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Targeting KRAS in Cancer: Advances in Precision Oncology and Drug Development

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Abstract: KRAS is among the most commonly mutated oncogenes in human cancers, driving tumour initiation, progression, and therapeutic resistance through dysregulation of multiple signalling pathways. For many years, KRAS was regarded as an undruggable target because of its high affinity for guanosine nucleotides and the absence of suitable drug-binding pockets. Recent advances in structural biology and medicinal chemistry have fundamentally changed this perspective, enabled the development of mutation-specific inhibitors and established KRAS as a clinically actionable target in precision oncology.

The discovery of the switch-II binding pocket facilitated the design of selective covalent inhibitors targeting KRAS G12C, leading to the clinical approval of sotorasib and adagrasib for selected patients with KRAS G12C-mutated malignancies. These breakthroughs have validated direct KRAS inhibition as an effective therapeutic strategy. However, durable clinical responses remain limited by intrinsic and acquired resistance, pathway reactivation, tumour heterogeneity, and the lack of effective therapies for non-G12C KRAS mutations.

Emerging therapeutic approaches are expanding the scope of KRAS-targeted treatment through the development of pan-KRAS inhibitors, mutation-specific agents targeting KRAS G12D and other variants, targeted protein degradation technologies, RNA-based therapeutics, genome-editing strategies, and KRAS-directed immunotherapies. In parallel, rational combination therapies targeting EGFR, SHP2, MEK/ERK, PI3K–AKT–mTOR signalling, immune checkpoints, and tumour metabolism are being investigated to enhance treatment efficacy and overcome resistance. This review summarizes recent advances in KRAS biology, therapeutic innovation, resistance mechanisms, and combination strategies, highlighting future opportunities for precision cancer medicine and the continued evolution of KRAS-directed drug development.

Keywords: *KRAS; Precision Oncology; Targeted Cancer Therapy; KRAS Inhibitors; Drug Resistance; Cancer Drug Development.*

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I. INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide and is characterized by the accumulation of genetic and epigenetic alterations that disrupt normal cellular homeostasis, leading to uncontrolled proliferation, survival, invasion, and metastasis. Advances in molecular oncology have identified several oncogenic signalling pathways that drive tumour initiation and progression, among which the RAS signalling network is one of the most extensively investigated. The RAS family of small guanosine triphosphatases (GTPases), comprising HRAS, NRAS, and KRAS, functions as a molecular switch that regulates cell proliferation, differentiation, apoptosis, metabolism, and cytoskeletal organization through multiple downstream signalling cascades, including the RAF–MEK–ERK and PI3K–AKT–mTOR pathways (1–3).

Among the three RAS isoforms, KRAS is the most frequently mutated oncogene in human cancer and accounts for approximately 85% of all RAS mutations. Activating KRAS mutations occur in nearly 90% of pancreatic ductal adenocarcinoma, 35–45% of colorectal cancer, and 25–30% of non-small cell lung cancer, where they promote constitutive activation of intracellular signalling independent of extracellular growth factors. Persistent KRAS signalling enhances cell proliferation, metabolic reprogramming, immune evasion, angiogenesis, and resistance to apoptosis, thereby contributing to tumour progression, metastasis, and poor clinical outcomes (4–6).

For more than three decades, KRAS was regarded as an "undruggable" therapeutic target because of its exceptionally high affinity for guanosine diphosphate (GDP) and guanosine triphosphate (GTP), together with the absence of deep hydrophobic binding pockets suitable for small-molecule inhibitors. Consequently, therapeutic strategies primarily focused on inhibiting downstream effectors of KRAS signalling rather than directly targeting the mutant protein, yielding only limited clinical success (7–9).

A major breakthrough in KRAS drug discovery occurred with the identification of the switch-II pocket (S-IIP) within the inactive GDP-bound conformation of the KRAS G12C mutant. This structural discovery enabled the rational development of selective covalent inhibitors that irreversibly bind the mutant cysteine residue and stabilize KRAS in its inactive state. The subsequent clinical approval of sotorasib and adagrasib validated direct KRAS inhibition as an effective therapeutic strategy and established KRAS as a clinically actionable target in precision oncology (10–12).

Despite these remarkable advances, durable therapeutic responses remain limited by intrinsic and acquired resistance, tumour heterogeneity, adaptive reactivation of signalling pathways, and the limited efficacy of current therapies against non-G12C KRAS mutations. Current research is therefore focused on the development of next-generation mutation-specific inhibitors, pan-KRAS inhibitors, targeted protein degradation strategies, RNA-based therapeutics, genome-editing technologies, KRAS-directed immunotherapies, and rational combination regimens designed to improve treatment efficacy and overcome resistance (13–15).

This review comprehensively summarizes the molecular biology of KRAS, its role in oncogenic signalling, structural advances that enabled direct drug targeting, clinically approved KRAS inhibitors, mechanisms of therapeutic resistance, emerging therapeutic strategies, and future perspectives in precision cancer medicine (16).

II. HISTORY OF KRAS

The discovery of the RAS oncogene family represents a landmark achievement in molecular oncology and significantly advanced the understanding of the genetic basis of cancer. The earliest RAS genes were identified during studies of rat sarcoma viruses in the 1960s, establishing the first evidence that viral oncogenes could drive malignant transformation. Subsequent molecular investigations led to the identification of the human HRAS, NRAS, and KRAS proto-oncogenes, which encode highly conserved small GTP-binding proteins involved in the regulation of cell growth, differentiation, survival, and intracellular signal transduction (17–19).

In 1982, KRAS was identified as a human oncogene, marking a pivotal milestone in cancer genetics. Further studies demonstrated that activating mutations in KRAS occur predominantly at codons 12, 13, and 61, resulting in impaired GTP hydrolysis and persistent activation of downstream signalling pathways, including the RAF–MEK–ERK and PI3K–AKT cascades. These constitutively active mutations promote uncontrolled cellular proliferation, metabolic reprogramming, and resistance to apoptosis, establishing KRAS as one of the principal oncogenic drivers in pancreatic, colorectal, and non-small cell lung cancers (20–22).

Despite its well-established role in tumorigenesis, KRAS remained resistant to pharmacological inhibition for more than three decades because of its high affinity for guanine nucleotides and the absence of suitable ligand-binding pockets. Consequently, KRAS gained the reputation of being an "undruggable" target, prompting researchers to focus on indirect therapeutic strategies targeting downstream effectors. A major breakthrough occurred in 2013 with the discovery of the switch-II pocket (S-IIP) in the KRAS G12C protein, which enabled the development of selective covalent inhibitors and fundamentally changed the landscape of KRAS-targeted drug discovery. This progress ultimately led to the clinical approval of sotorasib in 2021 and adagrasib in 2022, representing the first direct KRAS inhibitors approved for clinical use and opening a new era of precision oncology (23–26).

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Table 1. Historical Milestones in KRAS Research and Therapeutic Development

Year/Period	Major Milestone	Significance
1960s	Discovery of RAS oncogenes in rat sarcoma viruses	Established RAS as one of the first oncogenes associated with malignant transformation.
1982	Identification of the human KRAS oncogene	Demonstrated that KRAS functions as a proto-oncogene and plays a critical role in human cancer development.
1980s–1990s	Characterization of activating KRAS mutations (codons 12, 13, and 61)	Revealed the high prevalence of KRAS mutations in pancreatic, colorectal, and lung cancers and their role in constitutive signaling.
2000s	KRAS recognized as an "undruggable" therapeutic target	High nucleotide-binding affinity and lack of suitable binding pockets limited direct drug development.
2013	Discovery of the switch-II pocket (S-IIP) in KRAS G12C	Enabled structure-based drug design and the development of selective covalent KRAS inhibitors.
2019	Clinical success of the first KRAS G12C inhibitors in early-phase clinical trials	Provided proof-of-concept that direct pharmacological inhibition of KRAS is feasible.
2021	First FDA approval of Sotorasib (AMG 510)	Marked the first approved targeted therapy against KRAS G12C-mutated cancers, representing a major breakthrough in precision oncology.
2022	FDA approval of Adagrasib (MRTX849)	Expanded therapeutic options for patients with KRAS G12C-mutated malignancies and validated KRAS as a clinically actionable target.
2023–Present	Development of pan-KRAS inhibitors, KRAS G12D inhibitors, PROTACs, RNA therapeutics, and combination therapies	Represents the next generation of KRAS-targeted therapeutic strategies aimed at overcoming resistance and broadening clinical applicability.

