Targeting KRAS in colorectal cancer (Review)

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Abstract. RAS genes play crucial roles in regulating important biological processes such as cell growth, differentiation, and apoptosis in normal cells. When RAS genes undergo mutations or abnormal expression, they can become oncogenic drivers, and the oncogenic mechanism of KRAS mutations which drive cancer progression is highly complex. Colorectal cancer carrying KRAS mutation genes often exhibits poor prognosis. Despite the advent of KRAS G12C inhibitors, monotherapy demonstrates suboptimal clinical efficacy in colorectal cancer, which is attributed to primary resistance and limited coverage of prevalent KRAS mutations (such as G12D and G12V). Notably, combinatorial regimens integrating KRASG12C inhibitors with EGFR monoclonal antibodies (such as cetuximab) have doubled objective response rates, highlighting synergistic therapeutic potential.

Contents

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1. Introduction

The RAS gene is a common oncogene, named after the Rat Sarcoma virus, which was first discovered in a mouse sarcoma virus. The human genome contains three RAS genes (HRAS, KRAS and NRAS) that encode four RAS proteins (HRAS, KRAS4A, KRAS4B and NRAS) (1). They are involved in important biological processes such as cell growth, differentiation, and apoptosis in normal cells (2). However, when the RAS gene is mutated or abnormally expressed, it may become a carcinogenic driver gene and promote the carcinogenic process of cells. Research has shown that KRAS is the most common mutation in human cancers, accounting for ~16% of all cancer types (3). Nearly 40% of patients with advanced colorectal cancer carry mutations in RAS oncogenes (KRAS, NRAS and HRAS), with KRAS mutations being the most prevalent (4). KRASG12 hotspot missense mutations (a single point variation that replaces glycine with another amino acid at the 12th codon) account for 68% of all KRAS mutations, including G12D (33.6%), G12V (20.9%), and G12C (8.2%) (5). The RAS signaling pathway is complex. Mutant RAS molecules are difficult to be directly inhibited, which has hindered the development of effective treatments for RAS-mutated tumors and prevented a major therapeutic breakthrough for several years.

2. Carcinogenic KRAS mutations drive the pathogenesis of cancer

The carcinogenic KRAS mutation has been extensively studied for its roles in tumorigenesis and tumor maintenance. At the molecular level of signaling, the mutated KRAS protein with activating mutations eliminates guanosine triphosphate (GTP)ase activity and remains locked in a high-activity state bound to GTP. This results in sustained activation of downstream pro-proliferative and pro-survival pathways such as RAF/MEK/ERK and PI3K/AKT (6,7). Related research indicates that through alternative splicing, the KRAS transcript generates two mRNA isoforms, namely KRAS4A and KRAS4B (8), each encoding functionally distinct mutant proteins. Each variant protein can transform cells and promote tumor growth (9).

The carcinogenic KRAS mutation is intricately linked to the tumor immune microenvironment. Firstly, the innate

immune system predominantly relies on the phagocytic activity of macrophages for tumor surveillance. In early tumor formation, macrophages actively infiltrate tumor tissue and engulf tumor cells; subsequently, their phagocytic capabilities are gradually suppressed by tumor-derived inhibitory signals (10). KRAS mutations can directly activate cluster of differentiation (CD)47 in cancer cells. The binding of CD47 to its receptor, signal regulatory protein alpha, on macrophages, inhibits macrophage-mediated phagocytosis (11), rendering tumor cells insensitive to macrophage phagocytosis, thereby leading to evasion of innate immunity and aggressive tumor progression. Additionally, KRAS mutations can induce T-cell exhaustion and limit adaptive immune responses by upregulating programmed death ligand 1. Taken together, research suggests that mutated KRAS serves as a core driver of tumor immune evasion, as carcinogenic KRAS can impair both innate and adaptive immune antitumor capabilities (12).

