OFF) inhibitor, engineered to enhance both potency and selectivity of KRAS^{G12C} inhibition. Like sotorasib and adagrasib, it irreversibly binds to the GDP-bound conformation of KRAS^{G12C} but is reported to be 5–20 times more potent and up to 50 times more selective *in vitro*. In a phase I trial, divarasib demonstrated notable clinical activity, with an ORR of 53.4% and a median PFS of 13.1 months in patients with previously treated NSCLC. Long-term follow-up in patients treated at the 400 mg dose level revealed a notable median PFS of 15.3 months [82]. Among CRC patients, it achieved an ORR of 29.1% and a median PFS of 5.6 months [83]. The GO42144 study (NCT04449874) is now evaluating divarasib in combination with other anticancer agents, including programmed death-ligand 1 (PD-L1) inhibitors, PI3K inhibitors, bevacizumab, and cetuximab, in an attempt to overcome acquired resistance mechanisms [84]. A randomised phase III study (NCT06497556) is comparing divarasib to sotorasib or adagrasib in pretreated KRAS^{G12C}-mutated advanced NSCLC.

Most other next-generation KRAS^{G12C}(OFF) inhibitors remain in early-phase development, with ORRs in NSCLC ranging from 40–60%. For example, olomorasib (LY3537982) is a KRAS^{G12C}(OFF) inhibitor that has demonstrated an ORR of 41% in NSCLC patients previously treated with a first-generation KRAS^{G12C} inhibitor [85]. Another study evaluating olomorasib in combination with pembrolizumab across all lines of NSCLC treatment reported an ORR of 63% in 30 KRAS^{G12C} inhibitor-naïve patients, with median PFS not yet reached [86]. The ongoing SUNRAY-01 trial (NCT06119581) is assessing olomorasib in combination with pembrolizumab, with or without chemotherapy, as first-line treatment for metastatic NSCLC [87].

Opnurasib (JDQ-443) is another KRAS^{G12C}(OFF) inhibitor with a novel switch II binding mode, showing activity against several KRAS^{G12C} cell lines resistant to sotorasib and adagrasib [88]. In a phase Ib/II study, opnurasib achieved an ORR of 57% among 14 NSCLC patients treated at the recommended phase II dose (RP2D) of 200 mg twice daily [87,89]. MK-1084, also a KRAS^{G12C}(OFF) inhibitor, has shown efficacy in patients with previously treated KRAS^{G12C}-mutant solid tumours, both as monotherapy and in combination with pembrolizumab in NSCLC [90]. It has now entered a phase III trial (NCT06345729) evaluating MK-1084 with pembrolizumab as first-line treatment for NSCLC with a KRAS^{G12C} mutation and PD-L1 tumour proportion score (TPS) $\geq$50% [91].

Garsorasib (D-1553) has demonstrated a notable ORR of 50% in a phase II study including 123 patients with NSCLC previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor (ICI) [92]. In CRC, garsorasib monotherapy achieved an ORR of 19.2% in 26 patients, while garsorasib in combination with cetuximab achieved an ORR of 45.2% in 42 patients [93]. Glecirasib (JAB-21822) is another drug that has also been assessed in a phase II study in pretreated KRAS^{G12C}-mutated NSCLC patients, with a reported ORR of 47.9% and median PFS of 8.2 months in 117 patients [94]. Glecirasib has also been assessed in other solid tumours, including

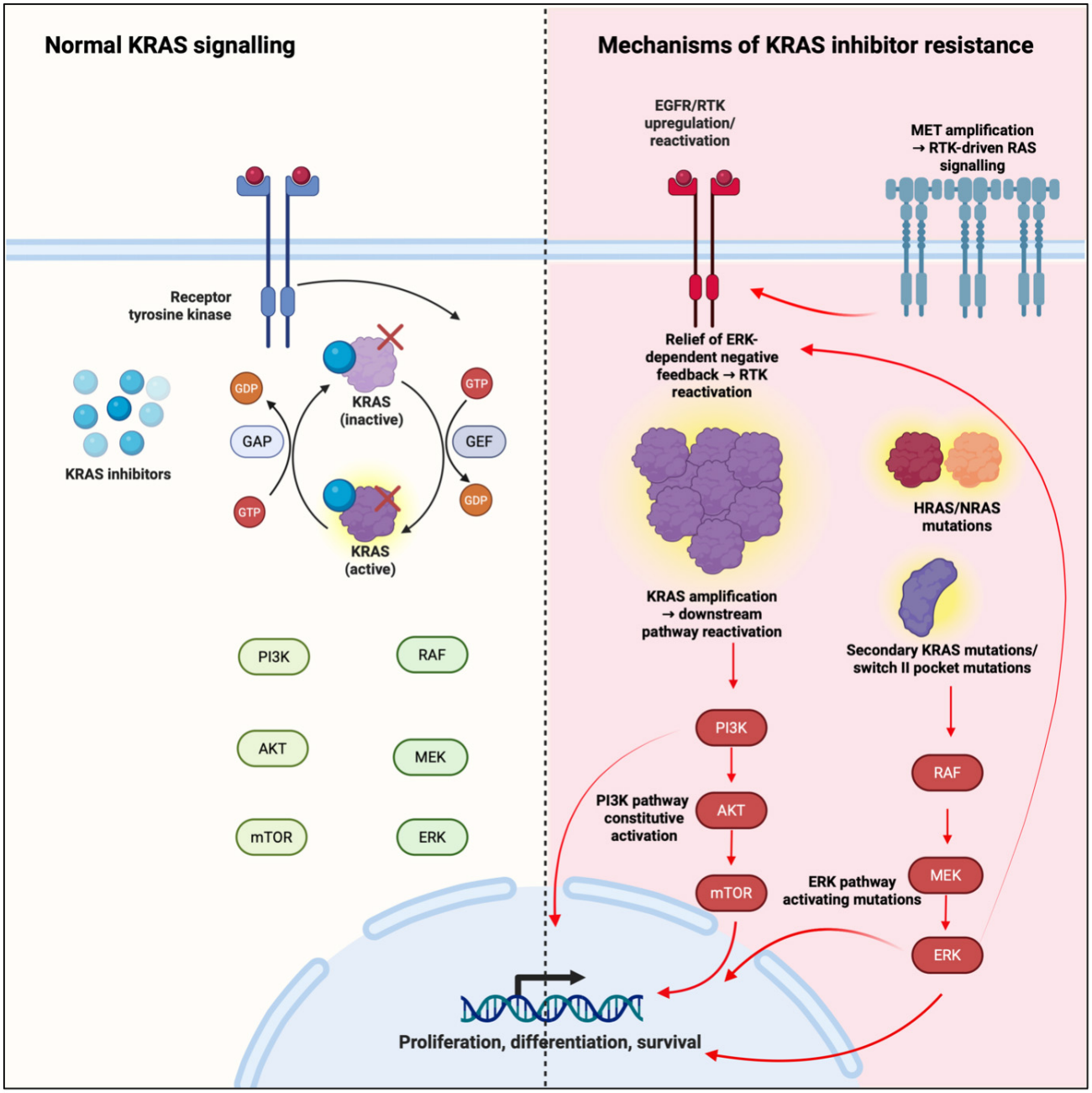

Fig. 2. Mechanisms of resistance to KRAS inhibition (created with BioRender.com). GAP, GTPase-activating protein; GDP, guanosine diphosphate; GTP, guanosine triphosphate; GEF, guanine nucleotide exchange factor; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; RAF, rapidly accelerated fibrosarcoma; MEK, MAPK/ERK kinase; ERK, extracellular signal-regulated kinase; EGFR, epidermal growth factor receptor; RTK, receptor tyrosine kinase; MET, mesenchymal-epithelial transition; HRAS, Harvey RAS oncogene homolog; NRAS, neuroblastoma RAS oncogene.

32 patients with PDAC where it demonstrated an ORR of 50.9% [95]. Other next generation $KRAS^{G12C}$(OFF) inhibitors with encouraging early-phase data include fulzerasib (IBI-351), BI-1823911, D3S-001, GEC255, and ZG19018 [84,96].

While next-generation $KRAS^{G12C}$ inhibitors demonstrate improved potency and encouraging clinical activity, it remains unclear whether they meaningfully overcome the key limitations observed with first-generation agents, particularly with respect to the durability of response. Cross-trial comparisons should be interpreted with caution, and there remains limited evidence that these improvements translate into substantially prolonged disease control. Table 1 provides a summary of investigational $KRAS^{G12C}$ inhibitors currently in clinical development.

$KRAS^{G12C}$(ON) inhibitors represent an emerging therapeutic strategy that can overcome important limitations of the existing KRAS inhibitors. Unlike KRAS(OFF)

Table 1. Investigational $KRAS^{G12C}$ inhibitors in clinical development.

