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Review Article

KRAS Inhibition in Colorectal Cancer: Current Insights, Clinical Successes, and Ongoing Challenges

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ABSTRACT

Introduction: Recent advancements in colorectal cancer (CRC) treatment have been significantly impacted by KRAS-targeted therapies, notably sotorasib and adagrasib, which specifically inhibit the KRAS G12C mutation. Despite these advancements, challenges persist, such as the rare occurrence of the KRAS G12C mutation in some tumors and complex resistance mechanisms. This review aims to assess recent developments in KRAS-targeted therapies, address ongoing challenges, and explore innovative strategies to improve treatment outcomes.

Material and Methods: The review examined recent studies on KRAS-targeted therapies, focusing on sotorasib and adagrasib's efficacy and resistance mechanisms. It explored emerging strategies like immune checkpoint inhibitors, RAS-related pathway inhibitors, PROTACs, and CRISPR interventions, and assessed personalized, multidisciplinary approaches integrating surgery, chemotherapy, and tailored therapies.

Results: Sotorasib and adagrasib have demonstrated effectiveness in targeting KRAS G12C, although success varies with individual patient profiles. Resistance to these therapies often involves secondary mutations or activation of alternative pathways. Innovative strategies, including immune checkpoint inhibitors and PROTACs, hold promise for overcoming these resistance challenges. Personalized, multidisciplinary approaches that incorporate KRAS mutation profiles and tissue-specific characteristics are proving beneficial.

Conclusion: KRAS-targeted therapies, such as sotorasib and adagrasib, represent significant advancements in CRC treatment, though challenges like mutation rarity and resistance persist. Emerging strategies and personalized, multidisciplinary treatment plans offer hope for overcoming these obstacles and improving patient outcomes. Continued research and innovation are essential for addressing these challenges and enhancing treatment efficacy.

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INTRODUCTION

It is anticipated that in 2023, there will be over 600,000 fatalities and 1.9 million new instances of cancer in the United States, with colorectal cancer (CRC) accounting for 153,000 of these diagnoses. Cancer represents a major social and healthcare burden [1]. The elderly represent 60% of newly diagnosed cases and 70% of cancer-related deaths; nevertheless, there is currently a knowledge gap about the best ways to treat them. Ages 65 and older are expected to account for 69% of the projected 2.4 million annual cancer diagnoses by

2040, with persons 85 years of age and older accounting for 13% of cases.

According to Sloka et al. (2023) [2], CRC ranked second among women and third among men globally in 2020, with almost 1.9 million new cases and 935,000 fatalities. Colon polyps, inflammatory bowel disorders, diabetes mellitus, cholecystectomy, and genetic predisposition are some of the variables that lead to colorectal cancer (CRC). For preventive and therapy to be effective, it is essential to understand these risk factors. Half of CRC cases develop recurrence and a significant number result in metastasis. Tumor extirpation, chemotherapy, radiation therapy, and targeted medications are some of the available treatment options. Lifestyle decisions significantly influence the development of CRC; maintaining an exercise regimen, eating a balanced diet, and avoiding toxins can reduce risk.

The American Cancer Society's 2023 update reveals alarming trends in CRC, with 52,550 projected fatalities and 153,020 new diagnoses [3]. Cases among people under 50 are increasing, making prompt detection more difficult. Although there has been progress in overall mortality, trends towards younger age, advanced stage, and left-sided tumors highlight the need for concentrated efforts to better understand incidence trends, increase access to screening, and address inequities, particularly among marginalized populations. Due to qualifying requirements, clinical studies frequently overlook older persons, which skew the representation of the healthiest portion of this population. Many older people are ineligible due to strict age restrictions and performance status standards, which makes it difficult to customize therapies. Even among people of the same chronological age, there are notable differences in functioning, geriatric syndromes, comorbid illnesses, frailty, social demands, and treatment tolerance, indicating the diversity and complexity of ageing trajectories. Chida et al. emphasize the complex nature of ageing heterogeneity and how heterogeneity increases with age [4].

KRAS G12C-mutant tumors, especially NSCLC, may be treated with sotorasib and adagrasib, two recent developments in KRAS-targeted therapy. A problem, though, is that the mutation is uncommon in some tumors. Complex pathways, such as alternate RAS-dependent activation and feedback reactivation of wild-type KRAS, are revealed by investigating resistance mechanisms. To combat this, scientists investigate combination treatments such as immune checkpoint inhibitors, inhibitors of the RAS-related system, and novel techniques like proteolysis-targeted chimaeras (PROTACs) and CRISPR-based genomic methods.

MATERIAL AND METHODS

This review thoroughly looks at the latest developments, difficulties, and future possibilities in colorectal cancer treatment using KRAS targeting. It examines drugs like sotorasib and adagrasib, addressing issues with KRAS mutations, resistance mechanisms, and cutting-edge tactics like PROTACs and CRISPR-based therapies, with a focus on molecular subtypes and treatment methods. With a focus on interdisciplinary approaches, the review delves into tissue-specific differences, tailored therapies, and the incorporation of immunotherapeutic tactics to offer significant perspectives for more efficient, tailored, and focused treatments for colorectal cancer.