The carcinogenic KRAS mutation intricately interacts with cellular metabolism. The expression of carcinogenic KRAS mutation is dependent on aerobic glycolysis metabolism, known as the Warburg effect (13). The carcinogenic KRAS mutation enhances aerobic glycolysis by upregulating the expression and activity of glucose transporters and glycolytic enzymes, including hexokinase (14). The metabolic intermediates of aerobic glycolysis, in turn, provide substrates for biosynthetic processes, generating proteins, lipids, and nucleotides to support rapid cell proliferation (15). To exert its biological activity, KRAS must be localized to the plasma membrane (PM) and organized spatially into proteinaceous assemblies called nanoclusters (KRAS-PM) (16). A study by Liu *et al* (13) revealed that acute glucose deprivation leads to the detachment of KRASG12V from the PM, which is independent of cellular ATP consumption, thereby demonstrating that KRAS-PM localization also requires glycolysis (13).

3. RAS signaling pathway and the mechanism of resistance to KRAS selective inhibitors

The proliferation, survival, differentiation and movement of cancer cells are regulated by different intracellular signaling pathways. Among them, the RAS/RASF/MEK/ERK (MAPK) pathway and the PI3K/AKT pathway have long been revealed to play roles in the pathogenesis of human cancers (17). The RAS molecule is at the core of these tumor signaling pathways and can respond to extracellular signals, such as the activation of epidermal growth factor receptor (EGFR), through effectors such as Src homology-2 protein tyrosine phosphatase (SHP2)/Son of Sevenless (SOS) molecules, leading to the activation of the MAPK, PI3K/AKT and other pathways (18,19). The continuous activation of the MAPK and PI3K pathways leads to uncontrolled cell growth and survival, ultimately resulting in carcinogenic transformation and progression.

Due to the numerous regulatory and regulated molecules, it is difficult to precisely locate a certain link in clinical treatment (19-21), and the pathways such as PI3K and MAPK interact with each other in multiple ways and mutually influence each other by jointly regulating their functions. Therefore, blocking one pathway often induces compensatory activation of another cascade reaction, thereby blocking the effect of KRAS selective inhibitors (22,23).

By contrast, the normal RAS protein cycles between the activated state bound to GTP (ON) and the inactive state bound to guanosine diphosphate (OFF). The cycling disorder of mutant RAS is likely to be in the activated state (24), and its affinity for GTP is extremely high. It is difficult to design small molecule drugs that can directly block its activation (21).

4. Progress of KRAS targeted therapy in colorectal cancer

Colorectal cancer carrying the KRAS mutation gene has a poor prognosis (25), and breakthrough treatments have been elusive for numerous years (19).

Currently, both domestic and international guidelines (26-28) recommend a combination of the anti-angiogenic agent bevacizumab with chemotherapy as the first-line standard treatment for advanced KRAS-mutant colorectal cancer, rather than the use of upstream KRAS molecular EGFR-targeted therapy such as cetuximab. In recent years, clinical research has focused on targeted therapies against other molecules associated with the RAS pathway (20,29). Among these, there has been significant progress in drugs targeting the MAPK pathway, notably MEK small molecule inhibitors. However, despite their use as monotherapy [trametinib (30), cobimetinib (31)], in combination with anti-human epidermal growth factor receptor (HER)2 or EGFR therapy [trametinib + lapatinib (32), selumetinib + cetuximab (33)], in combination with chemotherapy [selumetinib + irinotecan (34)], in combination with PI3K/mTOR inhibitors [trametinib + buparlisib (35), trametinib + GSK2126458 (36), efametinib + copanlisib (37)], or in combination with AKT inhibitors [cobimetinib + ipatasertib (38), selumetinib + MK-2206 (39)], none have shown significant clinical efficacy in advanced colorectal cancer, with minimal objective response rates (ORRs) and almost no objective remissions. Inhibitors targeting downstream molecules of MEK, such as ERK (40) and cyclin dependent kinase (CDK) (41), have also shown suboptimal efficacy as monotherapy.