Drug	Highest development phase	Cancer type(s)	Drug combinations
$KRAS^{G12C}$(OFF) inhibitors:			
Divarasib (GDC-6036)	Phase III	NSCLC, CRC, other solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed ICIs: Pembrolizumab, Atezolizumab Anti-EGFR mAb: Cetuximab Anti-VEGF mAb: Bevacizumab EGFR TKI: Erlotinib SHP2i: GDC-1971 PI3Ki: Inavolisib
Olomorasib (LY3537982)	Phase III	NSCLC, other solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed ICIs: Pembrolizumab, Durvalumab Anti-EGFR mAb: Cetuximab
Opnurasib (JDQ-443)	Phase III	NSCLC, other solid tumours	ICIs: Tislelizumab Anti-EGFR mAb: Cetuximab MEKi: Trametinib CDK4/6i: Ribociclib SHP2i: TNO155
MK-1084	Phase III	NSCLC, CRC, other solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed, 5-fluorouracil, Leucovorin, Oxaliplatin, ICIs: Pembrolizumab Anti-EGFR mAb: Cetuximab Anti-VEGF mAb: Bevacizumab SHP2i: MK-0472
Garsorasib (D-1553)	Phase III	NSCLC, other solid tumours	Chemotherapy: Docetaxel ICIs: Pembrolizumab Anti-EGFR mAb: Cetuximab SHP2i: GH21 FAKi: IN10018
Glecirasib (JAB-21822)	Phase III	NSCLC, CRC, other solid tumours	Anti-EGFR mAb: Cetuximab Anti-VEGF mAb: Bevacizumab SHP2i: JAB-3312
Fulzerasib (IBI-351/GFH925)	Phase II	NSCLC, CRC	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed, 5-fluorouracil, Leucovorin, Irinotecan ICIs: Sintilimab Anti-EGFR mAb: Cetuximab Anti-VEGF/PD-1 bispecific: Ivonescimab
HRS-7058	Phase II	Advanced solid tumours	Chemotherapy: Platinum-containing doublet ICIs: SHR-1316 Anti-EGFR mAb: Cetuximab Anti-MET ADC: SHR-1826
D3S-001	Phase I/II	Advanced solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed ICIs: Pembrolizumab Anti-EGFR mAb: Cetuximab
ZG19018	Phase I/II	Advanced solid tumours	NA
YL-15293	Phase I/II	Advanced solid tumours	NA

Table 1. Continued.

Drug	Highest development phase	Cancer type(s)	Drug combinations
HS-10370	Phase I/II	Advanced solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed, 5-fluorouracil, Leucovorin, Oxaliplatin, Irinotecan, Capecitabine ICIs: Adebrelimab Anti-EGFR/MET bispecific: HS-20117 Anti-B7-H3 ADC: HS-20093
SY-5933	Phase I/II	Advanced solid tumours	Multi-kinase inhibitor: Conleltinib (CT-707)
HYP-2090PTSA	Phase I/II	Advanced solid tumours	NA
HBI-2438	Phase I	Advanced solid tumours	NA
BI-1823911	Phase I	Advanced solid tumours	SOS1i: BI 1701963
GEC255	Phase I	Advanced solid tumours	NA
JMKX001899	Phase I	NSCLC	Chemotherapy: Carboplatin, Pemetrexed FAKi: IN10018
BEBT-607	Phase I	Advanced solid tumours	NA
KQB365	Phase I	Advanced solid tumours	Anti-EGFR mAb: Cetuximab
BPI-421286	Phase I	Advanced solid tumours	NA
GH35	Phase I	Advanced solid tumours	NA
$KRAS^{G12C}$(ON) inhibitors:			
Elironrasib (RMC-6291)	Phase I/II	NSCLC, other solid tumours	Pan-RASi: Daraxonrasib
$KRAS^{G12C}$(ON/OFF) inhibitors:			
FMC-376	Phase I/II	Advanced solid tumours	NA
BBO-8520	Phase I	NSCLC	ICIs: Pembrolizumab

*Phase classification refers to the most advanced stage of clinical evaluation publicly reported as of November 2025. Many agents are in multiple trials across different settings, tumour types, and lines of therapy.

*ADC, antibody-drug conjugate; Anti-EGFR mAb, anti-epidermal growth factor receptor monoclonal antibody; Anti-VEGF mAb, anti-vascular endothelial growth factor monoclonal antibody; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; FAKi, focal adhesion kinase inhibitor; MEKi, MEK inhibitor; NA, not applicable/no publicly reported combinations; Pan-RASi, pan-RAS inhibitor; PI3Ki, PI3K inhibitor; SHP2i, SHP2 inhibitor; SOS1i, SOS1 inhibitor.

inhibitors, KRAS(ON) inhibitors are designed to target its active, GTP-bound conformation. Elironrasib (RMC-6291) is a $KRAS^{G12C}$(ON) inhibitor that forms a tri-complex with GTP-bound $KRAS^{G12C}$ and the cellular chaperone protein cyclophilin A (CyPA), thereby blocking effector binding and preventing downstream signal transduction. Preliminary data from an ongoing phase I study have demonstrated promising clinical activity in patients who have progressed on first-generation $KRAS^{G12C}$ inhibitors, with an ORR of 42% [97,98]. RM-018 is another tri-complex, $KRAS^{G12C}$(ON) inhibitor that appears capable of overcoming resistance driven by secondary KRAS mutations, including the Y96D alteration [77]. In addition, FMC-376 and BBO-8520 are novel $KRAS^{G12C}$(ON/OFF) inhibitors that can bind both the active and inactive conformations, potentially addressing both intrinsic and acquired resistance to current KRAS(OFF) therapies [99,100]. However, clinical data remain early, and it is not yet established whether $KRAS^{G12C}$(ON) inhibition will result in more durable pathway suppression or simply shift the spectrum of resistance mechanisms.

5.4 Allele-Specific Inhibitors Beyond G12C

While G12C mutations are relatively common in NSCLC, they represent only a minority of KRAS mutations in CRC and PDAC, where G12D and G12V predominate. Unlike G12C, these variants lack a reactive cysteine residue, making them more challenging to target with covalent inhibitors. As a result, no $KRAS^{G12D}$ or $KRAS^{G12V}$-selective inhibitors have yet been approved for clinical use. However, using the lessons learned from the development of $KRAS^{G12C}$ inhibitors, recent preclinical advances have

led to the development of allele-specific inhibitors for these variants, several of which are now progressing through early-phase clinical trials.

$KRAS^{G12D}$ has been particularly challenging to target due to the negatively charged aspartic acid residue, which disrupts the binding of small molecules at the switch II pocket [101]. MRTX1133, a non-covalent and selective $KRAS^{G12D}$(OFF) inhibitor, demonstrated promising preclinical efficacy in PDAC and CRC models. It binds the inactive, GDP-bound form of $KRAS^{G12D}$ with high affinity, effectively suppressing ERK signalling and inducing tumour regression in xenograft models [102,103,104]. Preclinical studies also suggested synergy between MRTX1133 and 5-fluorouracil (5-FU) chemotherapy in PDAC and CRC cell lines [105]. However, early evidence of acquired resistance has already been observed *in vitro* [106], and clinical evaluation of MRTX1133 in a phase I trial was terminated due to high pharmacokinetic (PK) variability [107]. This highlights a key translational challenge in targeting $KRAS^{G12D}$, where achieving adequate and consistent drug exposure can be difficult *in vivo*, potentially limiting effective pathway suppression and underscoring the need for improved drug design and optimisation. LY3962673 is another non-covalent $KRAS^{G12D}$(OFF) inhibitor that has shown robust anti-tumour activity in preclinical models [108], and has now entered an early-phase clinical trial (NCT06586515) as a monotherapy and in combination with other anticancer therapies in advanced $KRAS^{G12D}$-mutated solid tumours [109].

G12D-specific KRAS(ON) inhibitors are also under clinical investigation. Zoldonrasib (RMC-9805) is a selective $KRAS^{G12D}$(ON) tri-complex inhibitor that forms a stable complex with GTP-bound $KRAS^{G12D}$ and CyPA, thereby preventing effector binding and downstream signalling. In a phase I/Ib study involving patients with pretreated $KRAS^{G12D}$-mutant solid tumours, zoldonrasib demonstrated encouraging preliminary activity, with an ORR of 61% among 18 patients with NSCLC and 30% among 40 patients with PDAC [110,111]. Notably, a reduction in circulating tumour DNA (ctDNA) of greater than 50% was observed in 86% of PDAC patients [111].