RESULTS

Targeting KRAS in CRC

KRAS Inhibitors: Shaping CRC Future

Treatment for metastatic colorectal cancer (CRC) necessitates a multidisciplinary strategy that includes targeted therapies, chemotherapy, and surgery. Differential molecular profiles impact tumor behaviour, requiring customized treatments based on distinct genetic characteristics. It is essential to conduct ongoing translational research to classify CRC subtypes and comprehend the responses to targeted therapies, with a focus on preclinical investigations and large-scale clinical trials involving tumor tissue sequencing. Promising approaches to transforming cancer treatment include combining immune checkpoint inhibitors with KRAS inhibitors, investigating mRNA-based vaccines, and adoptive T-cell therapy [5]. Targeted therapy also includes investigating the difficult KRASG12D mutation, particularly with the inhibitor MRTX1133. Concurrent activation of the EGFR pathway reduces MRTX1133's ability to induce growth arrest; hence, more research is required to determine how MRTX1133, KRASG12D, and EGFR interact. The significance of customized treatment approaches based on tissue origin and particular mutant KRAS alleles is highlighted by tissue-specific reactions to KRAS mutations.

Dual Inhibition: KRAS and EGFR

Studies demonstrate the critical function of wild-type RAS isoforms, particularly H-RAS and N-RAS, in mediating downstream signalling following MRTX1133-induced EGFR activation. Suppressing reactivation by EGFR inhibition is an effective treatment option. According to Feng et al., simultaneous inhibition of KRASG12D and EGFR

disturbs essential downstream signalling pathways and has a high efficacy in disrupting cancer cell viability. Epigenetic changes and dysregulated Wnt/β-catenin and KRAS pathways aid in the development of colorectal cancer. Personalized medicine and targeted medicines targeting EGFR, PI3K, and BRAF hold the potential for better treatment outcome [6].

Integrating Therapies for KRAS in CRC

Targeting the Kirsten Rat Sarcoma (KRAS) pathway presents both obstacles and advancements, as the gene is mutated in 60% of colorectal cancer (CRC) patients. Emphasis is placed on investigating kinase-substrate compounds and undruggable kinases as targets for CRC medication development. Combination therapy, which tries to slow the formation of resistance, particularly MEK and PI3K inhibitors, shows promise in metastatic colorectal cancer. The evolution of therapeutic methods, which consider drug-resistance mechanisms and genetic subtypes, demonstrates the complexity of colorectal cancer.

SNORD50A/B and KRAS Inhibition Dynamics

The prognosis and therapy of colorectal cancer are influenced by molecular subtyping, which is why it should be considered in upcoming clinical studies. In forthcoming colorectal cancer trials, the focus of the research is on developing biomarker-driven medicines for personalized medicine [7]. Another study reveals the antagonistic interactions between certain SNARE proteins and SNORD50A/B non-coding RNAs, exploring the molecular processes of KRAS inhibition. This information provides insight into the location, signalling, and carcinogenesis of KRAS. These results are validated by numerous tests and data analysis, offering important new information for the treatment of colorectal cancer [8].

The Evolving Landscape of KRAS Inhibition

Treatment response is complicated by the KRAS gene mutation, which affects 45% of cases of colorectal cancer (CRC), particularly right-sided microsatellite-stable CRC. The discovery of KRASG12C inhibitors, such as sotorasib and adagrasib, represents a major advancement in CRC treatment and shows potential when paired with EGFR inhibitors. Nonetheless, continued investigation into novel combinations is motivated by resistance mechanisms involving reactivation of RAS signalling. Trials investigating combinations such as adagrasib with palbociclib and sotorasib with everolimus are now in progress, highlighting the intricate therapeutic landscape for colorectal cancer, particularly about KRAS mutations. Although the field of targeted therapy is growing due to advances in identifying and treating non-G12C KRAS mutations through creative methods, worries about adverse effects and the necessity of resistance-building tactics still exist [9]. Oncology has entered a revolutionary phase with the recent progress in using covalent KRASG12C inhibitors, such as sotorasib and adagrasib, to target the often-mutated KRAS gene in colorectal cancer. These inhibitors have shown remarkable effectiveness in CRC patients with