Forty years after the first discovery of KRAS, in 2013, scientists (18) revealed a novel approach to drug development for this target: A binding pocket exists below the switch II region of the KRAS G12C mutant, where small molecule drugs can be designed to covalently bind, altering the conformation of the KRAS molecule and locking it in an inactive (OFF) state (24,29), without directly targeting GTP. These small molecules that covalently bind to the KRAS G12C mutant are termed 'allosteric inhibitors'. Following this approach, a series of KRAS G12C allosteric inhibitors have been developed, with the earliest and most representative being sotorasib and adagrasib. Sotorasib, based on the excellent efficacy demonstrated in Phase I/II CodeBreaK100 lung cancer trial, has become the first globally approved KRAS inhibitor (42,43); however it performed poorly in colorectal cancer, with an ORR of only 9.7% for patients with treated KRAS G12C-mutant advanced colorectal cancer (44). Adagrasib exhibited an ORR of 19% and a median duration of response of 4.3 months in the same patient population (44). Subsequent development of KRAS G12C inhibitors GFH925 and JAB-21822 revealed monotherapy ORRs of up to 31% (45) and 33% (46) in patients with colorectal cancer, respectively.

Table I. Summary of global clinical trials of direct KRAS-targeted therapy for colorectal cancer.

Registration number	Start year	Test drug	Mechanisms	Target	Combination strategies (target)	Cancer species	Lines of therapy	Preliminary efficacy results	(Refs.)
NCT03101839	2017	AZD-4785	siRNA	Extensive KRAS	NA	Solid tumor	Second	N/A	
NCT03600883	2018	Sotorasib	RAS (OFF) inhibitor	KRAS G12C	NA	Solid tumor	Second	ORR, 9.7% (6/62); DCR 82.3%	(44)
NCT04185883	2019				Trametinib (MEK) Panitumumab (EGFR) AMG404 (PD-1) RMC-4630 (SHP2) TNO-155 (SHP2) Palbociclib (CDK4/6) Everolimus (mTOR) Bevacizumab (VEGF) BI-1701963 (SOS1) FOLFIRI/FOLFOX		First/ Second	Sotorasib + Panitumumab group: A total of 40 patients; ORR, 30%; DCR 90% Sotorasib + Panitumumab + FOLFIRI group: A total of 31 evaluable patients; affirmative ORR, 58.1%; DCR, 93.5%	(57) (50)
NCT05198934	2022				Panitumumab (EGFR)	Colorectal cancer	Second	Sotorasib + Panitumumab group: A total of 31 patients; adjusted OR, 6.0; HR for PFS was 0.85 vs. TAS102 plus bev	(60)
NCT06252649	2024						First	N/A	
NCT03785249	2019	Adagrasib	RAS (OFF) inhibitor	KRAS G12C	Cetuximab (EGFR)	Solid tumor	Second	Monomer drug compatibility group: A total of 43 evaluable patients; ORR, 19%; mDOR, 4.3 months; mPFS 5.6 months Combination cetuximab group: A total of 28 evaluable patients; ORR, 46%; mDOR, 7.6 months; mPFS, 6.9 months	(44)
NCT04330664	2020				TNO-155 (SHP2)	Solid tumor	Second	N/A	
CTR20220199	2021				Cetuximab (EGFR)	Colorectal cancer	Second	N/A	
NCT04975256	2021				BI-1701963 (SOS1)	Solid tumor	Second	N/A	
NCT05722327	2023				Cetuximab (EGFR) Irinotecan	Colorectal cancer	Second	N/A	
NCT05848843	2023				Durvalumab (PD-L1)	Lung cancer/ Colorectal cancer	First/ Second	N/A	

Table I. Continued.