$KRAS^{G12D}$(ON/OFF) inhibitors represent another promising therapeutic strategy. HRS-4642 is a long-acting, non-covalent $KRAS^{G12D}$(ON/OFF) inhibitor that disrupts the interaction of GDP-bound $KRAS^{G12D}$ with SOS1 and the GTP-bound form with RAF, thereby blocking downstream MEK-ERK signalling [112]. It is currently being evaluated in early-phase trials, with preliminary data showing anti-tumour activity and a tolerable safety profile [113]. Recently presented data evaluating HRS-4642 in combination with gemcitabine and nab-paclitaxel as first-line treatment for metastatic PDAC reported an ORR of 63.3% and a 6-month PFS rate of 89.3%, although a significant rate of grade ≥3 haematological toxicity was observed [114]. Median PFS data remain immature, so the durability of response is not yet known. However, these early results provide proof-of-concept that combining $KRAS^{G12D}$ inhibitors with first-line chemotherapy is feasible and may reduce tumour heterogeneity and delay the emergence of acquired resistance.

GFH375 is another $KRAS^{G12D}$(ON/OFF) inhibitor that has demonstrated greater potency than MRTX1133 and zoldonrasib in reducing RAF-bound $KRAS^{G12D}$ and inhibiting proliferation in preclinical models [115]. It has also shown efficacy in intracranial tumour models [115] and is under evaluation in early-phase trials, where it has demonstrated encouraging anti-tumour activity with favourable tolerability [116]. In a cohort of 59 patients with pretreated metastatic PDAC, an ORR of 40.7% and DCR of 96.7% was observed with GFH375 monotherapy. Of note, the majority of patients included in this study had received at least two prior lines of chemotherapy [117]. Other $KRAS^{G12D}$(ON/OFF) inhibitors include INCB161734, which potently inhibits SOS1-dependent GDP/GTP exchange and has demonstrated efficacy in multiple PDAC and CRC xenograft models [118], and TSN1611 which has shown early efficacy in a first-in-human phase I/II trial (NCT06385925) involving patients with treatment-refractory solid tumours [119]. Table 2 provides a summary of investigational $KRAS^{G12D}$ inhibitors currently in clinical development.

Direct targeting of other KRAS alleles remains less advanced, with most agents still in preclinical or early translational development. RMC-048, a $KRAS^{G12V}$(ON)-selective inhibitor, has induced tumour regression in xenograft models [120]. RMC-5127 has also shown potent *in vitro* activity and evidence of CNS penetration in murine models [121], while JAB-23000 represents another $KRAS^{G12V}$-selective inhibitor currently under preclinical investigation [122]. In addition, QTX3544, a multi-KRAS inhibitor with enhanced selectivity for G12V, has demonstrated preclinical favourable activity and has recently entered phase I clinical evaluation (NCT06715124) [123].

$KRAS^{G13D}$ accounts for approximately 15% of KRAS mutations in CRC but has not yet been successfully targeted with a direct inhibitor. CSC01, identified through *in silico* modelling, has shown early promise as a selective $KRAS^{G13D}$ inhibitor [124]. Interestingly, retrospective analyses have suggested that patients with $KRAS^{G13D}$ mutations may derive modest benefit from anti-EGFR therapies, representing a notable exception compared with other KRAS mutations, which are typically associated with resistance [31]. RMC-8839, a tri-complex $KRAS^{G13C}$(ON) inhibitor, has demonstrated activity in preclinical models and is advancing toward clinical evaluation [125]. Preclinical studies have also suggested synergy between RMC-8839 and taxane chemotherapy in NSCLC models [126].

Finally, mutations at codon Q61 (e.g., Q61H, Q61L, Q61R) are less common in KRAS than other RAS isoforms but occur more frequently in NRAS-driven melanomas and

Table 2. Investigational $KRAS^{G12D}$ inhibitors in clinical development.

Drug	Highest development phase	Cancer type(s)	Drug combinations
$KRAS^{G12D}$(OFF) inhibitors:			
LY3962673	Phase I	Advanced solid tumours	Chemotherapy: 5-fluorouracil, Leucovorin, Oxaliplatin, Irinotecan, Gemcitabine, Nab-paclitaxel Anti-EGFR mAb: Cetuximab
QTX3046	Phase I	Advanced solid tumours	Anti-EGFR mAb: Cetuximab
$KRAS^{G12D}$(ON) inhibitors:			
Zoldonrasib (RMC-9805)	Phase I/II	NSCLC, PDAC, and advanced solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed, 5-fluorouracil, Leucovorin, Oxaliplatin, Irinotecan, Gemcitabine, nab-paclitaxel ICIs: Pembrolizumab Anti-EGFR mAb: Cetuximab Anti-VEGF mAb: Bevacizumab Pan-RASi: Daraxonrasib PRMT5i: TNG462
$KRAS^{G12D}$(ON/OFF) inhibitors:			
HRS-4642	Phase II	PDAC, biliary tract cancer, advanced solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed, Gemcitabine, Nab-paclitaxel ICIs: Adebrelimab Anti-EGFR mAb: Nimotuzumab Anti-EGFR/MET bispecific: SHR-9839 CLDN18.2 ADC: SHR-A1904 HER2 ADC: SHR-A1811 Nectin-4 ADC: SHR-A2102
GFH375	Phase II	PDAC, advanced solid tumours	NA
TSN1611	Phase I/II	Advanced solid tumours	NA
AZD0022	Phase I/II	Advanced solid tumours	Anti-EGFR mAb: Cetuximab
INCB161734	Phase I	Advanced solid tumours	Chemotherapy: 5-fluorouracil, Leucovorin, Oxaliplatin, Irinotecan, Gemcitabine, Nab-paclitaxel ICIs: Retifanlimab Anti-EGFR mAb: Cetuximab Anti-PD-1/TGFβR2 bispecific: INCA33890
GDC-7035	Phase I	Advanced solid tumours	NA
$KRAS^{G12D}$ inhibitors with mechanism of action not yet reported:			
KQB548	Phase I	Advanced solid tumours	NA
INCB186748	Phase I	Advanced solid tumours	Chemotherapy: 5-fluorouracil, Leucovorin, Oxaliplatin, Irinotecan, Gemcitabine, Nab-paclitaxel Anti-EGFR mAb: Cetuximab
HRS-6093	Phase I	Advanced solid tumours	NA
HS-10529	Phase I	Advanced solid tumours	NA
QLC1101	Phase I/II	Advanced solid tumours	Chemotherapy: Docetaxel ICIs: QL2107, QL1706 Anti-EGFR mAb: QL1203

*Phase classification refers to the most advanced stage of clinical evaluation publicly reported as of November 2025. Many agents are in multiple trials across different settings, tumour types, and lines of therapy.

*ADC, antibody-drug conjugate; Anti-EGFR mAb, anti-epidermal growth factor receptor monoclonal antibody; Anti-VEGF mAb, anti-vascular endothelial growth factor monoclonal antibody; CLDN18.2, claudin-18.2; NA, not applicable/no publicly reported combinations; Pan-RASi, pan-RAS inhibitor; PRMT5i, protein arginine methyltransferase 5 inhibitor; TGF-βR2, transforming growth factor-β receptor type 2.

haematologic malignancies. Like G12 and G13 mutations, Q61 alterations impair intrinsic GTPase activity and reduce sensitivity to GAP-mediated hydrolysis, resulting in persistent activation of the GTP-bound state [127]. RM-047 is a preclinical Q61H-selective RAS(ON) inhibitor that has demonstrated efficacy in PDAC cell lines [128], while RMC-0708 is also under preclinical development [129].

Collectively, these data highlight the rapid expansion of allele-specific KRAS targeting beyond G12C, with multiple strategies demonstrating promising early clinical activity. However, most data remain preliminary, with small patient numbers, immature survival outcomes, and limited understanding of resistance mechanisms. It is not yet clear whether these agents will achieve durable disease control as monotherapies or, similar to first-generation $KRAS^{G12C}$ inhibitors, will require rational combination strategies to overcome adaptive pathway reactivation and tumour heterogeneity.

5.5 Pan-KRAS Inhibitors

Despite the success of allele-specific inhibitors, the heterogeneity of KRAS mutations across cancer types has prompted the development of broader strategies, such as pan-KRAS and pan-RAS inhibitors, to bypass allele specificity altogether.

Among the most advanced preclinical agents, BI-2865 is a non-covalent KRAS(OFF) inhibitor that preferentially binds the inactive form of KRAS, while sparing HRAS and NRAS. It inhibits nucleotide exchange and blocks activation of 18 of the 24 most common KRAS mutants, including G12C/D/V, G13C/D, and Q61H. Its activity against $KRAS^{G12C}$ is comparable to that of sotorasib [130]. BI-2493, a structural analogue of BI-2865 optimised for *in vivo* use, has demonstrated similar potency [131].

