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Targeting KRAS – The previously undruggable mutations in oncology

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Abstract

The characterization of oncogenic driver mutations has revolutionized cancer biology, but certain genetic alterations—such as KRAS, NRAS, and MYC—remained long considered "undruggable" due to structural and functional constraints. Recent advances in structural biology, covalent inhibitor design, and targeted protein degradation have transformed this paradigm, leading to the development of selective agents against previously elusive targets. KRAS mutations, particularly KRAS^G12C^, have emerged as prominent therapeutic candidates with the advent of covalent inhibitors such as Sotorasib and Adagrasib, which exploit unique allosteric pockets. Parallel innovations, including PROTAC technology, synthetic lethality strategies, and RNA-based therapeutics, further expand the therapeutic landscape. Despite encouraging clinical activity, resistance mechanisms—both adaptive and acquired—pose significant challenges, necessitating rational combination therapies and biomarker-driven patient selection. This review summarizes the evolution from "undruggable" to "drugged" targets, highlights the structural and biochemical breakthroughs enabling KRAS inhibition, and explores the future directions of integrating these agents into precision oncology frameworks.

Introduction

Cancer is fundamentally a genetic disease, driven by the accumulation of somatic mutations that disrupt normal cellular signalling, proliferation, and survival mechanisms. Over the past three decades, advances in genomic profiling have enabled the identification of numerous oncogenic "driver" mutations, leading to the development of targeted therapies that have transformed outcomes for certain cancers.[1,2] However, not all oncogenic alterations are amenable to pharmacological intervention. A subset of these, including mutations in KRAS, NRAS, MYC, and p53, were historically classified as "undruggable" because of structural, biochemical, or functional properties that precluded effective targeting.[3] This designation reflected challenges such as the absence of deep,

druggable pockets on the protein surface, high affinity for endogenous ligands, or critical roles in protein–protein interactions that resisted small-molecule disruption.[4]

Among these targets, the Kirsten rat sarcoma viral oncogene homolog (KRAS) has been particularly notorious. Mutations in KRAS occur in approximately 25% of all human cancers, with especially high prevalence in pancreatic ductal adenocarcinoma (~90%), colorectal cancer (~40%), and non-small cell lung cancer (NSCLC) (~30%).[5,6] These mutations, most commonly affecting codons 12, 13, and 61, lock the KRAS protein in a constitutively active GTP-bound state, thereby driving persistent downstream signalling through pathways such as MAPK and PI3K–AKT–mTOR.[7] The oncogenic potency of KRAS, combined with its high mutational frequency, made it an appealing therapeutic target—but its small, smooth surface and picomolar affinity for GTP/GDP thwarted decades of drug discovery efforts.[8,9]

The "undruggable" label have been challenged with the advent of advanced structural biology techniques, including high-resolution X-ray crystallography and cryo-electron microscopy, which revealed previously hidden allosteric binding pockets.[10] In the case of bKRAS^G12C^, a cysteine residue introduced by the mutation enable the design of covalent inhibitors that irreversibly lock KRAS in its inactive GDP-bound form.[11] The development of Sotorasib (AMG 510) and Adagrasib (MRTX849) marked historic milestones, demonstrating not only the clinical feasibility of KRAS inhibition but also the broader potential to tackle other long-elusive oncogenic drivers.[12,13] The successful "drugging" of KRAS has also reinvigorated efforts to target other previously resistant proteins through diverse strategies, such as targeted protein degradation (PROTACs), synthetic lethality approaches, stapled peptides, and RNA-based therapeutics.[14-16] Moreover, the integration of computational chemistry, AI-driven drug discovery, and fragment-based screening is accelerating the identification of novel ligands for difficult targets.[17,18] However, despite initial clinical success, resistance to KRAS inhibitors—via secondary mutations, adaptive signalling reprogramming, or bypass pathway activation—remains a major obstacle.[19] Addressing these challenges will require combination therapy strategies, biomarker-guided patient selection, and continued innovation in drug design.

This review explores the journey from the concept of "undruggable" mutations to the emergence of effective therapeutics, with a particular focus on KRAS. It discusses the historical barriers, the structural and biochemical breakthroughs that made targeting possible, the clinical impact of first-generation inhibitors, mechanisms of resistance, and the future directions that may shape the next decade of oncology therapeutics.