Registration number	Start year	Test drug	Mechanisms	Target	Combination strategies (target)	Cancer species	Lines of therapy	Preliminary efficacy results	(Refs.)
NCT03948763	2019	mRNA-5671	Tumor vaccine	Multiple KRAS	Pembrolizumab (PD-1)	Solid tumor	Second	N/A	
NCT04006301	2019	JNJ-74699157	RAS (OFF) inhibitor	KRAS G12C	NA	Solid tumor	Second	N/A	
NCT04165031	2019	LY-3499446	RAS (OFF) inhibitor	KRAS G12C	Cetuximab (EGFR) Erlotinib (EGFR) Abemaciclib (CDK4/6)	Solid tumor	Second	N/A	
NCT04449874	2020	Divarasib	RAS (OFF) inhibitor	KRAS G12C	Atezolizumab (PD-L1) Cetuximab (EGFR) Bevacizumab (VEGF) Erlotinib (EGFR) RLY-1971 (SHP2) Inavolisib (PI3K)	Solid tumor	Second	Monotherapy for patients with colorectal cancer; affirmative ORR, 20% (8/41) Combination with cetuximab; affirmative ORR, 62%(18/29)	(58) (51)
NCT04929223	2021				Cetuximab (EGFR) FOLFOX	Colorectal cancer	Second	N/A	
NCT04585035	2020	D-1553	RAS (OFF) inhibitor	KRAS G12C	NA	Solid tumor	Second	A total of 24 patients with colorectal cancer; affirmative ORR, 20.8% (5/24); DCR, 95.8% (23/24); mPFS, 7.62 months	(61)
NCT05383898	2021				NA	Solid tumor	Second		
NCT05379946	2022				IN10018 (FAK)	Lung cancer/ Colorectal cancer	Second	N/A	
NCT04678648	2021	RSC-1255	Small molecule drug (undisclosed)	Multiple RAS	NA	Solid tumor	Second	N/A	
NCT04699188	2021	JDQ443	RAS (OFF) inhibitor	KRAS G12C	Tislelizumab (PD-1) TNO-155 (SHP2)	Solid tumor	Second	N/A	
NCT05358249	2022				Trametinib (MEK) Rebosini (CDK4/6) Cetuximab (EGFR)	Lung cancer/ Colorectal cancer	Second	N/A	
NCT05009329	2021	JAB-21822	RAS (OFF) inhibitor	KRAS G12C	NA	Solid tumor	Second		

Table I. Continued.

Registration number	Start year	Test drug	Mechanisms	Target	Combination strategies (target)	Cancer species	Lines of therapy	Preliminary efficacy results	(Refs.)
NCT05002270	2021				Cetuximab (EGFR)	Solid tumor	Second	Monotherapy: ORR, 33% (11/33); DCR, 90% (30/33); mPFS, 6.9 months Combination with cetuximab: ORR, 62.8% (27/43); DCR, 93% (40/43)	(47)
NCT05194995	2022				Cetuximab (EGFR)	Colorectal cancer/ Carcinoma of the small intestine	Second	N/A	
NCT05288205	2022				JAB-3312 (SHP2)	Solid tumor	Second	N/A	
NCT04956640	2021	LY-3537982	RAS (OFF) inhibitor	KRAS G12C	Cetuximab (EGFR) Abemaciclib (CDK4/6) Pembrolizumab (PD-1) LY3295668 (Aurora A)	Solid tumor	First/ Second	N/A	
NCT04973163	2021	BI-1823911	RAS (OFF) inhibitor	KRAS G12C	BI-1701963 (SOS1)	Solid tumor	Second	N/A	
NCT05315180	2021	BPI-421286	RAS (OFF) inhibitor	KRAS G12C	NA	Solid tumor	Second	N/A	
NCT05005234	2021	Fulzerasib	RAS (OFF) inhibitor	KRAS G12C	NA	Solid tumor	Second	Data analysis of patients with colorectal cancer from two phase I studies with 42 evaluable patients in the 600 mg BID group; affirmative ORR, 31.0% (13/42); DCR, 88.1% (37/42)	(45)
NCT05497336	2022				Cetuximab (EGFR)	Colorectal cancer	Second		
GFH925X0301	2024				NA	Colorectal cancer	Third	N/A	
NCT04853017	2021	ELI-002	Tumor vaccine	Multiple RAS	NA	Solid tumor	Adjuvant	N/A	
NCT05726864	2023				NA	Solid tumor	Adjuvant	N/A	
NCT05768321	2021	GEC-255	RAS (OFF) inhibitor	KRAS G12C	NA	Lung cancer/ Colorectal cancer	Second	N/A	
NCT05173805	2022	YL-15293	RAS (OFF) inhibitor	KRAS G12C	NA	Solid tumor	Second	N/A	

Table I. Continued.