LY4066434 is another highly potent pan-KRAS inhibitor with broad activity in patient-derived xenograft (PDX) models of NSCLC, PDAC, CRC, and gastric cancer, including intracranial metastasis models. In PDX models, its combination with cetuximab and chemotherapy has demonstrated enhanced efficacy across various KRAS mutations [132]. To date, the most advanced pan-KRAS inhibitor is BBO-11818, a non-covalent pan-KRAS(ON/OFF) inhibitor currently in early clinical development, with activity against multiple mutants, including $KRAS^{G12D}$ and $KRAS^{G12V}$. It has shown strong antitumour activity in preclinical NSCLC, CRC, and PDAC models, and appears to provide additional benefit when combined with cetuximab or anti-programmed death-1 (PD-1) therapies [133]. BBO-11818 is currently being evaluated in a first-in-human phase I trial as monotherapy and in combination with cetuximab or pembrolizumab (with or without chemotherapy) (NCT06917079), which will provide initial safety, tolerability, and preliminary efficacy data for this emerging drug class.

5.6 Pan-RAS Inhibitors

Another family of compounds under investigation has been developed to inhibit all RAS isoforms, known as pan-RAS inhibitors. These agents are currently at various stages of development, but several examples suggest that they could represent important additions to the therapeutic armamentarium targeting RAS-driven cancers. Notably, rather than directly targeting specific mutant alleles, many pan-RAS inhibitors have been developed to disrupt critical protein-protein interactions, either by preventing RAS engagement with regulatory factors required for its activation or by blocking interactions with key downstream effector proteins.

The most advanced compound is daraxonrasib (RMC-6236), a tri-complex RAS(ON) inhibitor that targets a broad range of mutations across classical RAS isoforms, including select NRAS and HRAS mutations. It functions by forming a tri-complex with RAS and CyPA, thereby preventing downstream signal activation. In preclinical models of NSCLC, PDAC, and CRC, daraxonrasib has demonstrated activity across KRAS mutations [134]. It has also shown efficacy in models resistant to first-generation $KRAS^{G12C}$ inhibitors, including those harbouring secondary NRAS mutations, wild-type KRAS amplification, or RTK amplifications [135]. Additionally, daraxonrasib appears to synergise with ICIs, producing durable responses in preclinical models [134]. In preliminary data from a phase I trial involving 40 patients with previously treated RAS-mutated NSCLC, daraxonrasib demonstrated an ORR of 38% with a median duration of response of 15.1 months, median PFS of 6.8 months, and median OS of 17.7 months [136]. It has also shown encouraging activity in a phase I study involving pretreated PDAC, reporting an ORR of 36%, a median PFS of 8.8 months, and a median OS not yet reached in $KRAS^{G12X}$-mutated cancers treated at the 300 mg dose level. The phase III RASolute 302 trial is currently ongoing in patients with pretreated PDAC, comparing daraxonrasib to the investigator's choice of chemotherapy [137].

Unfortunately, although clinical experience remains limited, resistance to daraxonrasib also appears to emerge in treated patients. As previously mentioned, resistance to daraxonrasib appears distinct from that observed with $KRAS^{G12C}$(OFF) inhibitors. In an analysis of paired pre- and end-of-treatment ctDNA from 44 PDAC patients treated with daraxonrasib for over three months, no acquired secondary KRAS mutations were detected. Instead, KRAS mutant allele amplification emerged as the most frequent alteration, occurring in 36% of patients. Additional resistance mechanisms included mutations in RTKs and ERK/PI3K pathway components, human epidermal growth factor (HER2) overexpression, and *MYC* amplification [81].

In resistant PDAC models, combination treatment with daraxonrasib and trastuzumab deruxtecan or amivan-

tamab induced deep and durable tumour regressions [81], highlighting the potential of rational combination strategies to overcome adaptive resistance. In particular, dual RAS(ON) inhibitor doublets, combining a pan-RAS inhibitor with an allele-specific KRAS inhibitor, represent a promising strategy to deepen pathway suppression and overcome resistance. In preclinical PDAC models, combination therapy with daraxonrasib and the $KRAS^{G12D}$-selective inhibitor zoldonrasib reversed acquired resistance to pan-RAS inhibition. This regimen not only restored tumour sensitivity in previously resistant models but also extended PFS in $KRAS^{G12D}$ allograft models and enhanced ERK inhibition [81].

Similar synergy has been observed in KRAS-mutant CRC, where doublet therapy with daraxonrasib and either zoldonrasib (G12D-selective) or elironrasib (G12C-selective) improved the depth and durability of responses in PDX models compared with monotherapy, achieving ORRs of 40–76% and DCRs up to 100% [138]. In NSCLC, the daraxonrasib-elironrasib combination induced deep and durable regressions in PDX models, including those resistant to $KRAS^{G12C}$(OFF) inhibitors. Mechanistically, this was achieved by simultaneous inhibition of both mutant and wild-type RAS isoforms [139]. Clinical evaluation of this doublet in combination with pembrolizumab is now underway in first-line metastatic $KRAS^{G12C}$-mutant NSCLC (NCT06162221).

RMC-7977, which shares a similar mechanism of action as daraxonrasib, has shown encouraging preclinical activity but has not yet entered clinical studies [140]. TEB-17231, another multi-RAS inhibitor, has demonstrated robust anti-tumour activity in both *in vitro* and *in vivo* models of various KRAS, NRAS, and HRAS mutations, and can overcome resistance to first-generation $KRAS^{G12C}$ inhibitors [141].

A different strategy was used to develop LUNA18, a pan-RAS(OFF) inhibitor that binds both mutant and wild-type RAS, disrupting interactions between inactive RAS and GEFs such as SOS1. In $KRAS^{G12C}$-mutant cell lines, combination treatment with LUNA18 and a $KRAS^{G12C}$ inhibitor resulted in more potent suppression of cell proliferation than either agent alone. This enhanced efficacy is thought to arise from LUNA18's ability to counteract ERK pathway reactivation driven by wild-type RAS, a known mechanism of resistance to $KRAS^{G12C}$ inhibitors. In xenograft models, the addition of LUNA18 significantly delayed or prevented the emergence of resistance to $KRAS^{G12C}$ inhibitor monotherapy [142].

BBO-10203 is a novel small molecule that uses an alternative approach, as it covalently binds to the RAS-binding domain of PI3K, thereby blocking its activation by RAS isoforms, including KRAS, HRAS, and NRAS. In preclinical studies, BBO-10203 has demonstrated potent inhibition of PI3K signalling in tumours harbouring *KRAS* or *PIK3CA* mutations, as well as those with HER2 overexpression. In $KRAS^{G12X}$-mutant cell lines, its anti-tumour activity was comparable to that of daraxonrasib [143]. VVD-159642 is an optimised analogue of BBO-10203 that has advanced into clinical evaluation in a phase I trial, both as a monotherapy and in combination with either sotorasib or trametinib, in patients with advanced solid tumours (NCT06804824). Table 3 summarises pan-KRAS and pan-RAS inhibitors currently in clinical development.

Collectively, pan-KRAS and pan-RAS inhibitors represent a significant conceptual advance by enabling broader suppression of RAS signalling across multiple mutant and wild-type isoforms. Early clinical data with agents such as daraxonrasib suggest encouraging activity across tumour types and resistance settings, including those refractory to $KRAS^{G12C}$ inhibition. However, these approaches also introduce new challenges, including toxicity related to inhibition of wild-type RAS signalling and the emergence of alternative resistance mechanisms driven by pathway amplification and parallel signalling networks. As such, while pan-RAS strategies may overcome some limitations of allele-specific inhibition, their optimal role will likely depend on rational combination approaches and careful patient selection.

6. KRAS Degraders

Proteolysis-targeting chimeras (PROTACs) represent a novel therapeutic strategy that enables the selective degradation of intracellular proteins by hijacking the cell's ubiquitin-proteasome system. Unlike traditional inhibitors that transiently block enzymatic activity, PROTACs are heterobifunctional molecules that simultaneously bind the target protein (e.g., KRAS) and an E3 ubiquitin ligase, promoting ubiquitination and subsequent proteasomal degradation of the target [144]. This catalytic mode of action offers the potential for sustained suppression of KRAS protein function, even in cases where mutation-specific inhibition is less effective. However, their relatively large molecular size and physicochemical properties often necessitate intravenous administration and may limit tissue penetration.