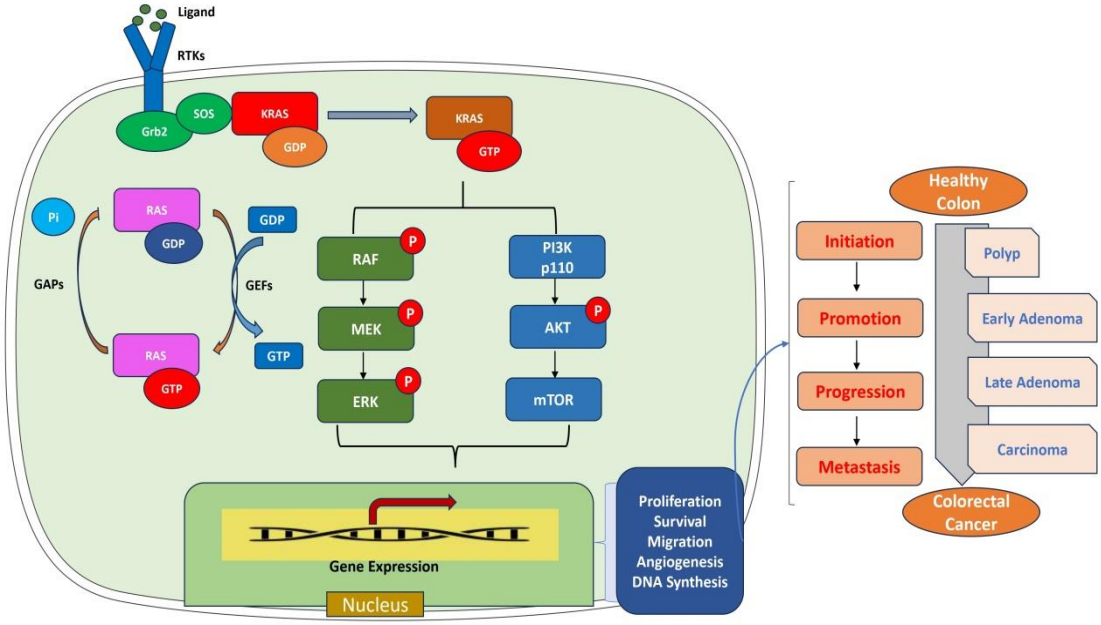

Fig. 1. The KRAS Signalling Pathway and Its Role in CRC Development and Progression

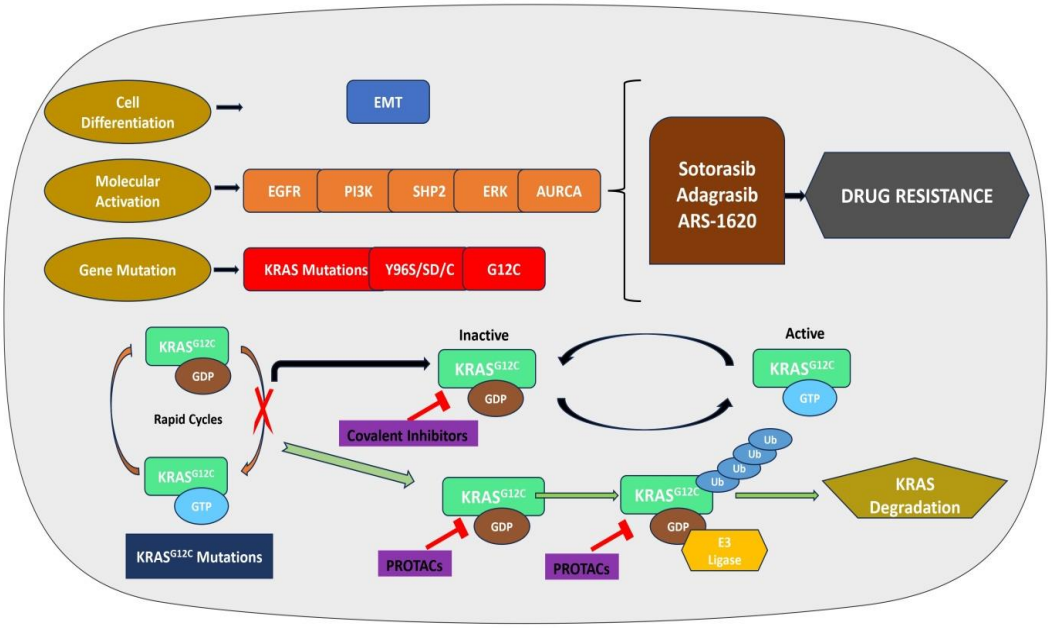

Fig. 2. The KRAS-mediated Drug Resistance Mechanism and Its Degradation by KRAS Inhibitors

KRASG12C mutations; nonetheless, difficulties, especially those related to acquired drug resistance, need investigation of combination approaches, such as the use of EGFR and KRASG12C inhibitors. Novel strategies including immunotherapy and focusing on important KRAS signaling effectors are being researched. Though there is cause for hope, caution is necessary to ensure the safety and acceptability of prolonged RAS inhibition; current research efforts are concentrated on addressing resistance and other drawbacks related to available inhibitors.

Selective KRASG12C Inhibitors

Excellent tolerance is exhibited by selective KRASG12C inhibitors, which opens a lot of possibilities for combination therapy. It is important to pay close attention to managing overlapping toxicities, particularly when using them in combination with other RTK/RAS/MAPK/PI3K pathway inhibitors. The effectiveness of non-covalent inhibitors that target certain oncogenic KRAS mutations, such as KRASG12D, is still unknown and their limited focus presents difficulties. Wide-ranging potential for targeting different KRAS mutations and additional RAS forms, such as HRAS or NRAS, that do not have approved targeted medicines is provided by mutation-independent KRAS inhibitors. Potential tactics include indirect inhibition via SHP2 or SOS1 or direct active state RAS inhibition; however, more study is needed to address concerns about selectivity and on-target effects. Pending additional research, PROTACs and cancer vaccines may improve therapeutic potential [10].