Registration number	Start year	Test drug	Mechanisms	Target	Combination strategies (target)	Cancer species	Lines of therapy	Preliminary efficacy results	(Refs.)
CTR20220296	2022	ZG-19018	RAS (OFF) inhibitor	KRAS G12C	NA	Solid tumor	Second	A total of 12 evaluable patients, including 2 with colorectal cancer, 1 PR and 1 SD	(59)
NCT05379985	2022	RMC-6236	RAS (ON) inhibitor	Multiple KRAS	NA	Non-small cell lung cancer/ Colorectal cancer	Second	N/A	
NCT06445062	2024					Colorectal/ Pancreatic cancer	N/A	N/A	
NCT06162221	2024					Solid tumor	First	N/A N/A	
NCT05382559	2022	ASP3082	Protein deactivator	KRAS G12D	Cetuximab (EGFR)	Solid tumor	Second	N/A	
NCT05462717	2022	RMC-6291	RAS (ON) inhibitor	KRAS G12C	NA	Colorectal/Lung/ Pancreatic cancer	Second	N/A	
CTR20222296	2022	GH-35	RAS (OFF) inhibitor	KRAS G12C	NA	Colorectal/Lung/ Pancreatic cancer	Second	N/A	
NCT05737706	2023	MRTX-1133	RAS (OFF) inhibitor	KRAS G12D	NA	Solid tumor	Second	N/A	
CTR20231811	2023	BEBT-607	RAS (OFF) inhibitor	KRAS G12C	NA	Solid tumor	Second	N/A	
CTR20233052	2023	TEB-17231	RAS (OFF) inhibitor	Multiple KRAS	NA	Solid tumor	Second	N/A	
CTR20242253	2024	GFH-375	K-Ras (OFF) inhibitor	Multiple KRAS	NA	Solid tumor	N/A	N/A	
NCT06447662	2024	PF-07934040	K-Ras (OFF) inhibitor	Multiple KRAS	NA	Colorectal/Lung/ Pancreatic cancer	Second	N/A	
CTR20250063	2024	BGB-53038	RAS (OFF) inhibitor	Multiple KRAS	Tislelizumab (PD-1)	Solid tumor	N/A	N/A	
NCT06412198	2024	adagrasib	RAS (OFF) inhibitor	Multiple KRAS	Cetuximab (EGFR) Cemiplimab (PD-1)	Colorectal	Second	N/A	
CTR20241863	2024	TSN-1611	RAS (OFF) inhibitor	Multiple KRAS	NA	Solid tumor	Second	N/A	
CTR20240981	2024	AST-NS2101	RAS (OFF) inhibitor	KRAS G12D	NA	Solid tumor	Second	N/A	

Table I. Continued.

Registration number	Start year	Test drug	Mechanisms	Target	Combination strategies (target)	Cancer species	Lines of therapy	Preliminary efficacy results	(Refs.)
NCT06244771	2024	HYP-2090PTSA	RAS (OFF) inhibitor	KRAS G12C	NA	Colorectal/Lung/ Pancreatic cancer	Second	N/A	
CTR20220296	2024	ZG-19018	RAS (OFF) inhibitor	KRAS G12C	NA	Solid tumor	Second	N/A	
NCT06227377	2024	QTX-3034	RAS (OFF) inhibitor	KRAS G12D	NA	Colorectal/Lung/ Pancreatic cancer	Second	N/A	
NCT06179160	2024	INCB-161734	RAS (OFF) inhibitor	KRAS G12D	NA	Solid tumor	Second	N/A	
NCT06162221	2024	RMC-6291	RAS (OFF) inhibitor	Multiple KRAS	NA	Solid tumor	First	N/A	
TrialTroveID-487614	2024	JAB-23400	RAS (OFF) inhibitor	Multiple KRAS	NA	Colorectal/Lung/ Pancreatic cancer	N/A	N/A	

ORR, objective response rate; DCR, disease control rate; mPFS, median progression-free survival; EGFR, epidermal growth factor receptor; MEK, mitogen-activated protein kinase kinase; SHP2, Src homology-2 protein tyrosine phosphatase; NA, not applicable; N/A, not available; OR, odds ratio value; HR , hazard ratio; mDOR, median duration of response; SOS1, son of sevenless homolog 1; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; FAK, focal adhesion kinase; PR, partial response; SD, stable disease.