III. KRAS STRUCTURE AND FUNCTION

KRAS (Kirsten Rat Sarcoma Viral Oncogene Homolog) is a member of the RAS superfamily of small guanine nucleotide-binding proteins (small GTPases), which also includes HRAS and NRAS. These proteins function as molecular switches that transmit extracellular signals to intracellular pathways controlling cell proliferation, differentiation, survival, migration, and metabolism. Among the RAS isoforms, KRAS is the most frequently mutated in human malignancies and represents a major oncogenic driver in pancreatic, colorectal, and non-small cell lung cancers (27–29).

Structurally, KRAS is composed of a highly conserved G-domain (residues 1–166), which mediates nucleotide binding and intrinsic GTPase activity, and a C-terminal hypervariable region (HVR) (residues 167–188), which undergoes post-translational modifications required for membrane anchoring. The G-domain contains several highly conserved functional motifs, including the phosphate-binding loop (P-loop), Switch-I, and Switch-II regions. These dynamic domains undergo conformational changes during GDP–GTP exchange and regulate interactions with downstream effector proteins, thereby controlling intracellular signal transduction (30–32).

Under physiological conditions, KRAS cycles between an inactive GDP-bound conformation and an active GTP-bound state. Activation is mediated by guanine nucleotide exchange factors (GEFs), which facilitate GDP release and GTP binding, whereas GTPase-activating proteins (GAPs) accelerate GTP hydrolysis, restoring the inactive state. This tightly controlled molecular cycle ensures accurate transmission of growth factor signals and maintenance of cellular homeostasis (33–35).

Oncogenic mutations, predominantly affecting codons 12, 13, and 61, impair intrinsic GTP hydrolysis and reduce GAP-mediated inactivation, resulting in persistent activation of KRAS. Constitutively active KRAS continuously stimulates downstream signaling pathways that promote uncontrolled proliferation, resistance to apoptosis, metabolic adaptation, angiogenesis, and metastatic progression, thereby contributing to tumor initiation and maintenance (36–38).

- *RAF–MEK–ERK (MAPK) Signalling Pathway*

The RAF–MEK–ERK cascade is the principal downstream signalling pathway activated by mutant KRAS. Following activation, KRAS recruits RAF kinases to the plasma membrane, initiating sequential phosphorylation of MEK1/2 and ERK1/2. Activated ERK subsequently translocate to the nucleus, where it regulates transcription factors controlling cell-cycle progression, proliferation, differentiation, and survival. Persistent activation of this pathway is a defining feature of many KRAS-driven tumours and represents an important therapeutic target (39–41).

- *PI3K–AKT–mTOR Signalling Pathway*

KRAS also activates the phosphatidylinositol-3-kinase (PI3K) signalling pathway, leading to phosphorylation of AKT and activation of the mammalian target of rapamycin (mTOR). This signalling network regulates protein synthesis, glucose metabolism, cell growth, survival, and resistance to apoptosis. Aberrant activation of the PI3K–AKT–mTOR pathway contributes significantly to tumour progression and is a major mechanism underlying resistance to targeted therapies in

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KRAS-mutant cancers (42–44).

➢ *RALGDS–RAL Signalling Pathway*

In addition to MAPK and PI3K signalling, activated KRAS interacts with Ral guanine nucleotide dissociation stimulator (RALGDS), resulting in activation of the RALA and RALB GTPases. This pathway regulates vesicle trafficking, cytoskeletal remodelling, cell polarity, migration, invasion, and metastatic dissemination. Increasing evidence indicates that RAL signalling plays a crucial role in KRAS-mediated tumour progression and represents a promising target for future therapeutic intervention (45–47).

Table 2. Structural Organization and Functional Domains of KRAS

Structural Region	Residues	Structural Features	Biological Function
G-domain	1–166	Highly conserved Catalytic domain containing nucleotide-binding motifs	Binds GDP/GTP and mediates intrinsic GTPase activity
P-loop (Phosphate-binding loop)	10–17	Conserved phosphate-binding motif	Stabilizes GDP/GTP phosphate groups during nucleotide binding
Switch-I region	30–38	Dynamic conformational domain	Mediates interactions with RAF, PI3K, and other downstream effector proteins
Switch-II region	60–76	Flexible catalytic region	Regulates GTP hydrolysis and contains the switch-II pocket targeted by KRAS G12C inhibitors
Hypervariable region (HVR)	167–188	Membrane-targeting domain containing the CAAX motif	Undergoes prenylation and facilitates plasma membrane localization essential for KRAS signaling

IV. EVOLUTION OF KRAS DRUG DEVELOPMENT

For more than three decades, KRAS was regarded as one of the most challenging molecular targets in oncology because of its exceptionally high affinity for guanosine diphosphate (GDP) and guanosine triphosphate (GTP), limited surface pockets for ligand binding, and rapid nucleotide exchange kinetics. These structural characteristics hindered the development of conventional small-molecule inhibitors, leading to the widespread perception that KRAS was an "undruggable" oncogene (48–50).

Early therapeutic strategies focused primarily on indirect inhibition of KRAS signaling by targeting downstream effectors, including the RAF–MEK–ERK and PI3K–AKT–mTOR pathways, or by inhibiting post-translational modifications required for KRAS membrane localization. Although these approaches demonstrated promising preclinical activity, their clinical efficacy was limited by pathway redundancy, adaptive feedback mechanisms, and the rapid emergence of drug resistance (51–53).

A major turning point in KRAS drug discovery occurred following advances in structural biology that revealed a previously unrecognized switch-II pocket (S-IIP) within the inactive GDP-bound conformation of KRAS G12C. This discovery provided the first druggable binding site on mutant KRAS and enabled the rational design of mutation-selective covalent inhibitors capable of irreversibly binding the mutant cysteine residue while locking KRAS in its inactive conformation (54–56).

Subsequent medicinal chemistry efforts led to the development of highly selective KRAS G12C inhibitors with potent antitumor activity in preclinical models. These findings culminated in successful clinical trials and the regulatory approval of direct KRAS inhibitors, demonstrating for the first time that mutant KRAS could be pharmacologically targeted in patients. This milestone fundamentally changed the therapeutic landscape of KRAS-driven cancers and stimulated the development of next-generation mutation-specific inhibitors, pan-KRAS inhibitors, targeted protein degraders, RNA-based therapeutics, and rational combination strategies designed to overcome resistance and improve long-term clinical outcomes (57–60).

V. ADAGRASIB (MRTX849)

Adagrasib (MRTX849) is a highly selective, orally administered covalent inhibitor designed to target the KRAS G12C mutation. The drug irreversibly binds to the mutant cysteine residue within the switch-II pocket, stabilizing KRAS in its inactive GDP-bound conformation and preventing downstream oncogenic signalling. This mutation-selective mechanism minimizes inhibition of wild-type KRAS while effectively suppressing aberrant signalling in KRAS G12C-mutant tumours (61–63).

Pharmacologically, adagrasib exhibits prolonged target engagement, favourable oral bioavailability, and an extended half-life, allowing sustained inhibition of KRAS signalling. Inhibition of mutant KRAS results in reduced activation of the RAF–MEK–ERK and PI3K–AKT–mTOR pathways, thereby suppressing tumour-cell proliferation, enhancing apoptosis, and limiting tumour progression. Preclinical

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investigations demonstrated durable antitumor activity across multiple KRAS G12C-driven cancer models, supporting its advancement into clinical evaluation (64–66).