Targeting KRASG12C: Therapeutic Breakthroughs

Due to its strong affinity for guanosine triphosphate (GTP) and deficiency in ideal small molecule binding sites, the Kirsten rat sarcoma virus oncogene homolog (KRAS) presents difficulties in cancer therapy [11]. Drug companies are focusing on treating the KRASG12C mutation, which substitutes cysteine for glycine 12. Promising covalent direct inhibitors that bind to cysteine 12 on KRASG12C include AMG 510 and MRTX849. The idea that KRAS is "undruggable" is called into question by preliminary evidence on these inhibitors [11]. KRAS G12C inhibitors in colorectal cancer (CRC) are successful, but they also need to address the frequency of KRASG12D and KRASG12V mutations [12]. It is essential to comprehend resistance mechanisms and take a holistic approach that takes toxicity, safety, and multi-omics data into account [12]. Due to downstream genetic changes, KRAS G12C inhibitors are difficult to use in colorectal cancer (CRC) but show clinical benefit in non-small cell lung cancer (NSCLC) [13]. The best course of action for various KRAS mutations is still being investigated [13]. Targeted therapy is necessary since the KRAS G12C mutation is linked to poor outcomes in colorectal cancer (CRC) [14]. The idea that KRAS is incurable is being challenged by the development of allele-specific inhibitors, opening new options [12]. However, while

Table 1. KRAS Inhibitors in Clinical Trials for CRC

Drug	Clinical Trial	Phase	Mechanism of Action	Combination	Reference
AMG510	NCT03600883	Phase 1	Apoptotic, cell cycle and DNA damage pathways	None	[20]
JNJ-74699157	NCT04006301	Phase 1	Direct KRAS G12C inhibitor	None	[21]
MRTX849	NCT03785249	Phase 1	Direct KRAS G12C inhibitor	None	[22]
TNO155	NCT03114319	Phase 1	Direct KRAS G12C inhibitor	None	[23]
AMG510	NCT03082209	Phase1/2	Apoptotic, cell cycle and DNA damage pathways	ABBV-621+ FOLFIRI + bevcizumab	[24]
Onvansertib	NCT03829410	Phase1/2	Direct KRAS G12C inhibitor	FOLFIRI + bevcizumab	[25]
TRAIL receptor agonist	NCT02906059	Phase 1	Apoptosis	Chemotherapy + anti-VEGF therapy	[26]
PLK1 inhibitor	NCT03981614	Phase 2	Cell cycle	Chemotherapy + anti-VEGF therapy	[9]
Wee 1 inhibitor	NCT03714958	Phase 1	Cell cycle	Chemotherapy	[24]
CDK4/6 inhibitor + MEK inhibitor	NCT02953782	Phase 1/2	Cell cycle + MAPK	None	[9]
MDM2 inhibitor + MEK inhibitor	NCT03271047	Phase 1/2	MDM2/p53 + MAPK	None	[27]
Binimetinib + Nivolumab + Ipilimumab	NCT03290937	Phase 1/2	MEK + PD-1 + CTLA-4	None	[24]
Utolimumab + Cetuximab + Irinotecan	NCT03271047	Phase 1/2	4-1BB/CD137 + EGFR + Topoisomerase I	None	[28]
MEK inhibitor + anti-PD1 therapy + anti-CTLA4 therapy	NCT03290937	Phase 1/2	MEK + PD-1 + CTLA-4	None	[29]
4-1BB/CD137 agonist + anti-EGFR therapy + Chemotherapy	NCT03290937	Phase 1/2	4-1BB/CD137 + EGFR + Chemotherapy	None	[29]
anti-CD47 therapy + anti-EGFR therapy	NCT03290937	Phase 1/2	CD47 + EGFR	None	[24]
Vitamin C + FOLFOX + bevacizumab	NCT02980029	Phase 1	Metabolic pathway	None	[29]
FASN enzyme inhibitor	NCT02969681	Phase 3	Metabolic pathway	None	[30]
Chemotherapy + anti-VEGF therapy + GAPDH enzyme inhibitor	NCT02980029	Phase 1	Metabolic pathway	Chemotherapy + anti-VEGF therapy	[30]

developing combination methods, taking toxicity and resistance as a mechanism into account is crucial [12] (**Fig. 1** and **2**).

Effective therapy of KRAS-mutant CRC requires the discovery of a variety of allele-specific inhibitors, investigation of resistance mechanisms, and patient safety as the priority [12]. Despite being uncommon in the Chinese population, the KRAS G12C mutation necessitates more research to determine the best course of action [13]. G12C is a KRAS mutation that has a major effect on CRC prognosis, therapy, and diagnosis [15]. Targeted treatment prospects have improved with the development of KRASG12C allele-specific inhibitors [15]. Potential treatment approaches might be gained by comprehending the metabolic variations among KRAS mutations [16]. In colorectal cancer, the combination of EGFR and KRAS G12C inhibitors shows promise [17]. It has been shown that medications such as 4-acetyl-antroquinonol B can desensitize KRAS-mutant CRC cells to cetuximab [18]. Examining KRAS mutations in Bulgarian patients with colorectal cancer offers important information for treatment selection and patient follow-up [19]. All things considered, developing effective treatments for colorectal cancer requires a multimodal strategy that considers a variety of KRAS mutations, resistance mechanisms, and patient safety [12]. **Table 1** show highlights KRAS inhibitors in clinical trials for CRC.