KRAS G12C allosteric inhibitors indeed have the potential to alter the treatment landscape of advanced colorectal cancer with KRAS mutations. However, the two following major issues have been noted: i) Monotherapy for colorectal cancer has shown inferior efficacy compared with lung cancer, with a short duration of response, indicating both primary and acquired resistance. This may be related to the different degrees of reliance on the RAS pathway in different cancer types, activation of bypass signaling pathways, and secondary mutations in the KRAS molecule itself (47-49) KRAS G12C mutations represent only a small fraction of molecular abnormalities in advanced colorectal cancer, and the most common mutations (G12D, G12V and G13D) are unresponsive to G12C inhibitors (29).

To explore the latest trends in KRAS-targeted therapy for colorectal cancer and to address the aforementioned issues, the Trialtrove database was utilized (https://www.citeline.com/en/products-services/clinical/trialtrove) to extract data on ongoing clinical trials worldwide as of June 1st, 2024, involving direct targeting of the KRAS protein or encoding nucleic acids, with study subjects including patients with colorectal cancer, resulting in a total of 85 trials. The start year, drug name, mechanism, combination strategies, study population, and preliminary efficacy results are displayed for each project (Table I).

It was found that combination therapy is a potential strategy to improve the response rate of KRAS-targeted therapy in colorectal cancer. Among the aforementioned 85 clinical trials, 53 (62.4%) involved combination therapy, which presented the following three main directions: i) Blocking upstream KRAS signaling, using combination therapies with EGFR monoclonal antibodies (such as cetuximab and panitumumab), or inhibitors of effectors such as SHP2 and SOS1; ii) blocking downstream KRAS signaling, using combination therapies with MEK, PI3K, or CDK inhibitors; and iii) the use of combination of therapies with immunotherapy or chemotherapy. The first approach has shown some efficacy, with both sotorasib combined with panitumumab (50) and adagrasib (51), divarasib (52), or JAB-21822 (47) combined with cetuximab achieving a doubling of ORR compared with monotherapy, along with a prolonged duration of response. Although the combination with SHP2 inhibitors has not yet been reported in clinical data, it also holds great potential based on mechanism and preclinical research results (53,54).

Unfortunately, since the 'backbone' drugs for combination therapy are all KRAS G12C inhibitors, the aforementioned strategies are only effective for this rare subtype of colorectal cancer, making it difficult to overcome other types of KRAS mutations. The activation/inactivation cycling rate of other KRAS mutants is different from G12C, and there is no clear allosteric binding pocket, making it difficult for them to be locked in an inactive state (55). Certain studies have examined the use of targeted drugs directly to GTP-bound KRAS molecules, forming a ternary complex with farnesyl (22,56). These drugs, termed RAS (ON) inhibitors, not only inhibit G12C mutations but may also be effective against other types of mutations, laying the foundation for the development of pan-KRAS targeted drugs (22). In addition to conventional small molecule targeted drugs, tumor vaccines and protein degraders targeting other KRAS, or even RAS mutants, are also in early development stages. The aforementioned drugs hold promise in changing the current situation where the common KRAS mutation subtypes G12D, G12V, and G13D in colorectal cancer are considered 'intractable'.

5. Conclusions

Collectively, the findings indicate that the KRAS mutation is the most common molecular abnormality in colorectal cancer. Drug therapy targeting this mutation has also undergone arduous exploration. Despite the advent of KRAS G12C inhibitors, monotherapy demonstrates suboptimal clinical efficacy in colorectal cancer, attributed to primary resistance and limited coverage of prevalent KRAS mutations (such as G12D and G12V). Combination therapy with KRAS G12C targeted drugs, notably in combination with EGFR monoclonal antibodies, has effectively increased the ORR. Novel drugs that exploit the mechanim of action of KRAS and target other KRAS mutation types are also in early clinical development. Colorectal cancer KRAS-targeted therapy is a major scientific topic for novel drug development, and the future looks promising.