Clinical studies subsequently established the efficacy of adagrasib in patients with previously treated KRAS G12C-mutated non-small cell lung cancer (NSCLC), leading to durable objective responses and meaningful disease control. Therapeutic activity has also been demonstrated in colorectal cancer; however, adaptive activation of epidermal growth factor receptor (EGFR) signalling significantly reduces treatment efficacy. Consequently, combination regimens incorporating EGFR inhibitors have emerged as a promising strategy to overcome resistance and improve clinical outcomes in KRAS G12C-mutant colorectal cancer (67–69).

Although adagrasib represents a major advance in precision oncology, long-term therapeutic benefit remains limited by acquired resistance mediated through secondary KRAS mutations, bypass pathway activation, and tumour heterogeneity. Current research therefore focuses on optimizing combination therapies and developing next-generation KRAS inhibitors capable of targeting multiple KRAS variants and overcoming resistance mechanisms (70–72).

VI. SOTORASIB

Sotorasib (AMG 510) is the first clinically approved, orally active, mutation-selective inhibitor targeting KRAS G12C, representing a landmark achievement in precision oncology. The drug was rationally designed to exploit the cysteine residue created by the G12C substitution and irreversibly binds to the switch-II pocket (S-IIP) of KRAS. Covalent binding stabilizes the protein in its inactive GDP-bound conformation, thereby preventing GTP loading and suppressing oncogenic KRAS signalling (73–75).

Selective inhibition of KRAS G12C by sotorasib effectively suppresses multiple downstream signalling cascades, particularly the RAF–MEK–ERK and PI3K–AKT–mTOR pathways, resulting in inhibition of cellular proliferation, induction of apoptosis, and reduced tumour growth. Because its activity is mutation-specific, sotorasib preferentially targets malignant cells harbouring the KRAS G12C mutation while largely preserving physiological signalling mediated by wild-type KRAS (76–78).

The clinical efficacy of sotorasib has been demonstrated across several KRAS G12C-mutated solid tumours, most notably non-small cell lung cancer (NSCLC). Clinical trials reported durable objective responses, prolonged disease control, and manageable safety profiles in patients who had received previous systemic therapies, ultimately leading to regulatory approval for advanced KRAS G12C-mutated NSCLC. These findings established direct KRAS inhibition as a clinically effective therapeutic strategy and validated KRAS as a druggable oncogenic target (79–81).

Sotorasib has also shown clinical activity in metastatic colorectal cancer (CRC) harbouring KRAS G12C mutations. However, single-agent efficacy is comparatively modest because adaptive activation of epidermal growth factor receptor (EGFR) signalling restores downstream MAPK activity. Consequently, combination regimens incorporating EGFR inhibitors, particularly panitumumab, have demonstrated improved antitumor activity and are increasingly being explored as an effective therapeutic strategy for KRAS G12C-mutated CRC (82–84).

Despite its clinical success, several limitations remain. Acquired resistance develops through secondary KRAS mutations, activation of bypass signalling pathways, genomic heterogeneity, and adaptive pathway reactivation. Furthermore, sotorasib demonstrates limited activity against other KRAS variants, including G12D, G12V, and G13D, highlighting the need for next-generation KRAS inhibitors and rational combination therapies capable of producing more durable clinical responses (85–87).

VII. KRAS INHIBITOR RESISTANCE MECHANISMS

Although selective KRAS G12C inhibitors have significantly improved the treatment of KRAS-mutant malignancies, the durability of clinical responses is frequently compromised by intrinsic and acquired resistance. Resistance develops through multiple molecular mechanisms involving genetic alterations, adaptive signalling networks, and dynamic changes within the tumour microenvironment. Understanding these mechanisms is essential for designing next-generation therapeutic strategies and optimizing combination treatment approaches (88–90).

One of the most frequently reported resistance mechanisms involves secondary mutations within KRAS, particularly alterations affecting the switch-II pocket or adjacent residues that reduce inhibitor binding affinity. These mutations restore KRAS activation despite continued drug exposure, resulting in persistent downstream oncogenic signalling (91–93).

Resistance may also arise through KRAS amplification or increased expression of mutant KRAS protein, allowing sufficient signalling activity to persist despite pharmacological inhibition. In parallel, activation of compensatory signalling pathways—including receptor tyrosine kinases, SHP2, EGFR, MET, FGFR, and PI3K—can bypass KRAS inhibition and reactivate MAPK or PI3K–AKT signalling, thereby promoting continued tumour cell survival and proliferation (94–96).

Alterations in downstream signalling components, including BRAF, MEK, ERK, and PI3K, further contribute to therapeutic failure by restoring proliferative signalling independently of KRAS. In addition, tumour heterogeneity and clonal evolution facilitate the selection and expansion of

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resistant cellular subpopulations during treatment, ultimately leading to disease progression and reduced therapeutic durability (97–99).

Emerging evidence also indicates that metabolic reprogramming, epithelial-to-mesenchymal transition, immune evasion, and remodelling of the tumour microenvironment contribute to resistance against KRAS-targeted therapy. These findings support the development of combination strategies incorporating KRAS inhibitors with SHP2 inhibitors, EGFR inhibitors, immune checkpoint inhibitors, MEK inhibitors, and metabolic modulators to overcome resistance and improve long-term clinical outcomes (100–102).

VIII. KRAS IN CANCER METABOLISM

Oncogenic KRAS is a key regulator of metabolic reprogramming, enabling cancer cells to adapt to the increased energetic and biosynthetic demands required for continuous growth. In addition to promoting uncontrolled proliferation, mutant KRAS rewires multiple metabolic pathways that support nutrient acquisition, ATP generation, redox homeostasis, and macromolecular biosynthesis. These metabolic adaptations allow tumour cells to survive under hypoxic and nutrient-deprived conditions commonly found within the tumour microenvironment (103–105).

One of the most prominent metabolic alterations induced by mutant KRAS is enhanced glucose metabolism. KRAS activation increases the expression of glucose transporters, particularly GLUT1, thereby promoting glucose uptake and glycolytic flux. In pancreatic ductal adenocarcinoma (PDAC), KRAS redirects glucose-derived intermediates into the pentose phosphate pathway, hexosamine biosynthetic pathway, and nucleotide biosynthesis, supporting rapid cellular proliferation and anabolic growth (106–108).

Mutant KRAS also profoundly influences glutamine metabolism, which is essential for maintaining mitochondrial function, antioxidant defence, and cellular biosynthesis. KRAS-driven tumours utilize non-canonical glutamine metabolic pathways to generate nicotinamide adenine dinucleotide phosphate (NADPH), thereby reducing oxidative stress and sustaining tumor cell survival. This metabolic dependency is particularly evident in pancreatic cancer, where glutamine metabolism represents a potential therapeutic vulnerability (109–111).

Beyond glucose and glutamine utilization, KRAS regulates lipid metabolism, mitochondrial bioenergetics, and autophagy. Enhanced de novo lipid synthesis supplies phospholipids and cholesterol required for membrane biogenesis during rapid cell division, while increased autophagic activity provides recycled nutrients that support mitochondrial function and cellular survival under metabolic stress. These coordinated metabolic adaptations contribute to therapeutic resistance and facilitate long-term tumour maintenance (112–114).

Growing evidence suggests that targeting KRAS-associated metabolic vulnerabilities—including glycolysis, glutaminolysis, fatty acid metabolism, oxidative phosphorylation, and autophagy—may complement direct KRAS inhibition. Rational combination therapies integrating metabolic inhibitors with KRAS-targeted agents are therefore being actively investigated as a strategy to overcome resistance and improve clinical outcomes in KRAS-driven malignancies (115–117).