ASP3082 is the most clinically advanced KRAS degrader and the first PROTAC targeting $KRAS^{G12D}$ to enter human trials. ASP3082 links a $KRAS^{G12D}$-binding moiety to a ligand that recruits the E3 ubiquitin ligase cereblon. In preclinical models, ASP3082 induced selective degradation of $KRAS^{G12D}$ while sparing wild-type KRAS, leading to potent downstream ERK pathway inhibition and tumour regression in xenograft models of PDAC, CRC, and NSCLC. In a first-in-human phase I study (NCT05703891), ASP3082 is being evaluated in patients with advanced solid tumours harbouring $KRAS^{G12D}$ mutations. Preliminary results in 98 patients, including those with PDAC, CRC, NSCLC, and other $KRAS^{G12D}$-mutant malignancies, revealed limited efficacy for lower dose levels, although an ORR of 33% and a DCR of 75% at the highest dose level, with a favourable safety profile [145].

Table 3. Pan-KRAS and Pan-RAS inhibitors in clinical development.

Drug	KRAS target	Highest phase	Cancer type(s)	Drug combinations
Daraxonrasib (RMC-6236)	Pan-RAS(ON)	Phase III	PDAC, NSCLC, GI solid tumours, advanced solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed, 5-fluorouracil, Leucovorin, Oxaliplatin, Irinotecan, Gemcitabine, Nab-paclitaxel, Docetaxel ICIs: Pembrolizumab Anti-EGFR mAb: Cetuximab Anti-VEGF mAb: Bevacizumab $KRAS^{G12C}$i: Elironrasib $KRAS^{G12D}$i: Zoldonrasib PRMT5i: TNG462, AMG193
JAB-23E73	Pan-KRAS (ON/OFF)	Phase I/II	Advanced solid tumours	Monotherapy
BBO-11818	Pan-KRAS	Phase I	Advanced solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed ICIs: Pembrolizumab Anti-EGFR mAb: Cetuximab
BGB-53038	Pan-KRAS	Phase I	Advanced solid tumours	ICIs: Tislelizumab Anti-EGFR mAb: Cetuximab
PF-07934040	Pan-KRAS	Phase I	Advanced solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed, 5-fluorouracil, Leucovorin, Oxaliplatin, Gemcitabine, Nab-paclitaxel, Paclitaxel ICIs: Pembrolizumab, Sasanlimab Anti-EGFR mAb: Cetuximab Anti-VEGF mAb: Bevacizumab
PF-07985045	Pan-KRAS	Phase I	Advanced solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed, 5-fluorouracil, Leucovorin, Oxaliplatin, Gemcitabine, Nab-paclitaxel, Paclitaxel ICIs: Pembrolizumab Anti-EGFR mAb: Cetuximab Anti-VEGF mAb: Bevacizumab SHP2i: PF-07284892
BBO-10203	RAS-PI3Kα	Phase I	Advanced solid tumours	Chemotherapy: 5-fluorouracil, Leucovorin, Oxaliplatin Anti-HER2 mAb: Trastuzumab Anti-VEGF mAb: Bevacizumab CDK4/6i: Ribociclib
LY4066434	Pan-KRAS	Phase I	Advanced solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed, 5-fluorouracil, Leucovorin, Oxaliplatin, Irinotecan, Gemcitabine, Nab-paclitaxel ICIs: Pembrolizumab Anti-EGFR mAb: Cetuximab
VVD-159642	RAS-PI3Kα	Phase I	Advanced solid tumours	$KRAS^{G12C}$i: Sotorasib MEKi: Trametinib
QTX3034	Multi-KRAS (**G12D(OFF)** selectivity)	Phase I	Advanced solid tumours	Anti-EGFR mAb: Cetuximab
QTX3544	Multi-KRAS (**G12V** selectivity)	Phase I	Advanced solid tumours	Anti-EGFR mAb: Cetuximab

*Phase classification refers to the most advanced stage of clinical evaluation publicly reported as of November 2025. Many agents are in multiple trials across different settings, tumour types, and lines of therapy.

*Anti-EGFR mAb, anti-epidermal growth factor receptor monoclonal antibody; Anti-VEGF mAb, anti-vascular endothelial growth factor monoclonal antibody; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; $KRAS^{G12C}$i, $KRAS^{G12C}$ inhibitor; $KRAS^{G12D}$i, $KRAS^{G12D}$ inhibitor; MEKi, MEK inhibitor; NA, not applicable/no publicly reported combinations; PRMT5i, protein arginine methyltransferase 5 inhibitor; SHP2i, SHP2 inhibitor.

Table 4. KRAS degraders currently in clinical development.

Drug	KRAS target	Highest phase	Cancer type(s)	Drug combinations
ARV-806	$KRAS^{G12D}$	Phase I/II	Advanced solid tumours	NA
RNK-08954	$KRAS^{G12D}$	Phase I/II	Advanced solid tumours	NA
ASP3082	$KRAS^{G12D}$	Phase I	Advanced solid tumours	Chemotherapy: Carboplatin, Cisplatin, Pemetrexed, 5-fluorouracil, Leucovorin, Oxaliplatin, Irinotecan, Gemcitabine, Nab-paclitaxel, Docetaxel ICIs: Pembrolizumab Anti-EGFR mAb: Cetuximab
ASP4396	$KRAS^{G12D}$	Phase I	Advanced solid tumours	NA
ASP5834	Pan-KRAS	Phase I	Advanced solid tumours	Anti-EGFR mAb: Panitumumab

*Anti-EGFR mAb, anti-epidermal growth factor receptor monoclonal antibody; NA, not applicable/no publicly reported combinations.

Other $KRAS^{G12D}$-specific PROTACs in early-phase clinical development include ASP4396 (NCT06364696), ARV-806 (NCT07023731), and RNK-08954 (NCT06667544).

In addition, pan-KRAS degraders are also under investigation. ASP5834 is the first such agent to enter human trials (NCT07094204) and is designed to degrade multiple KRAS variants, including G12D, G12V, and G12C, via a mutation-agnostic mechanism. In the preclinical setting, YN14 is a $KRAS^{G12C}$-directed PROTAC that has demonstrated efficacy in cell-based assays and xenograft models, promoting selective $KRAS^{G12C}$ degradation and suppression of downstream ERK signalling. However, its clinical development has been limited due to PK constraints [146]. Table 4 summarises KRAS degraders currently in clinical development.

Collectively, KRAS degraders represent a promising alternative to conventional inhibition by enabling sustained suppression of KRAS protein levels. However, early clinical experience suggests that achieving sufficient target degradation while maintaining favourable PKs and tolerability remains challenging. In addition, the extent to which degradation of mutant KRAS alone is sufficient to overcome pathway redundancy, particularly in tumours where pathway reactivation and wild-type RAS signalling limit the efficacy of allele-specific inhibitors, is not yet fully understood. As such, similar to other KRAS-targeting strategies, the future success of KRAS degraders will likely depend on optimisation of drug design and rational combination approaches.

7. Indirect RAS Inhibition & Targeting RAS Regulators

Although direct inhibition of RAS proteins has gained momentum, several therapeutic strategies remain focused on targeting upstream regulators and accessory proteins that control RAS activation and signalling.

7.1 SOS1 Inhibitors

SOS1 is a GEF that catalyses the exchange of GDP for GTP on RAS, switching it to its active state (see Figs. 2,3). Inhibition of SOS1 impairs activation of wild-type and mutant RAS isoforms, potentially across multiple alleles. Furthermore, SOS1 inhibition may delay or prevent resistance to KRAS inhibitors by blocking compensatory feedback reactivation of upstream signalling pathways [96]. This is particularly relevant in tumours where RTK-mediated feedback reactivation and wild-type RAS signalling drive resistance to allele-specific KRAS inhibitors, providing a strong rationale for combining SOS1 inhibitors with direct KRAS-targeted therapies.

MRTX0902 is the most clinically advanced SOS1 inhibitor, designed to allosterically disrupt the SOS1-KRAS interaction. In preclinical models, it demonstrated robust suppression of ERK signalling and tumour growth, both as monotherapy and in combination with sotorasib or adagrasib [147]. It is currently being evaluated in a phase I/II clinical trial for patients with KRAS-mutant solid tumours (NCT05578092).

BI-1701963 is a pan-KRAS-SOS1 interaction inhibitor that binds directly to SOS1. It has demonstrated preclinical activity across a wide spectrum of *KRAS* mutations, including G12D and G13D. Although an early study combining BI-1701963 with adagrasib was terminated due to toxicity [148], the compound is now under investigation in a new combination study with BI-1823911, a next-generation $KRAS^{G12C}$(OFF) inhibitor (NCT04973163). BI-3406 is another SOS1 inhibitor with potent anti-tumour activity. It has shown the ability to overcome secondary $KRAS^{Y96D/S}$ mutations that confer resistance to G12C inhibitors, particularly in combination with adagrasib [149] or trametinib [76].