Multiomic Insights into RAS-Mutant Tumors

Targetable pockets in the G12C-mutated KRAS isozyme were found, which sparked the creation of small-molecule inhibitors like sotorasib and adagrasib,

Table 2. Current Status and Combinations in Clinical Trials Evaluating KRAS-targeted Therapies across Different Disease Settings

Drug	Disease Setting	Study Phase	Recruitment Status	Combined With	Reference
AMG510 (Sotorasib)	NSCLC	Recruiting	Recruiting	Docetaxel	[40]
LY3499446	Solid Tumors	Recruiting	Recruiting	Docetaxel	[41]
MRTX849 (Adagrasib)	Metastatic NSCLC	Recruiting	Recruiting	Docetaxel	[42]
AMG510 (Sotorasib)	Solid Tumors	Recruiting	Recruiting	Erlotinib	[25]
AMG510 (Sotorasib)	Solid Tumors	Recruiting	Recruiting	TNO155	[25]
AMG510 (Sotorasib)	Solid Tumors	Recruiting	Recruiting	Selumetinib	[43]
AMG510 (Sotorasib)	Solid Tumors	Recruiting	Recruiting	Everolimus	[23]
MRTX849 (Adagrasib)	Solid Tumors	Recruiting	Recruiting	Cetuximab	[25]
MRTX849 (Adagrasib)	Metastatic CRC	Recruiting	Recruiting	Cetuximab	[44]
MRTX849 (Adagrasib)	NSCLC	Recruiting	Recruiting	TNO155	[45]
LY3499446	Advanced NSCLC	Recruiting	Recruiting	Abemaciclib	[41]
LY3499446	Advanced NSCLC	Recruiting	Recruiting	Erlotinib	[41]
GDC-6036	Solid Tumors	Recruiting	Recruiting	Cetuximab	[25]
GDC-6036	Solid Tumors	Recruiting	Recruiting	Bevacizumab	[46]
AMG510 (Sotorasib)	NSCLC	Recruiting	Recruiting	Pembrolizumab	[42]
AMG510 (Sotorasib)	NSCLC	Recruiting	Recruiting	Atezolizumab	[25]
MRTX849 (Adagrasib)	NSCLC	Recruiting	Recruiting	Pembrolizumab	[42]
MRTX849 (Adagrasib)	NSCLC	Not Yet Recruiting	Not Applicable	Pembrolizumab	[42]
GDC-6036	Solid Tumors	Active, Not Recruiting	Not Applicable	Atezolizumab	[25]

which are currently licensed to treat non-small cell lung cancer (NSCLC). Clinical research is being conducted on a wide range of KRAS G12C inhibitors, both singly and in combination. Adoptive T-cell therapy, cancer vaccines, and pan-KRAS PROTACs are examples of future strategies that will change the landscape of KRAS-targeted treatment. Research delving into the intricate genomic terrain of tumors harboring RAS mutations unveils selection mechanisms that are particular to malignancy and contingent on the environment. Integrated multiomic investigations are provided by the Cancer Genome Atlas (TCGA), which highlights context-dependent RAS signalling in different tumor types and shows differential genotype-driven gene expression profiles [31]. KRAS inhibition has shown promise in colorectal cancer. Nevertheless, cancer cells that survive can induce pro-tumorigenic traits in nearby fibroblasts, which could lead to treatment resistance [32].

Genetic Profiling in CRC Prognosis

About 20% of individuals with newly diagnosed colorectal cancer have metastases at the time of diagnosis, and another 25% do so later. Although unresectable disease still presents a barrier, popular treatments for metastatic colorectal cancer (CRC) include surgery, systemic medication, and liver-directed therapies. For unresectable metastatic colorectal cancer, the 5-year survival rate is only 20%. Treatment plans and prognosis are influenced by molecular profiling. The significance of precision medicine is underscored by this review, which also includes approved targeted medicines, examines CRC cell-signalling pathways, and highlights the impact of genetic profiling on prognosis [5]. KRAS G12C mutation-focused treatment for colorectal cancer is showing improvement. The KRAS G12C inhibitor sotorasib has been approved in Canada, and evidence-based guidelines for testing and therapy sequencing are provided. Therapy for NSCLC with a KRAS mutation is anticipated to be improved by ongoing studies and clinical trials [33].

Strategies beyond Mutation: Targeting KRAS Activation Steps

Adagrasib and sotorasib, two covalent KRASG12C inhibitors, have shown promise in treating KRAS, a difficult target for cancer therapy. Novel approaches and genetic marker-based tumor stratification provide optimism for successful treatments even in the face of acquired resistance [34].

CRISPR-Mediated Targeting of KRAS G12S: A Novel Therapeutic Approach

The carcinogenic KRAS G12S mutant allele was successfully targeted by engineered CRISPR systems, such as CRISPR/SpCas9 and dCas9-KRAB, which resulted in tumor regression in vivo and inhibition of cancer cell proliferation in vitro. According to [35], the SpCas9 system outperformed dCas9-KRAB in terms of efficacy, offering a viable method for editing mutations in a variety of cancerous alterations. Gene therapy employing CRISPR systems to target TP53 and KRAS abnormalities in colorectal cancer (CRC) holds potential for tailored treatment approaches. Comprehensive

mutational profiling, safety assessments, and cost-effectiveness considerations are necessary for successful translation. In CRC therapeutics, gene therapy heralds a revolutionary age that offers hope for efficient, individualized treatments [36].