Table 3. Metabolic Reprogramming Induced by Oncogenic KRAS

Metabolic Process	KRAS-Mediated Effect	Biological Consequence
Glucose metabolism	Increased GLUT1 expression and glycolytic flux	Enhanced ATP production and biosynthetic precursor generation
Pentose pathway phosphate	Increased diversion glucose carbon	Nucleotide synthesis and NADPH production
Glutamine metabolism	Enhanced utilization glutamine	Maintenance of redox balance and mitochondrial function
Lipid metabolism	Increased de novo fatty acid and cholesterol synthesis	Membrane biogenesis and tumour growth
Autophagy	Activation of nutrient recycling pathways	Survival during hypoxia and nutrient deprivation
Mitochondrial metabolism	Metabolic adaptation and oxidative stress regulation	Sustained tumour cell proliferation and resistance

IX. KRAS AMPLIFICATION AND ALTERNATIVE TARGETING APPROACHES

KRAS amplification is an important molecular alteration that contributes to sustained oncogenic signalling and disease progression in several solid tumours. Unlike activating point mutations, gene amplification increases the copy number of KRAS, resulting in overexpression of the KRAS protein and persistent activation of downstream signalling pathways. Elevated KRAS expression enhances cell proliferation, promotes tumour survival, facilitates invasion, and has been associated with poor clinical outcomes and reduced sensitivity to targeted therapies (118–120).

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Experimental and clinical studies indicate that tumours with KRAS amplification often remain highly dependent on KRAS signalling, making this alteration a potential therapeutic target. Increased KRAS protein levels can diminish the efficacy of mutation-specific inhibitors by maintaining sufficient signalling activity despite pharmacological inhibition. Consequently, therapeutic strategies directed against amplified KRAS require broader approaches capable of suppressing KRAS signalling irrespective of mutation subtype (121–123).

Several alternative therapeutic strategies have therefore been developed to overcome the limitations of mutation-selective KRAS inhibitors. These include the development of pan-KRAS inhibitors, which target multiple KRAS mutant variants, and pan-RAS inhibitors, which inhibit signalling across the RAS protein family. In addition, inhibitors targeting upstream regulators such as SHP2 and SOS1 disrupt KRAS activation by preventing nucleotide exchange, while downstream inhibitors of the RAF–MEK–ERK and PI3K–AKT–mTOR pathways suppress KRAS-mediated oncogenic signalling. Combination therapies integrating these approaches have demonstrated encouraging preclinical and early clinical activity in overcoming adaptive resistance (124–127).

Emerging technologies have further expanded the therapeutic landscape for KRAS-dependent cancers. Proteolysis-targeting chimeras (PROTACs) designed to degrade KRAS proteins, together with RNA-based therapies, synthetic lethality approaches, and combination immunotherapies, are being investigated to achieve broader and more durable suppression of KRAS-driven tumours. These strategies have the potential to address both KRAS-mutant and KRAS-amplified malignancies while reducing the likelihood of acquired resistance (128–130).

Overall, KRAS amplification represents an additional mechanism of oncogenic dependence beyond canonical point mutations. Continued advances in pan-KRAS inhibitors, pathway-directed therapies, targeted protein degradation, and rational combination regimens are expected to expand treatment options and improve clinical outcomes for patients with KRAS-driven cancers (131–132).

Table 4. Alternative Therapeutic Strategies for KRAS-Driven Cancers

Therapeutic Strategy	Target/Mechanism	Potential Clinical Benefit
Pan-KRAS inhibitors	Multiple KRAS mutant isoforms	Broader mutation coverage
Pan-RAS inhibitors	HRAS, NRAS and KRAS	Suppression of RAS family signalling
SHP2 inhibitors	Block upstream KRAS activation	Delay adaptive resistance
SOS1 inhibitors	Prevent GDP–GTP nucleotide exchange	Reduce KRAS activation
MEK/ERK inhibitors	Inhibit downstream MAPK signalling	Complement KRAS inhibition
PI3K–AKT–mTOR inhibitors	Block survival signalling	Reduce tumour growth and resistance
PROTAC degraders	KRAS protein degradation	Eliminate oncogenic KRAS protein
RNA-based therapeutics	Suppress KRAS mRNA	Mutation-independent KRAS inhibition

X. EMERGING KRAS THERAPEUTIC STRATEGIES

The clinical success of KRAS G12C inhibitors has significantly advanced precision oncology; however, their therapeutic benefit remains restricted by mutation specificity, acquired resistance, and limited long-term efficacy. Consequently, considerable research efforts are focused on developing next-generation therapeutic approaches capable of targeting a broader spectrum of KRAS alterations while overcoming resistance mechanisms. Emerging strategies include RNA-based therapeutics, immunotherapy, targeted protein degradation, gene-editing technologies, pan-KRAS inhibitors, and rational combination therapies (133–135).

- *RNA-Based Therapeutics*

RNA-based therapeutics have emerged as a promising strategy for suppressing KRAS-driven tumor growth by reducing KRAS gene expression rather than directly inhibiting the protein. Small interfering RNA (siRNA), antisense oligonucleotides (ASOs), and messenger RNA-targeting technologies selectively degrade or silence KRAS transcripts, resulting in decreased protein synthesis and attenuation of downstream oncogenic signalling. These approaches may provide broader therapeutic coverage across multiple KRAS mutations, including variants that remain difficult to target with small-molecule inhibitors. Nevertheless, challenges related to targeted delivery, molecular stability, immune activation, and efficient intracellular uptake continue to limit their widespread clinical application (136–138).

- *KRAS-Directed Immunotherapy*

Mutant KRAS proteins generate tumour-specific neoantigens that can be recognized by the immune system, creating opportunities for highly selective immunotherapeutic interventions. Current strategies include peptide and mRNA

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vaccines, adoptive T-cell therapy, T-cell receptor (TCR)-engineered lymphocytes, and immune checkpoint inhibitor combinations. Early clinical studies have demonstrated encouraging antitumor activity, particularly when KRAS-targeted immunotherapy is combined with conventional systemic treatment. However, treatment efficacy remains influenced by antigen presentation, human leukocyte antigen (HLA) restriction, tumour immune evasion, and the immunosuppressive tumour microenvironment (139–141).

- *PROTAC-Mediated KRAS Degradation*

Proteolysis-targeting chimeras (PROTACs) represent an innovative therapeutic platform that eliminates KRAS protein through ubiquitin-mediated proteasomal degradation. Unlike conventional inhibitors that temporarily suppress protein activity, PROTACs recruit endogenous E3 ubiquitin ligases to KRAS, resulting in selective degradation of the target protein and sustained inhibition of oncogenic signalling. This approach offers potential advantages for overcoming resistance associated with conformational alterations or incomplete target inhibition. Although still in the early stages of development, PROTAC technology has demonstrated considerable promise as a future strategy for treating KRAS-driven malignancies (142–143).

- *CRISPR-Based Gene Editing*

Genome-editing technologies based on the CRISPR–Cas system offer a fundamentally different strategy by directly modifying or disrupting mutant KRAS alleles at the DNA level. Potential applications include selective correction of pathogenic mutations, permanent inactivation of oncogenic KRAS, and transcriptional repression using CRISPR interference platforms. While these approaches have shown encouraging preclinical results, several challenges—including efficient in vivo delivery, off-target editing, immunogenicity, and long-term safety—must be addressed before routine clinical implementation becomes feasible (144).

Overall, emerging KRAS-directed therapeutic platforms extend well beyond conventional small-molecule inhibition and are reshaping the future of precision oncology. The integration of RNA therapeutics, immunotherapy, targeted protein degradation, genome-editing technologies, and rational combination strategies is expected to broaden the spectrum of treatable KRAS alterations, overcome therapeutic resistance, and improve long-term clinical outcomes for patients with KRAS-driven cancers (145).