Other SOS1-targeted agents in development include ZG2001 and BAY3498264, which have entered phase I clinical trials (NCT06237413/ NCT06659341), and BAY0293 and RMC-5845, which have demonstrated promising preclinical activity [96].

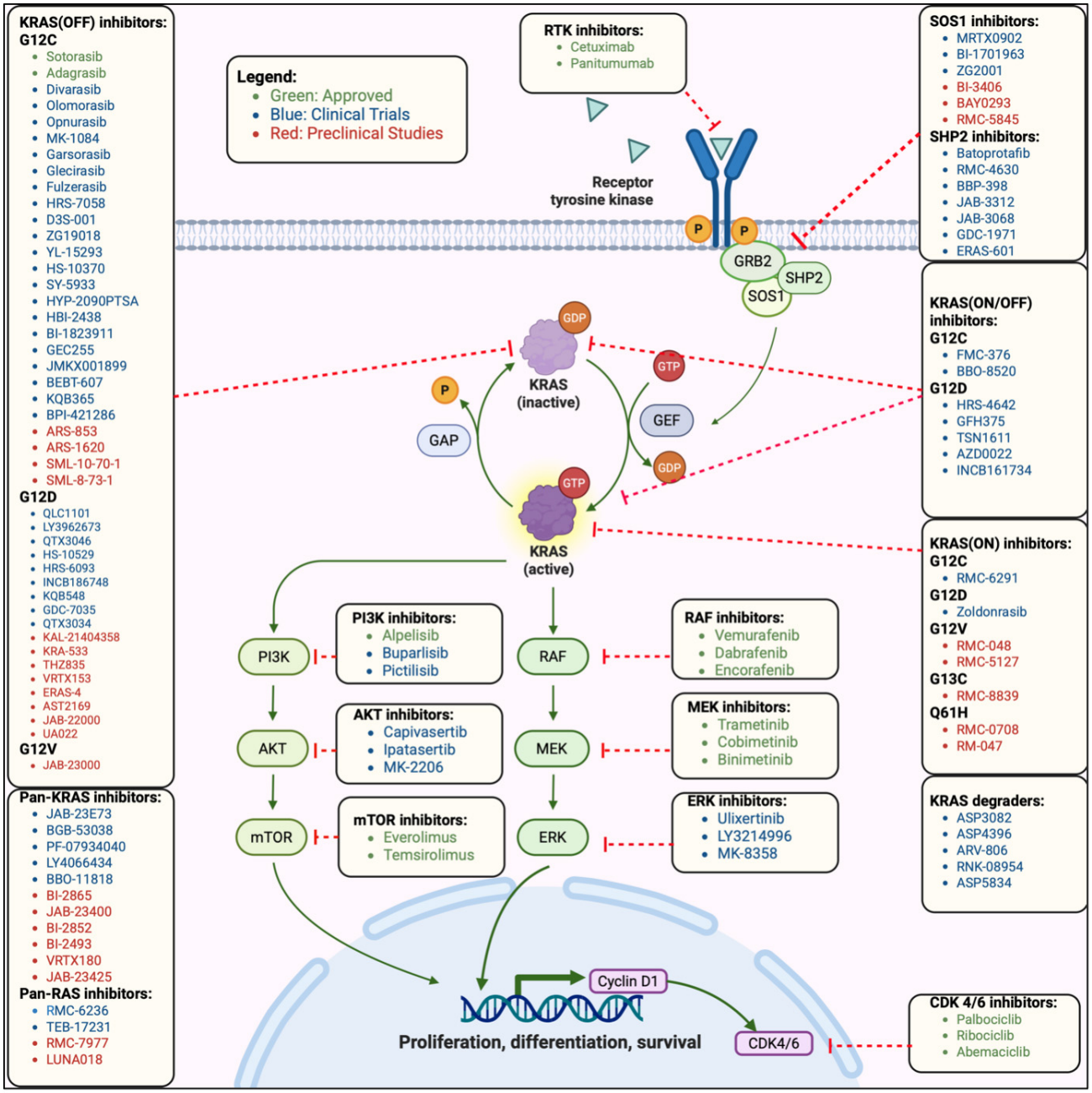

Fig. 3. Overview of therapeutic strategies targeting KRAS and its regulatory pathways (created with BioRender.com). *Direct KRAS inhibitors (OFF, ON, and ON/OFF), KRAS degraders, upstream regulators (RTKs, Son of Sevenless 1 (SOS1), Src homology-2 domain-containing phosphatase (SHP2)), and downstream signalling cascades (RAF/MEK/ERK, PI3K/AKT/mTOR, and CDK4/6) are shown. Compounds are colour-coded based on development stage: green (approved), blue (in clinical trial), and red (preclinical).

7.2 SHP2 Inhibitors

SHP2 is a non-receptor protein tyrosine phosphatase that plays a pivotal role in transmitting signals from RTKs to RAS by facilitating activation of SOS1. Specifically, SHP2 promotes the formation of the GRB2-SOS1 complex, enhancing GDP-GTP exchange on RAS and enabling its activation. As a central upstream regulator of RAS, SHP2 is a compelling therapeutic target in KRAS-mutant cancers [22]. Importantly, SHP2 inhibition may suppress both mutant and wild-type RAS activation, thereby mitigating adaptive resistance driven by RTK signalling and pathway reactivation. However, given the central role of SHP2 in normal cellular signalling, clinical development has been associated with dose-limiting toxicities, which may constrain the therapeutic window and necessitate combination strategies at lower, tolerable doses [150].

Several SHP2 inhibitors have progressed into clinical development. Batoprotafib (TNO155) is a selective SHP2 inhibitor that has demonstrated anti-tumour activ-

ity in KRAS-mutant cancers, both as monotherapy and in combination with MEK or $KRAS^{G12C}$ inhibitors. In an ongoing phase Ib/II trial (NCT04330664), batoprotafib is being evaluated in combination with opnurasib in advanced $KRAS^{G12C}$-mutated solid tumours. In preliminary data among 12 NSCLC patients previously treated with a $KRAS^{G12C}$ inhibitor, the ORR was 33.3% and DCR was 66.7% for this combination [151].

Vociprotafib (RMC-4630) is a potent and selective SHP2 inhibitor that has shown synergy with $KRAS^{G12C}$ inhibitors in preclinical models. In a phase I/II study (NCT03989115), vociprotafib combined with sotorasib demonstrated early clinical activity in NSCLC patients who were previously $KRAS^{G12C}$ inhibitor-naïve [152]. BBP-398 is another SHP2 inhibitor under evaluation in a phase I/II trial (NCT05480865), in combination with sotorasib or osimertinib. It is being explored as a strategy to delay or prevent resistance in EGFR- or KRAS-driven tumours [153]. JAB-3312 has also shown promise in early-phase trials. In a phase I/IIa study (NCT05288205) evaluating JAB-3312 plus glecirasib, NSCLC patients receiving the recommended dose of glecirasib 800 mg and JAB-3312 2 mg achieved an ORR of 77.8% and a DCR of 92.6% [154]. Table 5 summarises SOS1 and SHP2 inhibitors currently in clinical development. See Fig. 3 for an overview of KRAS inhibition strategies, including direct KRAS inhibitors and degraders, as well as inhibitors of upstream regulators and downstream effectors.

Collectively, targeting upstream regulators such as SOS1 and SHP2 represents a complementary strategy to direct KRAS inhibition by preventing RAS activation and mitigating adaptive pathway reactivation. Early clinical data suggest that these approaches may enhance the depth and durability of response when combined with KRAS inhibitors. However, their broad effects on normal signalling pathways introduce challenges related to on-target toxicity and therapeutic selectivity.

7.3 Combinations With Cell Cycle Inhibitors

Activation of KRAS signalling promotes cell cycle progression via upregulation of cyclin D1 expression and the subsequent activation of cyclin-dependent kinases 4/6 (CDK4/6), enabling G1-S phase transition. This provides a mechanistic rationale for combining RAS pathway inhibitors with clinically approved CDK4/6 inhibitors to synergistically block proliferation. This strategy is particularly relevant in the context of adaptive resistance, where reactivation of downstream ERK signalling can sustain cyclin D1 expression despite upstream KRAS inhibition. Preclinical studies in KRAS-mutant NSCLC and PDAC have demonstrated synthetic lethality when CDK4/6 inhibitors such as palbociclib are combined with allele-specific inhibitors. Combinations of CDK4/6 inhibitors with $KRAS^{G12C}$ inhibitors (sotorasib) and $KRAS^{G12D}$ inhibitors (MRTX1133) have been shown to induce sustained cell cycle arrest [155]. Similar synergy has also been observed between CDK4/6 inhibition and ERK inhibition, a combination that has now progressed into early-phase clinical trials (NCT03454035) [156]. However, clinical translation of these combinations remains limited, with potential challenges including overlapping toxicity and uncertainty regarding optimal sequencing and patient selection.