In colorectal cancer (CRC), mutant KRAS primarily controls fibroblast characteristics, while cancer cells also influence fibroblast behaviour on their own. Fibroblast activation is influenced by factors secreted by colorectal cancer (CRC) cells, particularly those with a KRAS mutation. This highlights the complex nature of KRAS-driven interactions within the CRC microenvironment [32].

From 'Undruggable' to 'Druggable': Revolutionizing KRAS Therapeutics

Cancer treatment appears to benefit from the use of small-molecule medicines that target KRAS signalling, especially G12Ci in clinical trials. However, overcoming resistance and targeting a variety of KRAS mutations remain difficult tasks. Effective personalized methods require an understanding of the intricate topography of KRAS inhibition and the ability to exploit weaknesses [37]. KRAS mutations, particularly KRASG12C, are now addressed by potent inhibitors despite previously being thought to be undruggable, underscoring the continuous change in CRC treatment [38]. Promising results from ongoing clinical trials on KRAS inhibitors across solid tumors, especially about direct-targeted KRASG12C inhibitors, call for a multimodal strategy to improve efficacy and manage resistance [39]. **Table 2** highlights current status and combinations in clinical trials evaluating KRAS-targeted therapies across different disease settings.

Challenges and Limitations

In addition to MSI/MMR status, standard molecular testing for metastatic colorectal cancer looks for mutations in the BRAF, NRAS, and KRAS genes. However new subtypes including NTRK fusions, HER2 amplification, and PIK3CAmut pose a threat to established testing procedures. Accessibility, cost, and interpretation concerns must be addressed to adapt treatments to changing molecular profiles and incorporate novel subtypes into clinical practice [47]. Although the molecular subtypes of colorectal cancer and their treatment implications have been better understood, problems with tumor heterogeneity, testing scope expansion, treatment plan evolution, innovative test implementation, and predictive biomarker identification still exist. To improve the effectiveness of KRAS-targeted treatment in patients with colorectal cancer, these challenges must be overcome [48].

The review highlights the importance of biomarkers, such as NTRK fusions, extended RAS mutations, BRAF mutations, MSI-H/dMMR status, and HER2 gene amplification. Expanding biomarker repertoires for accurate patient classification and therapy selection in colorectal cancer is the goal of future research, which holds the promise of a more customized and effective method of patient care [48].

CONCLUSION

KRAS-targeted colorectal cancer therapy appears promising, as demonstrated by drugs such as sotorasib and adagrasib. One challenge is that KRAS G12C mutations are uncommon in some tumors, which means that efforts to broaden targeted therapy must continue. The investigation of novel approaches such as immune checkpoint inhibitors and CRISPR-based therapies is motivated by the need to address resistance mechanisms. In the case of metastatic colorectal cancer, interdisciplinary techniques present a positive path. Even with these developments, more research and clinical trials are necessary to improve treatment strategies and overcome obstacles such as tumor heterogeneity and narrow testing breadth.

The potential for revolutionizing cancer treatment paradigms is indicated by the integration of immunotherapeutic approaches, customized combinations, and innovative procedures in KRAS-targeted therapy. The need for customized therapy based on tissue of origin and particular mutant KRAS alleles is highlighted by tissue-specific differences in KRAS mutations. Future research could lead to the development of more individualized, focused, and efficacious treatments for people with colorectal cancer.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

Abbreviations

BRAF: B-Raf Proto-Oncogene, Serine/Threonine Kinase
CRC: Colorectal Cancer
CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats
EGFR: Epidermal Growth Factor Receptor
GTP: Guanosine Triphosphate
HER2: Human Epidermal Growth Factor Receptor 2
KRAS: Kirsten Rat Sarcoma Virus Oncogene Homolog
MAPK: Mitogen-Activated Protein Kinase
MSI/MMR: Microsatellite Instability/ Mismatch Repair
NSCLC: Non-Small Cell Lung Cancer
NTRK: Neurotrophic Tyrosine Kinase
NRAS: Neuroblastoma RAS Viral Oncogene Homolog
PI3K: Phosphoinositide 3-Kinase
PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PROTACs: Proteolysis-Targeting Chimeras
SHP2: Src Homology 2 Domain-Containing Phosphatase 2
SOS1: Son of Sevenless Homolog 1
TCGA: The Cancer Genome Atlas