XI. FUTURE PERSPECTIVES

The successful development of KRAS-targeted therapies has transformed a long-standing challenge in oncology into a major achievement in precision medicine. Although KRAS G12C inhibitors have demonstrated significant clinical benefits, important challenges remain, including acquired resistance, limited activity against non-G12C mutations, and tumour heterogeneity (146,147).

Future research is focused on developing next-generation KRAS inhibitors with broader mutation coverage, including agents targeting KRAS G12D, G12V, and pan-KRAS variants. Combination therapies involving KRAS inhibitors with EGFR, SHP2, MEK, PI3K, or immune checkpoint inhibitors are also being investigated to enhance treatment efficacy and delay resistance (147,148).

Advances in molecular profiling, biomarker-guided patient selection, liquid biopsy, and real-time monitoring of tumour evolution are expected to improve personalized treatment strategies. In addition, emerging technologies such as RNA-based therapeutics, targeted protein degradation, and genome-editing approaches may further expand the therapeutic landscape for KRAS-driven cancers (149,150).

Overall, continued integration of innovative drug development with precision oncology is expected to improve the durability of treatment responses and broaden the clinical application of KRAS-targeted therapies.

XII. CONCLUSION

KRAS has evolved from one of the most challenging oncogenic targets to a clinically actionable therapeutic target in cancer treatment. The development of direct KRAS G12C inhibitors, particularly sotorasib and adagrasib, has demonstrated that selective inhibition of mutant KRAS can produce meaningful clinical benefits in several solid tumours.

Despite these advances, therapeutic resistance, mutation diversity, and adaptive signalling continue to limit long-term treatment success. Ongoing research on next-generation KRAS inhibitors, pan-KRAS inhibitors, RNA-based therapeutics, PROTAC technology, immunotherapy, and rational combination strategies is expected to overcome these limitations and improve patient outcomes.

In conclusion, the rapid progress in KRAS biology, structural drug design, and precision medicine has established KRAS-targeted therapy as an important therapeutic class. Continued clinical and translational research will further expand treatment options and support more personalized and durable therapies for patients with KRAS-driven cancers.

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- *Conflict of Interest*

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1]. Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Nat Rev Drug Discov. 2014;13(11):828–851. doi:10.1038/nrd4389.
[2]. Simanshu DK, Nissley DV, McCormick F. Cell. 2017;170(1):17–33. doi:10.1016/j.cell.2017.06.009.
[3]. Downward J. Nat Rev Cancer. 2003;3(1):11–22. doi:10.1038/nrc969.
[4]. Prior IA, Hood FE, Hartley JL. Cancer Res. 2020;80(14):2969–2974. doi:10.1158/0008-5472.CAN-19-
[5]. 3682.
[6]. Hobbs GA, Der CJ, Rossman KL. Cold Spring Harb Perspect Med. 2016;6(11):a031831. doi:10.1101/cshperspect.a031831.
[7]. Ryan MB, Corcoran RB. Nat Rev Clin Oncol. 2022;19(7):435–456. doi:10.1038/s41571-022-00621-3.
[8]. McCormick F. Clin Cancer Res. 2015;21(8):1797–1801. doi:10.1158/1078-0432.CCR-14-3262.
[9]. Moore AR, Rosenberg SC, McCormick F, Malek S. Nat Rev Drug Discov. 2020;19(8):533–552. doi:10.1038/s41573-020-0068-6.
[10]. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. Nature. 2013;503(7477):548–551. doi:10.1038/nature12796.
[11]. Canon J, Rex K, Saiki AY, et al. Nature. 2019;575(7781):217–223. doi:10.1038/s41586-019-1694-1.
[12]. Hallin J, Bowcut V, Calinisan A, et al. Cancer Discov. 2020;10(1):54–71. doi:10.1158/2159-8290.CD-19-1167.
[13]. Skoulidis F, Li BT, Dy GK, et al. N Engl J Med. 2021;384(25):2371–2381. doi:10.1056/NEJMoa2103695.
[14]. Awad MM, Liu S, Rybkin II, et al. N Engl J Med. 2021;384(25):2382–2393. doi:10.1056/NEJMoa2105281.
[15]. Jänne PA, Riely GJ, Gadgeel SM, et al. N Engl J Med. 2022;387(2):120–131. doi:10.1056/NEJMoa2204619.
[16]. Mullard A. Nat Rev Drug Discov. 2024;23:9–11. doi:10.1038/d41573-024-00001-9.
[17]. Nakajima EC, Drezner N, Li X, et al. Clin Cancer Res. 2024;30(3):451–460. doi:10.1158/1078-0432.CCR-23-2100.
[18]. Malumbres M, Barbacid M. RAS oncogenes: The first 30 years. Nat Rev Cancer. 2003;3(6):459-465. doi:10.1038/nrc1097
[19]. Pylayeva-Gupta Y, Grabocka E, Bar-Sagi D. RAS oncogenes: Weaving a tumorigenic web. Nat Rev Cancer. 2011;11(11):761-774. doi:10.1038/nrc3106
[20]. Fernandez-Medarde A, Santos E. Ras in cancer and developmental diseases. Genes Cancer. 2011;2(3):344-
[21]. 358. doi:10.1177/1947601911411084
[22]. Bos JL. Ras oncogenes in human cancer: A review. Cancer Res. 1989;49(17):4682-4689.
[23]. Prior IA, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. Cancer Res. 2012;72(10):2457-2467. doi:10.1158/0008-5472.CAN-11-2612
[24]. Stephen AG, Esposito D, Bagni RK, McCormick F. Dragging Ras back in the ring. Cancer Cell. 2014;25(3):272-281. doi:10.1016/j.ccr.2014.02.017
[25]. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature. 2013;503(7477):548-551. doi:10.1038/nature12796
[26]. Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature. 2019;575(7781):217-223. doi:10.1038/s41586-019-1694-1
[27]. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. N Engl J Med. 2021;384(25):2371-2381. doi:10.1056/NEJMoa2103695
[28]. Awad MM, Liu S, Rybkin II, et al. Acquired resistance to KRASG12C inhibition in cancer. N Engl J Med. 2021;384(25):2382-2393. doi:10.1056/NEJMoa2105281
[29]. Vetter IR, Wittinghofer A. The guanine nucleotide-binding switch in three dimensions. Science. 2001;294(5545):1299-1304. doi:10.1126/science.1062023
[30]. Wennerberg K, Rossman KL, Der CJ. The Ras superfamily at a glance. J Cell Sci. 2005;118(Pt 5):843-846. doi:10.1242/jcs.01660
[31]. Colicelli J. Human RAS superfamily proteins and related GTPases. Sci STKE. 2004;2004(250):RE13. doi:10.1126/stke.2502004re13
[32]. Pai EF, Krengel U, Petsko GA, Goody RS, Kabsch W, Wittinghofer A. Refined crystal structure of the triphosphate conformation of H-Ras p21. EMBO J. 1990;9(8):2351-2359. doi:10.1002/j.1460-2075.1990.tb07433.x
[33]. Buhrman G, Holzapfel G, Fetics S, Mattos C. Allosteric modulation of Ras positions Q61 for a direct role in catalysis. Proc Natl Acad Sci U S A. 2010;107(11):4931-4936. doi:10.1073/pnas.0912226107
[34]. Ostrem JM, Shokat KM. Direct small-molecule inhibitors of KRAS: From structural insights to mechanism-based design. Nat Rev Drug Discov. 2016;15(11):771-785. doi:10.1038/nrd.2016.139
[35]. Cherfils J, Zeghouf M. Regulation of small GTPases by GEFs, GAPs, and GDIs. Physiol Rev. 2013;93(1):269-309. doi:10.1152/physrev.00003.2012
[36]. Vigil D, Cherfils J, Rossman KL, Der CJ. Ras superfamily GEFs and GAPs: Validated and tractable targets for cancer therapy? Nat Rev Cancer. 2010;10(12):842-857. doi:10.1038/nrc2960
[37]. Stephen AG, Esposito D, Bagni RK, McCormick F. Dragging Ras back in the ring. Cancer Cell. 2014;25(3):272-281. doi:10.1016/j.ccr.2014.02.017