8. Immunological Strategies for Targeting KRAS-Mutant Tumours

8.1 Combination Therapy With Immune Checkpoint Inhibitors

KRAS-mutant tumours exhibit marked immunologic heterogeneity, shaped by both the specific KRAS allele and co-occurring genomic alterations such as *STK11*, *KEAP1*, or *TP53*. In NSCLC, *STK11* or *KEAP1* co-mutations are associated with immune-excluded phenotypes and resistance to ICIs, whereas *TP53* co-mutations correlate with inflamed microenvironments and improved immunotherapy responsiveness [157,158]. At a mechanistic level, oncogenic KRAS promotes an immunosuppressive tumour microenvironment (TME) through upregulation of interleukin-8 (IL-8) [159] and granulocyte-macrophage colony-stimulating factor (GM-CSF) [160], driving myeloid-derived suppressor cell (MDSC) expansion and impairment of cytotoxic T-cell function. KRAS activation can also increase CD47 expression and promote angiogenesis via pro-inflammatory cytokines and chemokines, collectively limiting immune surveillance and facilitating tumour immune evasion [161].

Building on these observations, direct $KRAS^{G12C}$ inhibition has been shown in preclinical models to partially reverse immunosuppression, enhancing interferon-γ signalling, promoting antigen presentation, and increasing $CD8^+$ T-cell activation [162]. These changes contribute to a more inflamed and immunologically active TME and underpin the synergistic activity observed when $KRAS^{G12C}$ inhibitors are combined with ICIs in murine models [163]. Similar immune-sensitising effects have been reported with the pan-RAS inhibitor daraxonrasib and RAS(ON) inhibitor doublets across $KRAS^{G12C}$-mutant NSCLC and $KRAS^{G12D}$-mutant microsatellite-stable (MSS) CRC models, including increased CD8+ T-cell infiltration, upregulation of antigen presentation and inflammatory programmes, and durable complete regressions when combined with anti-PD-1 therapy [138,139,164].

These immunologic effects are highly context-dependent and vary significantly across tumour types, with important implications for therapeutic strategy. In KRAS-mutant NSCLC, particularly in the presence of *TP53* co-mutations, tumours often exhibit an inflamed phenotype and have been associated with improved responsiveness to immune checkpoint blockade, supporting the rationale for KRAS inhibitor-ICI combinations in this setting [165]. In contrast, PDAC and MSS CRC are characterised by

Table 5. SOS1 and SHP2 inhibitors in clinical development.

Drug	Highest phase	Cancer type(s)	Drug combinations
SOS1 inhibitors:			
MRTX0902	Phase I/II	Advanced solid tumours	$KRAS^{G12C}$i: Adagrasib
ZG2001	Phase I/II	Advanced solid tumours	NA
BI-1701963	Phase I	Advanced solid tumours	Chemotherapy: Irinotecan $KRAS^{G12C}$i: Sotorasib, Adagrasib, BI-1823911 MEKi: Trametinib, BI-3011441
BAY3498264	Phase I	Advanced solid tumours	NA
SHP2 inhibitors:			
JAB-3312	Phase III	Advanced solid tumours	ICIs: Pembrolizumab EGFR TKI: Osimertinib $KRAS^{G12C}$i: Glecirasib, sotorasib MEKi: Binimetinib
Vociprotafib (RMC-4630)	Phase II	NSCLC, other advanced solid tumours	ICIs: Pembrolizumab EGFR TKI: Osimertinib $KRAS^{G12C}$i: Sotorasib, Adagrasib MEKi: Cobimetinib ERKi: LY3214996
Batoprotafib (TNO-155)	Phase I/II	Advanced solid tumours	ICIs: Spartalizumab, tislelizumab EGFR TKI: Nazartinib ALKi: Lorlatinib $KRAS^{G12C}$i: Sotorasib, adagrasib, opnurasib CDK4/6i: Ribociclib
JAB-3068	Phase I/II	Advanced solid tumours	ICIs: PD-1 inhibitor
ERAS-601	Phase I/II	Chordoma, other advanced solid tumours	ICIs: Pembrolizumab Anti-EGFR mAb: Cetuximab EGFR TKI: Osimertinib $KRAS^{G12C}$i: Sotorasib ERKi: ERAS-007
GDC-1971	Phase I	NSCLC, CRC, other advanced solid tumours	ICIs: Atezolizumab Anti-EGFR mAb: Cetuximab EGFR TKI: Osimertinib $KRAS^{G12C}$i: Divarasib
BBP-398	Phase I	NSCLC, other advanced solid tumours	ICIs: Nivolumab EGFR TKI: Osimertinib $KRAS^{G12C}$i: Sotorasib
SH3809	Phase I	Advanced solid tumours	NA
PF-07284892	Phase I	Advanced solid tumours	Pan-KRASi: PF-07985045
HBI-2376	Phase I	Advanced solid tumours	NA
ET0038	Phase I	Advanced solid tumours	NA
ICP-189	Phase I	Advanced solid tumours	ICIs: PD-1 inhibitor
BPI-442096	Phase I	Advanced solid tumours	NA

*ALKi, anaplastic lymphoma kinase inhibitor; Anti-EGFR mAb, anti-epidermal growth factor receptor monoclonal antibody; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ERKi, ERK inhibitor; $KRAS^{G12C}$i, $KRAS^{G12C}$ inhibitor; MEKi, MEK inhibitor; NA, not applicable/no publicly reported combinations; pan-KRASi, pan-KRAS inhibitor.

profoundly immunosuppressive TMEs, driven by stromal barriers, limited antigen presentation, and enrichment of immunosuppressive myeloid populations, rendering them largely refractory to ICIs [166,167,168]. In these tumours, KRAS inhibition alone is unlikely to overcome immune resistance, and combinatorial approaches incor-

porating stromal modulation, myeloid reprogramming, or neoantigen-targeting strategies such as vaccines or TCR-engineered therapies may be required. Collectively, these observations suggest that while KRAS inhibitor-ICI combinations appear most promising in selected NSCLC populations, alternative immunotherapeutic strategies may be necessary to achieve meaningful clinical benefit in PDAC and MSS CRC.

Despite a strong biological rationale, the translation of KRAS inhibitor-ICI combinations into clinical benefit has been limited by safety concerns, particularly hepatotoxicity. In the CodeBreaK-100/101 trials, sotorasib combined with pembrolizumab or atezolizumab resulted in grade 3–4 hepatotoxicity in 42–47% and 30–50%, respectively [169]. In contrast, the KRYSTAL-7 study reported a more favourable safety profile with adagrasib plus pembrolizumab, with <10% grade ≥3 liver toxicity and an ORR of 63% among patients with PD-L1 ≥50% [170]. The variability in hepatotoxicity observed between sotorasib- and adagrasib-based regimens may reflect differences in the underlying toxicity profiles of each drug. Emerging clinical observations, including case series demonstrating the feasibility of adagrasib following sotorasib-related hepatotoxicity, support the concept that these agents have distinct hepatotoxicity profiles, and suggest that adagrasib may be more compatible for ICI combinations [171]. In this context, early data from LOXO-RAS-200001 demonstrated encouraging activity with olomorasib plus pembrolizumab, achieving ORRs of 77% in treatment-naïve and 49% in pretreated $KRAS^{G12C}$-mutant NSCLC, with minimal hepatotoxicity [96]. These findings have prompted multiple phase III studies, including SUNRAY-01 (NCT06119581; olomorasib plus pembrolizumab), KANDLELIT-004 (NCT06345729; MK-1084 plus pembrolizumab), and Krascendo-2 (NCT06793215; divarasib plus pembrolizumab), evaluating $KRAS^{G12C}$-directed combinations in first-line NSCLC [87,90]. However, the durability of responses and their impact on OS remain to be established in ongoing phase III trials.

8.2 T-Cell Receptor-Engineered Cell Therapy

T-cell receptor (TCR)-engineered cell therapy is a personalised immunotherapeutic strategy in which patient- or donor-derived T-lymphocytes are genetically modified to express tumour-specific TCRs. Unlike chimeric antigen receptor (CAR) T-cell therapy, which targets extracellular antigens, TCR-T cells recognise intracellular neoantigens presented by major histocompatibility complex (MHC) molecules, making them particularly well suited to solid tumours such as PDAC and CRC [172].