REFERENCES

1. Sawicki T, Ruszkowska M, Danielewicz A, Niedzwiedzka E, Arlukowicz T, Przybylowicz KE. A Review of Colorectal Cancer in Terms of Epidemiology, Risk Factors, Development, Symptoms and Diagnosis. Cancers (Basel). 2021;13(9).
2. Sloka J, Madej M, Strzalka-Mrozik B. Molecular Mechanisms of the Antitumor Effects of Mesalazine and Its Preventive Potential in Colorectal Cancer. Molecules. 2023;28(13).
3. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. CA Cancer J Clin. 2023;73(3):233-54.
4. Ozluk AA, Outlaw D, Akce M, Fowler ME, Hess DL, Giri S, et al. Management of Older Adults With Colorectal Cancer: The Role of Geriatric Assessment. Clin Colorectal Cancer. 2023;22(4):390-401.
5. Ruff SM, Shannon AH, Pawlik TM. The Role of Targeted Therapy in the Multi-Disciplinary Approach to Colorectal Liver Metastasis. Cancers (Basel). 2023;15(13).
6. Malki A, ElRuz RA, Gupta I, Allouch A, Vranic S, Al Moustafa AE. Molecular Mechanisms of Colon Cancer Progression and Metastasis: Recent Insights and Advancements. Int J Mol Sci. 2020;22(1).
7. Teo MYM, Fong JY, Lim WM, In LLA. Current Advances and Trends in KRAS Targeted Therapies for Colorectal Cancer. Mol Cancer Res. 2022;20(1):30-44.
8. Che Y, Siprashvili Z, Kovalski JR, Jiang T, Wozniak G, Elcavage L, et al. KRAS regulation by small non-coding RNAs and SNARE proteins. Nat Commun. 2019;10(1):5118.
9. Nusrat M, Yaeger R. KRAS inhibition in metastatic colorectal cancer: An update. Curr Opin Pharmacol. 2023;68:102343.
10. Akhave NS, Biter AB, Hong DS. The Next Generation of KRAS Targeting: Reasons for Excitement and Concern. Mol Cancer Ther. 2022;21(11):1645-51.
11. Nagasaka M, Li Y, Sukari A, Ou SI, Al-Hallak MN, Azmi AS. KRAS G12C Game of Thrones, which direct KRAS inhibitor will claim the iron throne? Cancer Treat Rev. 2020;84:101974.
12. Zhu G, Pei L, Xia H, Tang Q, Bi F. Role of oncogenic KRAS in the prognosis, diagnosis and treatment of colorectal cancer. Mol Cancer. 2021;20(1):143.
13. Loong HH, Du N, Cheng C, Lin H, Guo J, Lin G, et al. KRAS G12C mutations in Asia: a landscape analysis of 11,951 Chinese tumor samples. Transl Lung Cancer Res. 2020;9(5):1759-69.
14. Henry JT, Coker O, Chowdhury S, Shen JP, Morris VK, Dasari A, et al. Comprehensive Clinical and Molecular Characterization of KRAS (G12C)-Mutant Colorectal Cancer. JCO Precis Oncol. 2021;5.
15. Chida K, Kotani D, Masuishi T, Kawakami T, Kawamoto Y, Kato K, et al. The Prognostic Impact of KRAS G12C Mutation in Patients with Metastatic Colorectal Cancer: A Multicenter Retrospective Observational Study. Oncologist. 2021;26(10):845-53.
16. Varshavi D, Varshavi D, McCarthy N, Veselkov K, Keun HC, Everett JR. Metabolic characterization of colorectal cancer cells harbouring different KRAS mutations in codon 12, 13, 61 and 146 using human SW48 isogenic cell lines. Metabolomics. 2020;16(4):51.
17. McFall T, Trogdon M, Guizar AC, Langenheim JF, Sisk-Hackworth L, Stites EC. Co-targeting KRAS G12C and EGFR reduces both mutant and wild-type RAS-GTP. NPJ Precis Oncol. 2022;6(1):86.
18. Chu YC, Tsai TY, Yadav VK, Deng L, Huang CC, Tzeng YM, et al. 4-Acetyl-Antroquinonol B Improves the Sensitization of Cetuximab on Both Kras Mutant and Wild Type Colorectal Cancer by Modulating the Expression of Ras/Raf/miR-193a-3p Signaling Axis. Int J Mol Sci. 2021;22(14).
19. Radanova M, Mihaylova G, Stoyanov GS, Draganova V, Zlatarov A, Kolev N, et al. KRAS Mutation Status in Bulgarian Patients with