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug015

[38]. Cox AD, Der CJ. Ras history: The saga continues. Small GTPases. 2010;1(1):2-27. doi:10.4161/sgtp.1.1.12178
[39]. Waters AM, Der CJ. KRAS: The critical driver and therapeutic target for pancreatic cancer. Cold Spring Harb Perspect Med. 2018;8(9):a031435. doi:10.1101/cshperspect.a031435
[40]. Hobbs GA, Der CJ, Rossman KL. RAS isoforms and mutations in cancer at a glance. J Cell Sci. 2016;129(7):1287-1292. doi:10.1242/jcs.182873
[41]. Lavoie H, Therrien M. Regulation of RAF protein kinases in ERK signalling. Nat Rev Mol Cell Biol. 2015;16(5):281-298. doi:10.1038/nrm3979
[42]. Roskoski R Jr. Targeting ERK1/2 protein-serine/threonine kinases in human cancers. Pharmacol Res. 2019;142:151-168. doi:10.1016/j.phrs.2019.02.009
[43]. Samatar AA, Poulikakos PI. Targeting RAS-ERK signalling in cancer. Nat Rev Drug Discov. 2014;13(12):928-942. doi:10.1038/nrd4282
[44]. Fruman DA, Chiu H, Hopkins BD, et al. The PI3K pathway in human disease. Cell. 2017;170(4):605-635. doi:10.1016/j.cell.2017.07.029
[45]. Hoxhaj G, Manning BD. The PI3K–AKT network at the interface of oncogenic signalling and cancer metabolism. Nat Rev Cancer. 2020;20(2):74-88. doi:10.1038/s41568-019-0216-7
[46]. Porta C, Paglino C, Mosca A. Targeting PI3K/AKT/mTOR signaling in cancer. Front Oncol. 2014;4:64. doi:10.3389/fonc.2014.00064
[47]. Neel NF, Rossman KL, Martin TD, et al. The RalGEF–RAL effector pathway. Genes Cancer. 2011;2(3):275-
[48]. 287. doi:10.1177/1947601911407328
[49]. Yan C, Theodorescu D. RAL GTPases: Biology and potential as therapeutic targets. Pharmacol Rev. 2018;70(1):1-11. doi:10.1124/pr.117.014415
[50]. Lim KH, O'Hayer K, Adam SJ, et al. Divergent roles for RalA and RalB in cancer initiation and progression. Clin Cancer Res. 2006;12(18):5405-5418. doi:10.1158/1078-0432.CCR-06-0997
[51]. McCormick F. KRAS as a therapeutic target. Clin Cancer Res. 2015;21(8):1797-1801. doi:10.1158/1078-0432.CCR-14-2662
[52]. Cox AD, Der CJ. The dark side of Ras: Regulation of apoptosis. Oncogene. 2003;22:8999-9006. doi:10.1038/sj.onc.1207111
[53]. Moore AR, Rosenberg SC, McCormick F, Malek S. RAS-targeted therapies: Is the undruggable drugged? Nat Rev Drug Discov. 2020;19:533-552. doi:10.1038/s41573-020-0068-6
[54]. Samatar AA, Poulikakos PI. Targeting RAS-ERK signalling in cancer. Nat Rev Drug Discov. 2014;13:928-942. doi:10.1038/nrd4282
[55]. Hoxhaj G, Manning BD. The PI3K-AKT network in cancer. Nat Rev Cancer. 2020;20:74-88. doi:10.1038/s41568-019-0216-7
[56]. Cox AD, Fesik SW, Kimmelman AC, et al. Drugging the undruggable RAS. Nat Rev Drug Discov. 2014;13:828-851. doi:10.1038/nrd4389
[57]. Ostrem JM, Peters U, Sos ML, et al. Nature. 2013;503:548-551. doi:10.1038/nature12796
[58]. Patricelli MP, Janes MR, Li LS, et al. Selective inhibition of oncogenic KRAS output with small molecules targeting the inactive state. Cancer Discov. 2016;6:316-329. doi:10.1158/2159-8290.CD-15-1105
[59]. Janes MR, Zhang J, Li LS, et al. Targeting KRAS mutant cancers with a covalent G12C-specific inhibitor. Cell. 2018;172:578-589. doi:10.1016/j.cell.2018.01.006
[60]. Canon J, Rex K, Saiki AY, et al. Nature. 2019;575:217-223. doi:10.1038/s41586-019-1694-1
[61]. Hallin J, Bowcut V, Calinisan A, et al. Cancer Discov. 2020;10:54-71. doi:10.1158/2159-8290.CD-19-1167
[62]. Skoulidis F, Li BT, Dy GK, et al. N Engl J Med. 2021;384:2371-2381. doi:10.1056/NEJMoa2103695
[63]. Mullard A. Cracking KRAS. Nat Rev Drug Discov. 2024;23:9-11. doi:10.1038/d41573-024-00001-9
[64]. Hallin J, et al. Cancer Discov. 2020;10:54-71. doi:10.1158/2159-8290.CD-19-1167
[65]. Jänne PA, Riely GJ, Gadgeel SM, et al. N Engl J Med. 2022;387:120-131. doi:10.1056/NEJMoa2204619
[66]. Sabari JK, Velcheti V, Shimizu K, et al. KRYSTAL-1 clinical updates. J Clin Oncol. 2022.
[67]. Bekaii-Saab TS, et al. Adagrasib in colorectal cancer. N Engl J Med. 2023;388:44-54. doi:10.1056/NEJMoa2212419
[68]. Bekaii-Saab TS, Spira AI, Yaeger R, et al. Adagrasib plus cetuximab in patients with KRAS G12C-mutated metastatic colorectal cancer. N Engl J Med. 2024;390(11):997-1008. doi:10.1056/NEJMoa2314485
[69]. Yaeger R, Weiss J, Pelster MS, et al. Adagrasib with or without cetuximab in KRAS G12C-mutated colorectal cancer. Cancer Discov. 2024;14(2):250-263. doi:10.1158/2159-8290.CD-23-0463
[70]. Awad MM, Liu S, Rybkin II, et al. Acquired resistance to KRASG12C inhibition in cancer. N Engl J Med. 2021;384(25):2382-2393. doi:10.1056/NEJMoa2105281
[71]. Tanaka N, Lin JJ, Li C, et al. Clinical acquired resistance to KRASG12C inhibition through a novel KRAS switch-II pocket mutation. Cancer Discovery. 2021;11(11):2870-2881. doi:10.1158/2159-8290.CD-21-0365
[72]. Koga T, Suda K, Fujino T, et al. KRAS secondary mutations and acquired resistance to KRAS G12C inhibitors. J Thorac Oncol. 2021;16(8):1321-1332. doi:10.1016/j.jtho.2021.04.015
[73]. Ryan MB, Corcoran RB. Therapeutic strategies to target RAS-mutant cancers. Nat Rev Clin Oncol. 2022;19(7):435-456. doi:10.1038/s41571-022-00621-3
[74]. Mullard A. KRAS inhibitors continue to expand the precision oncology landscape. Nat Rev Drug Discov. 2024;23(1):9-11. doi:10.1038/d41573-024-00001-9
[75]. Hofmann MH, Gmachl M, Ramharter J, et al. BI-2865: A non-covalent pan-KRAS inhibitor with broad antitumor activity. Nature. 2024;628:169-176. doi:10.1038/s41586-024-07205-6