KRAS mutations generate neoantigenic peptides capable of eliciting tumour-specific T-cell responses. A landmark study identified an HLA-C*08:02-restricted TCR capable of recognising $KRAS^{G12D}$-derived peptides in tumour-infiltrating lymphocytes (TILs) from CRC patients, enabling the first clinical applications of KRAS-specific TCR-T therapy [173]. In a notable case report, autologous $KRAS^{G12D}$-targeted TCR-engineered T-cells induced a partial response in a patient with metastatic PDAC, with a 62% reduction in lung metastases at one month, deepening to 72% at six months [174]. AFNT-211, a $KRAS^{G12V}$-specific TCR-T therapy, is currently under evaluation in a phase I clinical trial (NCT06105021) [175]. Despite promising early signals, the clinical applicability of TCR-engineered therapies remains constrained by HLA restriction, intratumoral heterogeneity, and challenges in achieving durable T-cell persistence in solid tumours, highlighting the need for improved engineering strategies that expand patient eligibility [176].

8.3 KRAS-Directed Vaccination Strategies

Cancer vaccines targeting *KRAS* mutations aim to elicit neoantigen-specific T-cell responses against KRAS-mutant tumour cells. Early-phase studies in PDAC using antigen-presenting cells pulsed with KRAS-mutant peptides induced KRAS-specific immune responses in a subset of patients and correlated with improved survival, providing early proof-of-concept despite modest response rates [177]. An ongoing early-phase trial is now evaluating a KRAS-mutant peptide vaccine in combination with ipilimumab and nivolumab, integrating neoantigen priming with checkpoint blockade (NCT05254184) [178]. More recently, the KRAS-directed vaccine ELI-002 2P, comprising amphiphile-modified $KRAS^{G12D/G12R}$ peptides with a CpG adjuvant, demonstrated robust immune activation in patients with KRAS-mutant solid tumours and minimal residual disease in the phase I AMPLIFY-201 trial. KRAS-specific immune responses were associated with significantly improved relapse-free and overall survival compared with non-responders [179,180].

DNA- and RNA-based vaccines offer broader antigenic coverage and enhanced immunogenicity. GI-4000, a recombinant yeast-based DNA vaccine encoding common KRAS variants (G12C, G12V, G12D), demonstrated safety and immunogenicity in a phase II study in early-stage NSCLC, with KRAS-specific T-cell responses observed in 50% of patients [181]. mRNA platforms have also entered clinical evaluation; however, mRNA-5671/V941, encoding multiple KRAS neoantigens, was discontinued following a phase I study (NCT03948763) [107]. This highlights several persistent challenges in KRAS-targeted vaccination strategies, including insufficient immunogenicity, tumour immune evasion, and the difficulty of generating durable, clinically meaningful responses in immunologically cold tumours. These findings underscore the need for improved antigen selection, more potent adjuvant systems, and rational combination strategies with ICIs or other immune-modulating agents to enhance therapeutic efficacy.

The multi-component immunotherapy platform KISIMA-02 is currently under investigation, com-

bining a $KRAS^{G12D/G12V}$-targeted peptide vaccine (ATP150/ATP152), a viral vector (VSV-GP154), and the ICI ezabenlimab in an ongoing clinical trial (NCT05846516) [182]. In parallel, individualised mRNA neoantigen vaccines combined with anti-PD-L1 therapy and chemotherapy have shown preliminary efficacy in surgery-eligible PDAC, eliciting T-cell responses and correlating with delayed disease recurrence (NCT04161755) [183]. While vaccine-based approaches remain promising, particularly in minimal residual disease settings, their role in advanced metastatic disease remains uncertain and will likely depend on rational combination strategies to overcome established immune resistance.

8.4 HapImmune Bispecific Antibodies

A novel strategy termed HapImmune therapy seeks to combine the molecular specificity of targeted inhibition with immune-mediated cytotoxicity. This approach exploits covalent KRAS inhibitors, such as sotorasib, which form stable drug-peptide conjugates upon binding mutant KRAS that are subsequently processed and presented on MHC molecules. Engineered bispecific antibodies then recognise the drug-peptide-MHC complex and CD3 on cytotoxic T-cells, redirecting T-cell-mediated killing of inhibitor-bound tumour cells [184]. This strategy represents a conceptual shift by converting a small molecule inhibitor into a neoantigen-generating platform, effectively bridging targeted therapy and immunotherapy. Preclinical studies have demonstrated potent activity against $KRAS^{G12C}$-mutant cells treated with sotorasib or adagrasib, particularly in HLA-A02 and HLA-A03 contexts [185,186].

Although promising, HapImmune therapy remains preclinical. Key challenges include HLA restriction, potential off-target toxicity, and the need to demonstrate consistent antigen presentation *in vivo*, as variability in MHC expression and antigen processing across tumour cells may limit broad clinical translation. Furthermore, the durability of responses and feasibility of this approach in heterogeneous TMEs remain to be established, and its role relative to other emerging immunotherapeutic strategies is yet to be defined.

9. Limitations

This review has several limitations. As a narrative review, it does not employ a systematic methodology for study selection and therefore may be subject to selection bias. Although we aimed to include the most relevant and recent data, it is possible that some studies were not captured or that emphasis reflects the authors' interpretation of the evolving literature. A substantial proportion of the data discussed are derived from early-phase clinical trials or preclinical studies, with some results available only in preliminary form. These datasets are often based on small patient numbers, and may report immature efficacy endpoints, limiting the ability to draw definitive conclusions regarding clinical benefit, durability of response, and OS. Cross-trial comparisons should therefore be interpreted with caution. Additionally, the field of KRAS-targeted therapy is evolving rapidly, with multiple ongoing trials and frequent updates from interim analyses. As such, some findings presented in this review may evolve as more mature data becomes available.

10. Conclusions

More than four decades after the discovery of the RAS family of oncoproteins, substantial progress has finally been made in the treatment of RAS-driven malignancies. This progress has been non-linear and marked by significant setbacks, yet several important lessons emerge from the body of work summarised in this review. Chief among these is the need to account for the fundamental biochemical and physiological properties of RAS proteins, recognising that individual isoforms and mutant alleles exhibit functionally distinct signalling dependencies. At the same time, it is increasingly clear that many aspects of RAS biology remain incompletely understood. As such, dogmatic assumptions should be avoided, and continued openness to unexpected mechanisms of tumour adaptation and resistance remains essential.

The development of allele-specific KRAS inhibitors over the past decade provides the clearest example of how long-held assumptions in oncology can be overturned, definitively demonstrating that direct pharmacologic targeting of RAS is feasible. However, the modest and often short-lived clinical responses observed with first-generation $KRAS^{G12C}$ inhibitors also underscore the limitations of targeting single mutant alleles in isolation. Notably, the absence of consistent OS benefit in randomised trials further emphasises the need to critically evaluate the true clinical impact of these agents. In response, a new generation of therapeutic strategies has emerged, including ON-state inhibitors, pan-KRAS and pan-RAS agents, KRAS degraders, and indirect approaches such as SHP2 or SOS1 inhibition. Collectively, these advances reflect a broader shift toward more comprehensive and durable suppression of RAS signalling. Emerging clinical data increasingly support the need for rational upfront combination strategies to prevent pathway reactivation, address tumour heterogeneity, and achieve sustained disease control.

In parallel, advances in KRAS-directed immunotherapies represent a complementary therapeutic avenue. KRAS-targeted vaccines, TCR-engineered cellular therapies, and other immune-based platforms have demonstrated that KRAS mutations can be effectively recognised by the immune system. Integration of these modalities with direct or indirect KRAS inhibitors has the potential to enhance both the depth and durability of antitumour responses.

Looking ahead, the increasing use of ctDNA to monitor treatment response and emerging resistance is likely

to play a central role in optimising KRAS-targeted therapies. This approach will enable earlier detection of resistance mechanisms, support adaptive treatment strategies, and help identify patients most likely to benefit from specific drug combination strategies. Ultimately, the future of KRAS-targeted therapy will depend on integrating molecular biology, clinical insight, and adaptive therapeutic strategies to move beyond transient responses toward durable disease control.

Availability of Data and Materials

No new datasets were generated or analysed during the preparation of this review. The article is based exclusively on previously published studies, which are cited in the reference list. Therefore, no additional data are available.

Author Contributions

CRF and AGD conceptualized and designed the review. CRF performed the literature review and drafted the manuscript. DM and WK contributed to the biological and mechanistic interpretation of RAS signaling. DC and AGD provided clinical input and critical review of the therapeutic sections. AGD provided overall supervision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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