Historical Context and Challenges

The quest to therapeutically target oncogenic mutations dates to the mid-20th century, when the molecular underpinnings of cancer began to be unravelled. The discovery of the RAS gene family in the early 1980s—HRAS, KRAS, and NRAS—provided a pivotal insight into the genetic basis of malignant transformation.[20] Mutations in these small GTPases were soon linked to uncontrolled cell proliferation and tumor progression, establishing them as prime oncogenic drivers across multiple cancer types.[21] However, early drug discovery

efforts in the 1980s and 1990s encountered immediate roadblocks. For KRAS, the first major challenge stemmed from its biochemical properties. As a molecular switch, KRAS cycles between an inactive GDP-bound state and an active GTP-bound state, tightly regulated by guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs).[22] Its picomolar affinity for GTP/GDP, coupled with the high intracellular concentration of these nucleotides, meant that competitive inhibition was virtually impossible under physiological conditions.[23] Furthermore, KRAS lacked deep hydrophobic pockets or grooves where a small molecule could bind with high specificity—earning it the "smooth surface" problem designation in medicinal chemistry circles.[24]

Early therapeutic approaches attempted indirect inhibition by targeting downstream effectors in the MAPK or PI3K pathways. While MEK and ERK inhibitors showed preclinical promise, their clinical efficacy in KRAS-mutant cancers was limited due to pathway redundancy and compensatory signalling.[25,26] Another strategy focused on preventing KRAS membrane localization, a prerequisite for its signalling activity. Farnesyl transferase inhibitors (FTIs) were developed to block the post-translational lipid modification essential for KRAS anchoring to the plasma membrane.[27] However, KRAS was found to bypass this blockade via alternative prenylation pathways, rendering FTIs largely ineffective in KRAS-driven tumours.[28] Technological limitations also played a role in the protracted stalemate. Until the late 2000s, structural insights into KRAS and other small GTPases were constrained by the resolution limits of available crystallographic methods.[29] Without precise knowledge of potential allosteric sites, rational drug design was largely speculative. Similarly, screening platforms of the era lacked the sensitivity and throughput required to identify weak or transient small-molecule interactions with KRAS.[30]

Beyond the structural and biochemical hurdles, there were biological and clinical complexities. KRAS mutations occur in tumours with inherently aggressive phenotypes and poor prognosis, such as pancreatic ductal adenocarcinoma (PDAC) and certain subsets of NSCLC.[31] These malignancies often present late, exhibit high genomic instability, and harbour additional mutations that confer therapy resistance.[32] Moreover, the tumour microenvironment (TME) in KRAS-driven cancers is characterized by dense stroma, hypoxia, and immunosuppressive signalling, all of which further reduce drug delivery and efficacy.[33] The combination of these factors created a persistent narrative within oncology that KRAS and similar oncogenes were "undruggable" targets—a label that discouraged many pharmaceutical programs from investing in direct inhibitor development.[34] It was not until the convergence of high-resolution structural biology, fragment-based drug discovery, and covalent chemistry in the 2010s that this dogma was successfully challenged.[35]

This historical backdrop underscores why the development of KRAS inhibitors such as Sotorasib and Adagrasib represented a paradigm shift—not merely in therapeutic capability but in the philosophy of drug discovery itself. The transition from decades of failed attempts to viable clinical agents exemplifies how technological innovation and a deeper molecular understanding can overturn long-held assumptions in oncology.

Breakthroughs in Targeting KRAS

The turning point in the decades-long effort to target KRAS came with the realization that specific mutations could create unique vulnerabilities not present in the wild-type protein. The landmark discovery of an exploitable allosteric pocket adjacent to the switch II region in the KRAS^G12C^ mutant—absent in other KRAS isoforms—was pivotal.[36] This mutation, a glycine-to-cysteine substitution at codon 12, introduced a nucleophilic thiol group that could be covalently bound by electrophilic small molecules.[7] Such covalent engagement enabled selective inhibition of the mutant protein without affecting normal KRAS function, overcoming the longstanding "no binding pocket" obstacle.[37] Fragment-based drug discovery and high-resolution X-ray crystallography played critical roles in this breakthrough.