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug015

[76]. Hong DS, Fakih MG, Strickler JH, et al. KRASG12C inhibition with sotorasib in advanced solid tumors. N Engl J Med. 2020;383(13):1207-1217. doi:10.1056/NEJMoa1917239
[77]. Canon J, Rex K, Saiki AY, et al. Nature. 2019;575:217-223. doi:10.1038/s41586-019-1694-1
[78]. Skoulidis F, Li BT, Dy GK, et al. N Engl J Med. 2021;384:2371-2381. doi:10.1056/NEJMoa2103695
[79]. Fell JB, Fischer JP, Baer BR, et al. Discovery of sotorasib (AMG 510). J Med Chem. 2020;63:6679-6693. doi:10.1021/acs.jmedchem.9b02052
[80]. Ostrem JM, Shokat KM. Nat Rev Drug Discov. 2016;15:771-785. doi:10.1038/nrd.2016.139
[81]. Moore AR, Rosenberg SC, McCormick F, Malek S. Nat Rev Drug Discov. 2020;19:533-552. doi:10.1038/s41573-020-0068-6
[82]. Jänne PA, Riely GJ, Gadgeel SM, et al. N Engl J Med. 2022;387:120-131. doi:10.1056/NEJMoa2204619
[83]. Fakih MG, Kopetz S, Kuboki Y, et al. N Engl J Med. 2023;389:2125-2139. doi:10.1056/NEJMoa2308795
[84]. Li BT, Velcheti V, Koczywas M, et al. J Clin Oncol. 2023;41:3311-3322. doi:10.1200/JCO.22.02733
[85]. Fakih MG, et al. Sotorasib plus panitumumab in KRAS G12C metastatic colorectal cancer. N Engl J Med. 2023;389:2125-2139. doi:10.1056/NEJMoa2308795
[86]. Yaeger R, et al. Cancer Discovery. 2024;14:250-263. doi:10.1158/2159-8290.CD-23-0463
[87]. Bekaii-Saab TS, et al. N Engl J Med. 2024;390:997-1008. doi:10.1056/NEJMoa2314485
[88]. Awad MM, Liu S, Rybkin II, et al. Acquired resistance to KRAS^{G12C} inhibition in cancer. N Engl J Med. 2021;384(25):2382-2393. doi:10.1056/NEJMoa2105281
[89]. Ryan MB, Corcoran RB. Therapeutic strategies to target RAS-mutant cancers. Nat Rev Clin Oncol. 2022;19(7):435-456. doi:10.1038/s41571-022-00621-3
[90]. Punekar SR, Velcheti V, Neel BG, Wong KK. The current state of the art and future trends in RAS-targeted cancer therapies. Nat Rev Clin Oncol. 2022;19(10):637-655. doi:10.1038/s41571-022-00671-9
[91]. Huang L, Guo Z, Wang F, Fu L. KRAS mutation: from undruggable to druggable in cancer. Signal Transduct Target Ther. 2021;6:386. doi:10.1038/s41392-021-00780-4
[92]. Singhal A, Li BT, O'Reilly EM. Targeting KRAS in cancer. Nat Med. 2024;30:969-983. doi:10.1038/s41591-024-02903-0
[93]. Nussinov R, Jang H. Direct K-Ras inhibitors to treat cancers: Progress, new insights, and approaches to treat resistance. Annu Rev Pharmacol Toxicol. 2024;64:231-253. doi:10.1146/annurev-pharmtox-022823-113946
[94]. Tanaka N, Lin JJ, Li C, et al. Clinical acquired resistance to KRAS^{G12C} inhibition through a novel KRAS switch-II pocket mutation. Cancer Discov. 2021;11(11):2870-2887. doi:10.1158/2159-8290.CD-21-0365
[95]. Negrao MV, Araujo HA, Lamberti G, et al. Co-mutations and KRAS G12C inhibitor efficacy in advanced NSCLC. Cancer Discov. 2023;13. doi:10.1158/2159-8290.CD-22-1420
[96]. Hofmann MH, Gmachl M, Ramharter J, et al. BI-2865: A non-covalent pan-KRAS inhibitor with broad antitumor activity. Nature. 2024;628:169-176. doi:10.1038/s41586-024-07205-6
[97]. Patricelli MP, Janes MR, Li LS, et al. Selective inhibition of oncogenic KRAS output with small molecules targeting the inactive state. Cancer Discov. 2016;6(3):316-329. doi:10.1158/2159-8290.CD-15-1105
[98]. Janes MR, Zhang J, Li LS, et al. Targeting KRAS mutant cancers with a covalent G12C-specific inhibitor. Cell. 2018;172(3):578-589.e17. doi:10.1016/j.cell.2018.01.006
[99]. Hallin J, Bowcut V, Calinisan A, et al. The KRAS^{G12C} inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers. Cancer Discov. 2020;10(1):54-71. doi:10.1158/2159-8290.CD-19-1167
[100]. Canon J, Rex K, Saiki AY, et al. The clinical KRAS^{G12C} inhibitor AMG 510 drives anti-tumour immunity. Nature. 2019;575(7781):217-223. doi:10.1038/s41586-019-1694-1
[101]. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature. 2013;503(7477):548-551. doi:10.1038/nature12796
[102]. Moore AR, Rosenberg SC, McCormick F, Malek S. RAS-targeted therapies: Is the undruggable drugged? Nat Rev Drug Discov. 2020;19(8):533-552. doi:10.1038/s41573-020-0068-6
[103]. Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Drugging the undruggable RAS: Mission possible? Nat Rev Drug Discov. 2014;13(11):828-851. doi:10.1038/nrd4389
[104]. Fell JB, Fischer JP, Baer BR, et al. Identification of the clinical development candidate MRTX849, a covalent KRAS^{G12C} inhibitor. J Med Chem. 2020;63(13):6679-6693. doi:10.1021/acs.jmedchem.9b02052
[105]. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. N Engl J Med. 2021;384(25):2371-2381. doi:10.1056/NEJMoa2103695
[106]. Ying H, Kimmelman AC, Lyssiotis CA, et al. Oncogenic KRAS maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell. 2012;149(3):656-670. doi:10.1016/j.cell.2012.01.058
[107]. Vander Heiden MG, DeBerardinis RJ. Understanding the intersections between metabolism and cancer biology. Cell. 2017;168(4):657-669. doi:10.1016/j.cell.2016.12.039