Advanced and Metastatic Colorectal Cancer. Int J Mol Sci. 2023;24(16).
20. Chen H, Zhao J. KRAS oncogene may be another target conquered in non-small cell lung cancer (NSCLC). Thorac Cancer. 2020;11(12):3425-35.
21. Grapsa D, Syrigos K. Direct KRAS inhibition: progress, challenges, and a glimpse into the future. Expert Rev Anticancer Ther. 2020;20(6):437-40.
22. Hallin J, Engstrom LD, Hargis L, Calinisan A, Aranda R, Briere DM, et al. The KRAS(G12C) Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients. Cancer Discov. 2020;10(1):54-71.
23. Krishnan T, Roberts-Thomson R, Broadbridge V, Price T. Targeting Mutated KRAS Genes to Treat Solid Tumours. Mol Diagn Ther. 2022;26(1):39-49.
24. Patelli G, Tosi F, Amatu A, Mauri G, Curaba A, Patane DA, et al. Strategies to tackle RAS-mutated metastatic colorectal cancer. ESMO Open. 2021;6(3):100156.
25. Indini A, Rijavec E, Ghidini M, Cortellini A, Grossi F. Targeting KRAS in Solid Tumors: Current Challenges and Future Opportunities of Novel KRAS Inhibitors. Pharmaceutics. 2021;13(5).
26. Huang JL, Chang YT, Hong ZY, Lin CS. Targeting DNA Damage Response and Immune Checkpoint for Anticancer Therapy. Int J Mol Sci. 2022;23(6).
27. Kobayashi Y, Lim SO, Yamaguchi H. Oncogenic signaling pathways associated with immune evasion and resistance to immune checkpoint inhibitors in cancer. Semin Cancer Biol. 2020;65:51-64.
28. Ingles Garces AH, Au L, Mason R, Thomas J, Larkin J. Building on the anti-PD1/PD-L1 backbone: combination immunotherapy for cancer. Expert Opin Investig Drugs. 2019;28(8):695-708.
29. Dienstmann R, Connor K, Byrne AT, Consortium C. Precision Therapy in RAS Mutant Colorectal Cancer. Gastroenterology. 2020;158(4):806-11.
30. Tang YL, Li DD, Duan JY, Sheng LM, Wang X. Resistance to targeted therapy in metastatic colorectal cancer: Current status and new developments. World J Gastroenterol. 2023;29(6):926-48.
31. Scharpf RB, Balan A, Ricciuti B, Fiksel J, Cherry C, Wang C, et al. Genomic Landscapes and Hallmarks of Mutant RAS in Human Cancers. Cancer Res. 2022;82(21):4058-78.
32. Dias Carvalho P, Mendonca S, Martins F, Oliveira MJ, Velho S. Modulation of Fibroblast Phenotype by Colorectal Cancer Cell-Secreted Factors Is Mostly Independent of Oncogenic KRAS. Cells. 2022;11(16).
33. Cheema PK, Banerji SO, Blais N, Chu QS, Juergens RA, Leighl NB, et al. Canadian Consensus Recommendations on the Management of KRAS G12C-Mutated NSCLC. Curr Oncol. 2023;30(7):6473-96.
34. Liu P, Wang Y, Li X. Targeting the untargetable KRAS in cancer therapy. Acta Pharm Sin B. 2019;9(5):871-9.
35. Gao Q, Ouyang W, Kang B, Han X, Xiong Y, Ding R, et al. Selective targeting of the oncogenic KRAS G12S mutant allele by CRISPR/Cas9 induces efficient tumor regression. Theranostics. 2020;10(11):5137-53.
36. Hasbullah HH, Musa M. Gene Therapy Targeting p53 and KRAS for Colorectal Cancer Treatment: A Myth or the Way Forward? Int J Mol Sci. 2021;22(21).
37. Hou P, Wang YA. Conquering oncogenic KRAS and its bypass mechanisms. Theranostics. 2022;12(13):5691-709.
38. 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):637-55.
39. Wu X, Song W, Cheng C, Liu Z, Li X, Cui Y, et al. Small molecular inhibitors for KRAS-mutant cancers. Front Immunol. 2023;14:1223433.
40. de Langen AJ, Johnson ML, Mazieres J, Dingemans AC, Mountzios G, Pless M, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRAS(G12C) mutation: a randomised, open-label, phase 3 trial. Lancet. 2023;401(10378):733-46.
41. Uprety D, Adjei AA. KRAS: From undruggable to a druggable Cancer Target. Cancer Treat Rev. 2020;89:102070.
42. Palma G, Khurshid F, Lu K, Woodward B, Husain H. Selective KRAS G12C inhibitors in non-small cell lung cancer: chemistry, concurrent pathway alterations, and clinical outcomes. NPJ Precis Oncol. 2021;5(1):98.
43. Naim N, Moukheiber S, Daou S, Kourie HR. KRAS-G12C covalent inhibitors: A game changer in the scene of cancer therapies. Crit Rev Oncol Hematol. 2021;168:103524.
44. Tabernero J, Bendell J, Corcoran R, Kopetz S, Lee J, Davis M, et al. P-71 KRYSTAL-10: A randomized phase 3 study of adagrasib (MRTX849) in combination with cetuximab vs chemotherapy in patients with previously treated advanced colorectal cancer with KRASG12C mutation. Annals of Oncology. 2021;32.
45. Pothuganti MK, Mitra S, Iyer P, Gowda N. Recent Developments, Challenges and Opportunities in Targeting the KRAS Pathway. Letters in Drug Design & Discovery. 2023;20(8):992-1004.

46. Alcaraz-Sanabria A, Cabanas Morafraile E, Fernandez-Hinojal G, Velasco G, Perez-Segura P, Pandiella A, et al. Transcriptomic Mapping of Non-Small Cell Lung Cancer K-RAS p.G12C Mutated Tumors: Identification of Surfaceome Targets and Immunologic Correlates. Front Immunol. 2021;12:786069.
47. DeStefanis RA, Kratz JD, Emmerich PB, Deming DA. Targeted Therapy in Metastatic Colorectal Cancer: Current Standards and Novel Agents in Review. Curr Colorectal Cancer Rep. 2019;15(2):61-9.
48. Chung C. Predictive and prognostic biomarkers with therapeutic targets in colorectal cancer: A 2021 update on current development, evidence, and recommendation. J Oncol Pharm Pract. 2022;28(4):850-69.