Discovery of the Switch-II Pocket

Ostrem et al. at the University of California, San Francisco, identified small molecules capable of binding irreversibly to KRAS^G12C^ by targeting the newly described switch II pocket (S-IIP).[12] These compounds trapped KRAS in its inactive GDP-bound state, effectively shutting down downstream MAPK signalling.[13] This pivotal breakthrough came with discovery of the switch-II pocket in KRAS G12C, enabled design of mutant-selective, covalent inhibitors such as Sotorasib (AMG510) and Adagrasib (MRTX849). These drugs lock KRAS G12C in its inactive state, selectively halting downstream signalling in cancer cells.[38,39]

Approved KRAS Inhibitors - The success of these early leads catalysed rapid medicinal chemistry optimization, culminating in the development of first-in-class clinical inhibitors such as Sotorasib (AMG 510) and Adagrasib (MRTX849).[40]

Sotorasib (AMG510): First-in-class KRAS G12C inhibitor, FDA-approved for NSCLC. Demonstrated response rates of ~37% and median progression-free survival of 6.8 months in clinical trials.[38,41] Sotorasib demonstrated unprecedented activity in KRAS^G12C^-mutant non-small cell lung cancer (NSCLC), achieving objective response rates (ORRs) of approximately 37% in pretreated patients.[42]42

Adagrasib (MRTX849): Another FDA-approved G12C inhibitor, response rates reported at ~43% in NSCLC.[41] Adagrasib, with a longer half-life and broader tissue penetration, has shown comparable efficacy, particularly in central nervous system metastases, which are frequent in KRAS-mutant NSCLC.[43]

Other Agents: Fulzerasib (GFH925/IBI351), Divarasib, and others in various stages of development targeting G12C and other KRAS mutations.[41,43]

The clinical development of these agents was facilitated by advances in biomarker-driven precision oncology. Routine next-generation sequencing (NGS) enabled rapid identification of KRAS^G12C^-positive tumours, streamlining patient selection for targeted therapy trials. In parallel, regulatory agencies embraced accelerated approval pathways, recognizing the high unmet need in this molecularly defined subgroup.[45] Importantly, breakthroughs in targeting KRAS have extended beyond G12C mutations. Novel strategies, such as targeting KRAS^G12D^ and KRAS^G12V^ variants, are now advancing through preclinical and

early clinical stages.[46] Approaches include covalent and non-covalent inhibitors, as well as indirect targeting via synthetic lethality—exploiting the dependency of KRAS-mutant cells on parallel pathways such as SHP2, SOS1, and CDK4/6.[47,48]

Another significant innovation is targeted protein degradation. Proteolysis-targeting chimeras (PROTACs) and molecular glue degraders are being engineered to recruit KRAS to E3 ubiquitin ligases, triggering selective proteasomal degradation of the mutant protein.35[35] While these agents remain largely preclinical, they hold the potential to circumvent resistance mutations that impair inhibitor binding.[49] The lessons learned from the KRAS^G12C^ inhibitor story have also reinvigorated interest in other historically undruggable oncogenes. The combination of structural biology, covalent chemistry, and precision diagnostics is now being applied to targets such as MYC, β-catenin, and transcription factor fusions.[50] Thus, the breakthroughs in KRAS drug development not only represent a triumph over a once "undruggable" target but also provide a blueprint for future oncology drug discovery.

Discussion

The therapeutic targeting of historically "undruggable" oncogenic mutations such as KRAS represents a paradigm shift in precision oncology. For decades, KRAS served as the prototypical example of a challenging drug target—its small, smooth surface and high GTP/GDP affinity prevented the identification of selective small-molecule inhibitors. The success of KRAS^G12C^ inhibitors such as Sotorasib and Adagrasib marks a watershed moment, not only in RAS-targeted drug development but in the overall drug discovery mindset, demonstrating that persistent structural and mechanistic challenges can be overcome through innovative chemistry, structural biology, and translational research.[4,12,51] From a molecular oncology standpoint, the breakthrough lies in the exploitation of a previously unrecognized allosteric pocket, accessible only in the inactive GDP-bound state of KRAS^G12C^. This pocket allows for covalent binding, achieving selectivity and potency without disrupting essential cellular GTPases. These inhibitors have shown promising clinical benefit, especially in non–small-cell lung cancer (NSCLC) patients harbouring KRAS^G12C^ mutations, with objective response rates (ORR) ranging from 32% to 43% in heavily pretreated populations.[12] However, the durability of these responses remains limited, with median progression-free survival (PFS) rarely exceeding 6–8 months.[41]