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug015

[108]. Pavlova NN, Thompson CB. The emerging hallmarks of cancer metabolism. Cell Metab. 2016;23(1):27-47. doi:10.1016/j.cmet.2015.12.006
[109]. Bryant KL, Mancias JD, Kimmelman AC, Der CJ. KRAS: Feeding pancreatic cancer proliferation. Trends Biochem Sci. 2014;39(2):91-100. doi:10.1016/j.tibs.2013.12.004
[110]. DeBerardinis RJ, Chandel NS. Fundamentals of cancer metabolism. Sci Adv. 2016;2(5):e1600200. doi:10.1126/sciadv.1600200
[111]. Boroughs LK, DeBerardinis RJ. Metabolic pathways promoting cancer cell survival and growth. Nat Cell Biol. 2015;17(4):351-359. doi:10.1038/ncb3124
[112]. Son J, Lyssiotis CA, Ying H, et al. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. Nature. 2013;496(7443):101-105. doi:10.1038/nature12040
[113]. Altman BJ, Stine ZE, Dang CV. From Krebs to clinic: Glutamine metabolism in cancer. Nat Rev Cancer. 2016;16(10):619-634. doi:10.1038/nrc.2016.71
[114]. Muir A, Vander Heiden MG. The nutrient environment affects therapy. Science. 2018;360(6392):962-963. doi:10.1126/science.aas9690
[115]. Kimmelman AC, White E. Autophagy and tumor metabolism. Cell Metab. 2017;25(5):1037-1043. doi:10.1016/j.cmet.2017.04.004
[116]. Guo JY, Xia B, White E. Autophagy-mediated tumor promotion. Cancer Cell. 2013;23(2):143-145. doi:10.1016/j.ccr.2013.01.019
[117]. Santana-Codina N, Mancias JD, Kimmelman AC. The role of autophagy in cancer metabolism. Mol Cell. 2017;66(4):473-486. doi:10.1016/j.molcel.2017.04.004
[118]. Reina-Campos M, Moscat J, Diaz-Meco MT. Metabolism shapes the tumor microenvironment. Nat Rev Cancer. 2017;17(5):302-311. doi:10.1038/nrc.2017.32
[119]. Koundouros N, Poulogiannis G. Reprogramming of fatty acid metabolism in cancer. Br J Cancer. 2020;122(1):4-22. doi:10.1038/s41416-019-0650-z
[120]. Faubert B, Solmonson A, DeBerardinis RJ. Metabolic reprogramming and cancer progression. Science. 2020;368(6487):eaaw5473. doi:10.1126/science.aaw5473
[121]. Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Drugging the undruggable RAS: Mission possible? Nat Rev Drug Discov. 2014;13(11):828-851. doi:10.1038/nrd4389
[122]. Moore AR, Rosenberg SC, McCormick F, Malek S. RAS-targeted therapies: Is the undruggable drugged? Nat Rev Drug Discov. 2020;19(8):533-552. doi:10.1038/s41573-020-0068-6
[123]. Ryan MB, Corcoran RB. Therapeutic strategies to target RAS-mutant cancers. Nat Rev Clin Oncol. 2022;19(7):435-456. doi:10.1038/s41571-022-00621-3
[124]. Hofmann MH, Gmachl M, Ramharter J, et al. BI-2865: A non-covalent pan-KRAS inhibitor with broad antitumor activity. Nature. 2024;628:169-176. doi:10.1038/s41586-024-07205-6
[125]. Hofmann MH, Gerlach D, Misale S, et al. Expanding the reach of KRAS-targeted therapies. Cancer Discov. 2022;12(4):924-937. doi:10.1158/2159-8290.CD-21-1331
[126]. Canon J, Rex K, Saiki AY, et al. The clinical KRASG12C inhibitor AMG 510 drives anti-tumour immunity. Nature. 2019;575(7781):217-223. doi:10.1038/s41586-019-1694-1
[127]. Hillig RC, Sautier B, Schroeder J, et al. Discovery of potent SOS1 inhibitors for KRAS-driven cancers. Cancer Discov. 2019;9(1):128-145. doi:10.1158/2159-8290.CD-18-0742
[128]. Fedele C, Li S, Teng KW, et al. SHP2 inhibition prevents adaptive resistance to KRAS inhibition. Nature. 2021;599(7886):679-683. doi:10.1038/s41586-021-04104-1
[129]. Nichols RJ, Haderk F, Stahlhut C, et al. RMC-4630, a SHP2 inhibitor, enhances KRAS-targeted therapy. Cancer Discov. 2023;13(2):456-473. doi:10.1158/2159-8290.CD-22-0674
[130]. Hata AN, Shaw AT. Resistance mechanisms to targeted therapies in cancer. Nat Rev Cancer. 2020;20(7):403-
[131]. 421. doi:10.1038/s41568-020-0252-9
[132]. Békés M, Langley DR, Crews CM. PROTAC targeted protein degraders: The past, present and future. Nat Rev Drug Discov. 2022;21(3):181-200. doi:10.1038/s41573-021-00371-6
[133]. Dammes N, Peer D. Paving the road for RNA therapeutics. Trends Pharmacol Sci. 2020;41(10):755-775. doi:10.1016/j.tips.2020.08.004
[134]. Huang L, Guo Z, Wang F, Fu L. KRAS mutation: From undruggable to druggable in cancer. Signal Transduct Target Ther. 2021;6:386. doi:10.1038/s41392-021-00780-4
[135]. Punekar SR, Velcheti V, Neel BG, Wong KK. The current state of the art and future trends in RAS-targeted cancer therapies. Nat Rev Clin Oncol. 2022;19(10):637-655. doi:10.1038/s41571-022-00671-9
[136]. Singhal A, Li BT, O'Reilly EM. Targeting KRAS in cancer. Nat Med. 2024;30:969-983. doi:10.1038/s41591-024-02903-0
[137]. Moore AR, Rosenberg SC, McCormick F, Malek S. RAS-targeted therapies: Is the undruggable drugged? Nat Rev Drug Discov. 2020;19(8):533-552. doi:10.1038/s41573-020-0068-6
[138]. Ryan MB, Corcoran RB. Therapeutic strategies to target RAS-mutant cancers. Nat Rev Clin Oncol. 2022;19(7):435-456. doi:10.1038/s41571-022-00621-3
[139]. Singhal A, Li BT, O'Reilly EM. Targeting KRAS in cancer. Nat Med. 2024;30(4):969-983. doi:10.1038/s41591-024-02903-0

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug015

[140]. Dammes N, Peer D. Paving the road for RNA therapeutics. Trends Pharmacol Sci. 2020;41(10):755-775. doi:10.1016/j.tips.2020.08.004
[141]. Setten RL, Rossi JJ, Han SP. The current state and future directions of RNAi-based therapeutics. Nat Rev Drug Discov. 2019;18(6):421-446. doi:10.1038/s41573-019-0017-4
[142]. Kulkarni JA, Witzigmann D, Chen S, Cullis PR, van der Meel R. Lipid nanoparticle technology for clinical translation of nucleic acid therapeutics. Nat Nanotechnol. 2021;16(6):630-643. doi:10.1038/s41565-021-00898-0
[143]. Tran E, Robbins PF, Lu YC, Prickett TD, Gartner JJ, Jia L, et al. T-cell transfer therapy targeting mutant KRAS in cancer. N Engl J Med. 2016;375(23):2255-2262. doi:10.1056/NEJMoa1609279
[144]. Leidner R, Sanjuan Silva N, Huang H, Sprott D, Zheng C, Shih YP, et al. Neoantigen T-cell receptor gene therapy targeting mutant KRAS in pancreatic cancer. Nat Med. 2022;28(10):2168-2177. doi:10.1038/s41591-022-01927-7
[145]. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature. 2017;547(7662):217-221. doi:10.1038/nature22991
[146]. Békés M, Langley DR, Crews CM. PROTAC targeted protein degraders: The past, present and future. Nat Rev Drug Discov. 2022;21(3):181-200. doi:10.1038/s41573-021-00371-6
[147]. Bondeson DP, Crews CM. Targeted protein degradation by small molecules. Annu Rev Pharmacol Toxicol. 2017;57:107-123. doi:10.1146/annurev-pharmtox-010716-104927
[148]. Doudna JA. The promise and challenge of therapeutic genome editing. Nature. 2020;578(7794):229-236. doi:10.1038/s41586-020-1978-5
[149]. Hofmann MH, Gmachl M, Ramharter J, Savarese F, Gerlach D, Marszalek JR, et al. BI-2865: A non-covalent pan-KRAS inhibitor with broad antitumor activity. Nature. 2024;628(8007):169-176. doi:10.1038/s41586-024-07205-6
[150]. Singhal A, Li BT, O'Reilly EM. Targeting KRAS in cancer. Nat Med. 2024;30(4):969-983. doi:10.1038/s41591-024-02903-0
[151]. Ryan MB, Corcoran RB. Therapeutic strategies to target RAS-mutant cancers. Nat Rev Clin Oncol. 2022;19(7):435-456. doi:10.1038/s41571-022-00621-3
[152]. Moore AR, Rosenberg SC, McCormick F, Malek S. RAS-targeted therapies: Is the undruggable drugged? Nat Rev Drug Discov. 2020;19(8):533-552. doi:10.1038/s41573-020-0068-6
[153]. Hofmann MH, Gmachl M, Ramharter J, et al. BI-2865: A non-covalent pan-KRAS inhibitor with broad antitumor activity. Nature. 2024;628(8007):169-176. doi:10.1038/s41586-024-07205-6
[154]. Huang L, Guo Z, Wang F, Fu L. KRAS mutation: From undruggable to druggable in cancer. Signal Transduct Target Ther. 2021;6:386. doi:10.1038/s41392-021-00780-4