The emergence of acquired resistance—via secondary KRAS mutations, activation of bypass signalling pathways (e.g., EGFR, FGFR2, MET), and adaptive feedback through SHP2 and SOS1—has shifted the therapeutic discussion toward rational combination approaches. Early-phase trials combining KRAS^G12C^ inhibitors with SHP2 inhibitors, EGFR inhibitors, or immune checkpoint blockade have shown preliminary efficacy and may address both primary and acquired resistance mechanisms.[42,51] The challenge lies in balancing additive efficacy with tolerability, as combinatorial regimens risk cumulative toxicity. The lessons learned from KRAS are broadly applicable to other "undruggable" targets such as KRAS^G12D^, MYC, β-catenin, and mutant p53.[13,52] For KRAS^G12D^, structure-guided drug design and fragment-based screening have yielded highly selective inhibitors such as MRTX1133,[13] which are now

advancing toward clinical trials. Meanwhile, targeted protein degradation strategies such as PROTACs[53,54] offer an alternative for proteins lacking accessible small-molecule binding sites, potentially bypassing the need for high-affinity ligand design.

Importantly, the KRAS journey underscores the need for an integrated drug development pipeline that aligns medicinal chemistry innovations with patient selection strategies and biomarker development. Without robust predictive biomarkers and real-time molecular monitoring, the clinical utility of these inhibitors will remain suboptimal. Liquid biopsy–based minimal residual disease (MRD) detection and circulating tumour DNA (ctDNA) profiling may enable earlier intervention and dynamic treatment adaptation. From a translational research perspective, KRAS targeting has also reinvigorated the concept of oncogene addiction in solid tumours, reaffirming that precise inhibition of a single oncogenic driver—even one as historically intractable as KRAS—can yield substantial therapeutic benefit. However, the heterogeneity of resistance mechanisms indicates that KRAS blockade is unlikely to function as a standalone curative strategy in most tumour types. The future of KRAS-targeted therapy will likely be defined by intelligent combination regimens, possibly integrating direct inhibitors with immunotherapy, metabolic targeting, or synthetic lethality approaches.

Additionally, the broader oncology community must address accessibility and equity considerations. The high cost of novel KRAS inhibitors, coupled with limited global availability, risks widening disparities in cancer care. Regulatory and policy frameworks should prioritize early access for high-burden populations, and clinical trials must incorporate diverse patient cohorts to ensure generalizability of results. Moreover, the journey from "undruggable" to "drugged" KRAS mutations illustrates the transformative potential of sustained scientific persistence, cross-disciplinary collaboration, and evolving drug discovery technologies. These insights not only expand therapeutic possibilities for KRAS-driven cancers but also redefine the scope of what is achievable for other challenging oncogenic targets in the years to come.

The successful transition of KRAS from an "undruggable" target to one with multiple clinically approved inhibitors represents not just a triumph of medicinal chemistry, but a paradigm shifts in oncology. However, while drugs such as Sotorasib and Adagrasib have demonstrated substantial clinical benefit, the durability of these responses remains constrained by adaptive resistance, tumour heterogeneity, and the complex crosstalk within the RAS–MAPK–PI3K network. This reality underscores the necessity of moving beyond short-term efficacy to long-term disease control strategies.

1. Precision Patient Stratification - In the future, treatment success will likely hinge on biomarker-driven patient selection that extends beyond KRAS mutation typing. Comprehensive genomic and transcriptomic profiling could identify co-mutations (e.g., STK11, KEAP1, TP53) that modulate drug response or predict early resistance.[41] Integration of circulating tumour DNA (ctDNA) monitoring could enable real-time resistance tracking and adaptive treatment switching before clinical progression.[61]

2. Combination Therapies for Pathway Redundancy - Monotherapy approaches, while effective initially, are susceptible to bypass pathway activation, particularly via SHP2-mediated reactivation of upstream RAS signalling or PI3K-AKT pathway activation.[64] Rational combination regimens are emerging as the logical next step: KRAS + SHP2 inhibitors to block upstream reactivation. KRAS + MEK inhibitors to suppress downstream signalling redundancy. KRAS + immunotherapy to harness T-cell–mediated clearance following tumour antigen release.[12]

   Future trials may involve triplet therapies combining KRAS inhibition, vertical pathway blockade, and immune checkpoint modulation.
3. Next-Generation KRAS Inhibitors - The current wave of inhibitors predominantly targets the KRAS^G12C^ mutant through covalent modification of cysteine 12. However, non-G12C KRAS mutations (e.g., G12D, G12V, Q61H) remain largely untreated. New chemotypes—such as KRAS^G12D^ selective inhibitors (e.g., MRTX1133) and pan-KRAS inhibitors—are in early-phase clinical evaluation.[35] Additionally, non-covalent allosteric inhibitors and RAS-membrane interaction disruptors are being designed to target broader mutational spectra.[56]
4. Protein Degradation Approaches - Emerging strategies such as proteolysis-targeting chimeras (PROTACs) and molecular glues may allow direct KRAS degradation rather than mere inhibition.[67,68] These approaches could circumvent resistance mutations that reduce inhibitor binding affinity and offer sustained pathway suppression.
5. Synthetic Lethality and Contextual Vulnerabilities - KRAS-driven cancers exhibit metabolic reprogramming, heightened dependence on autophagy, and altered redox homeostasis. Targeting such vulnerabilities—through synthetic lethality screens—could reveal drug combinations with high selectivity for KRAS-mutant cells.[66] For example, KRAS + autophagy inhibition is being explored in pancreatic ductal adenocarcinoma, while KRAS + metabolic modulators (e.g., glutaminase inhibitors) are under investigation.
6. AI-Accelerated Drug Discovery and Resistance Forecasting - The application of AI-driven structure-based drug design and deep learning for resistance pathway modelling holds promise for dramatically shortening the drug development cycle.[64] Predictive algorithms could identify high-probability resistance mutations before they emerge clinically, guiding pre-emptive drug design.
7. Integration of KRAS-Targeted Therapy into Multimodal Care - For many cancers, particularly lung and colorectal malignancies, KRAS inhibitors will increasingly be integrated into multimodal regimens alongside surgery, radiation, and locoregional therapies. Perioperative KRAS-targeted therapy could potentially reduce micro metastatic disease burden and improve surgical outcomes.
8. Long-Term Vision: Chronic KRAS Control - In the ultimate therapeutic landscape, KRAS-driven cancers may be managed more like chronic diseases, with sequential or rotating regimens to forestall resistance, akin to HIV therapy

strategies. This will require therapeutic sequencing frameworks that balance efficacy, toxicity, and resistance pressure over the patient's treatment lifespan.

The next decade of KRAS research is likely to see a shift from "drugging the undruggable" to sustaining control over the drugged. Achieving durable RAS pathway suppression will depend on integrating molecular diagnostics, rational drug combinations, innovative modalities like protein degradation, and adaptive, AI-guided treatment strategies. The lessons learned from KRAS will set a precedent for tackling other high-value targets in oncology once thought beyond therapeutic reach.

Lessons for Other "Undruggables" - The recent success in targeting KRAS—long considered a paradigmatic "undruggable" oncogene—offers a blueprint for approaching other challenging molecular targets in oncology. Several overarching lessons can be distilled from the KRAS experience, with broad applicability to future drug discovery efforts.

1. Mutation-Specific Targeting Over Broad Inhibition - One of the pivotal breakthroughs in KRAS inhibition was the recognition that not all KRAS mutations are alike. The development of covalent inhibitors such as Sotorasib and Adagrasib focused specifically on the G12C mutation, which is present in approximately 13% of non–small cell lung cancers (NSCLC) and smaller subsets of colorectal and pancreatic cancers.[12,41] This mutation-specific approach reduced off-target toxicity while allowing for selective engagement of a vulnerable cysteine residue in the switch-II pocket.4[4] A similar paradigm could be applied to other historically intractable proteins, such as p53 and MYC, where mutation- or conformation-specific vulnerabilities might be exploitable.[55]
2. Leveraging Advances in Structural Biology and Biophysics - The mapping of KRAS's transient switch-II pocket relied on high-resolution X-ray crystallography, NMR spectroscopy, and molecular dynamics simulations.[56] These technologies can reveal cryptic or transient pockets in proteins once thought to be featureless. For example, BET bromodomain inhibitors and allosteric BCR-ABL inhibitors emerged from similar fragment-based screening strategies.[57] Expanding such techniques could unlock draggability in other small GTPases or transcription factors.[58]
3. Covalent Chemistry as a Precision Tool - KRAS G12C inhibitors employ covalent chemistry to form irreversible bonds with the mutant cysteine, ensuring high target occupancy despite high intracellular GTP concentrations.[35] This approach is now being revisited for other "undruggables," including certain mutant kinases and E3 ligases.[59] While covalent drugs require careful safety and selectivity considerations, their potential to overcome affinity barriers is increasingly appreciated.[60]
4. Combination Strategy Mindset from the Outset - KRAS-targeted monotherapy has been hampered by rapid emergence of resistance through pathway reactivation and alternative signalling.[61] This underscores the importance of designing combination regimens early in development.

Similar logic applies to targets like MYC and β-catenin, where feedback loops and compensatory pathways are anticipated.[62] Combining targeted agents with immune checkpoint blockade, metabolic inhibitors, or synthetic lethal partners should be built into clinical development plans rather than pursued reactively.[63]

5. Integration of Computational and AI-Driven Drug Discovery - KRAS's success was accelerated by computational modelling that predicted ligand-binding conformations and prioritized synthesis candidates.[56] Artificial intelligence and machine learning platforms can similarly expedite drug discovery for other "undruggables" by predicting binding pockets, ranking fragment libraries, and simulating resistance evolution.[64] Such tools have already contributed to the identification of small-molecule binders for intrinsically disordered proteins like p53.[65]
6. Reframing "Undruggable" as "Not Yet Drugged" - The KRAS story exemplifies the danger of prematurely labelling targets as permanently inaccessible. Once considered a static property of the protein, "undruggability" is now understood as a dynamic, technology-dependent assessment.[66] Emerging modalities—including proteolysis-targeting chimeras (PROTACs), molecular glues, and RNA-based therapeutics—may open entirely new avenues for targets once dismissed.[67,68] The field's mindset has shifted from resignation to persistent innovation, supported by multidisciplinary collaborations.

The dismantling of KRAS's "undruggable" status was not the product of a single eureka moment, but rather the culmination of structural insights, chemical ingenuity, computational modelling, and targeted clinical strategy. These principles, applied systematically, hold the promise of transforming other historically intractable oncogenic drivers into druggable vulnerabilities.

Conclusion

The journey from considering KRAS an "undruggable" target to the development of clinically approved inhibitors such as sotorasib and adagrasib is a testament to the progress of precision oncology. This transformation was driven by decades of biochemical insights, advances in covalent inhibitor chemistry, improved structural biology, and a renewed understanding of RAS signalling dynamics. While KRAS G12C inhibitors have achieved measurable clinical success, particularly in non–small-cell lung cancer (NSCLC), they also revealed the adaptive complexity of oncogenic signalling. Rapid emergence of resistance—through on-target mutations, bypass pathway activation, and tumour microenvironment influences—highlights that single-agent therapy is unlikely to deliver durable control. The clinical and translational progress in targeting KRAS has also served as a blueprint for pursuing other historically intractable oncogenes. Innovative approaches, including targeting KRAS beyond G12C (e.g., G12D, G12V), disrupting upstream or downstream signalling nodes, leveraging proteolysis-targeting chimeras (PROTACs), and integrating KRAS inhibition with immunotherapy, represent the next wave of interventions. Combination regimens involving SHP2 inhibitors, MEK inhibitors, and immune checkpoint

blockade are already in early clinical development, aiming to pre-empt resistance and deepen responses.

Furthermore, the KRAS story has broader implications for oncology drug discovery. It demonstrates that "undruggable" is not a static label but a reflection of current technological and conceptual limitations. As novel modalities—such as RNA-based therapeutics, molecular glues, and targeted protein degraders—become more refined, it is plausible that many other elusive cancer drivers will follow KRAS down the path from theoretical impossibility to clinical reality. Looking forward, the goal will be not just transient tumour regression but durable remission and prevention of relapse. Achieving this will require integrating KRAS inhibitors into multi-pronged treatment strategies, guided by predictive biomarkers, adaptive trial designs, and real-time molecular monitoring. The lessons learned from KRAS are reshaping how the field approaches drug discovery, resistance management, and therapeutic sequencing. In this evolving landscape, the term "undruggable" may soon become a historical artifact rather than a therapeutic dead end.

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Conflict of Interest

None.

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