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Availability of data and materials

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Authors' contributions

XY and NL contributed to manuscript conception. MZ and DW were the major contributors in writing the manuscript. YT, LZ, SZ and WL provided assistance in the literature search. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Rossi JK, Nuevo-Tapioles C and Philips MR: Differential functions of the KRAS splice variants. Biochem Soc Trans 51: 1191-1199, 2023.
2. García-España A and Philips MR: Origin and evolution of RAS membrane targeting. Oncogene 42: 1741-1750, 2023.
3. Prior IA, Lewis PD and Mattos C: A comprehensive survey of Ras mutations in cancer. Cancer Res 72: 2457-2467, 2012.
4. Dienstmann R, Connor K and Byrne AT; COLOSSUS Consortium: Precision therapy in RAS mutant colorectal cancer. Gastroenterology 158: 806-811, 2020.
5. Patelli G, Tosi F, Amatu A, Mauri G, Curaba A, Patanè DA, Pani A, Scaglione F, Siena S and Sartore-Bianchi A: Strategies to tackle RAS-mutated metastatic colorectal cancer. ESMO Open 6: 100156, 2021.
6. Drosten M and Barbacid M: Targeting the MAPK pathway in KRAS-driven tumors. Cancer Cell 37: 543-550, 2020.
7. Schwartz S, Wongvipat J, Trigwell CB, Hancox U, Carver BS, Rodrik-Outmezguine V, Will M, Yellen P, de Stanchina E, Baselga J, *et al*: Feedback suppression of PI3Kα signaling in PTEN-mutated tumors is relieved by selective inhibition of PI3Kβ. Cancer Cell 27: 109-122, 2015.
8. Tsai FD, Lopes MS, Zhou M, Court H, Ponce O, Fiordalisi JJ, Gierut JJ, Cox AD, Haigis KM and Philips MR: K-Ras4A splice variant is widely expressed in cancer and uses a hybrid membrane-targeting motif. Proc Natl Acad Sci USA 112: 779-784, 2015.
9. Voice JK, Klemke RL, Le A and Jackson JH: Four human ras homologs differ in their abilities to activate Raf-1, induce transformation, and stimulate cell motility. J Biol Chem 274: 17164-17170, 1999.
10. Mantovani A and Sica A: Macrophages, innate immunity and cancer: Balance, tolerance, and diversity. Curr Opin Immunol 22: 231-237, 2010.
11. Barclay AN and van den Berg TK: The interaction between signal regulatory protein alpha (SIRPα) and CD47: Structure, function, and therapeutic target. Annu Rev Immunol 32: 25-50, 2014.
12. Hu H, Cheng R, Wang Y, Wang X, Wu J, Kong Y, Zhan S, Zhou Z, Zhu H, Yu R, *et al*: Oncogenic KRAS signaling drives evasion of innate immune surveillance in lung adenocarcinoma by activating CD47. J Clin Invest 133: e153470, 2023.
13. Liu J, van der Hoeven R, Kattan WE, Chang JT, Montufar-Solis D, Chen W, Wong M, Zhou Y, Lebrilla CB and Hancock JF: Glycolysis regulates KRAS plasma membrane localization and function through defined glycosphingolipids. Nat Commun 14: 465, 2023.
14. Patra KC, Wang Q, Bhaskar PT, Miller L, Wang Z, Wheaton W, Chandel N, Laakso M, Muller WJ, Allen EL, *et al*: Hexokinase 2 is required for tumor initiation and maintenance and its systemic deletion is therapeutic in mouse models of cancer. Cancer Cell 24: 213-228, 2013.
15. Hosios AM, Hecht VC, Danai LV, Johnson MO, Rathmell JC, Steinhauser ML, Manalis SR and Vander Heiden MG: Amino acids rather than glucose account for the majority of cell mass in proliferating mammalian cells. Dev Cell 36: 540-549, 2016.
16. Nan X, Tamgüney TM, Collisson EA, Lin LJ, Pitt C, Galeas J, Lewis S, Gray JW, McCormick F and Chu S: Ras-GTP dimers activate the mitogen-activated protein kinase (MAPK) pathway. Proc Natl Acad Sci USA 112: 7996-8001, 2015.
17. De Luca A, Maiello MR, D'Alessio A, Pergameno M and Normanno N: The RAS/RAF/MEK/ERK and the PI3K/AKT signalling pathways: Role in cancer pathogenesis and implications for therapeutic approaches. Expert Opin Ther Targets 16 (Suppl 2): S17-S27, 2012.
18. Parikh K, Banna G, Liu SV, Friedlaender A, Desai A, Subbiah V and Addeo A: Drugging KRAS: Current perspectives and state-of-art review. J Hematol Oncol 15: 152, 2022.
19. Moore AR, Rosenberg SC, McCormick F and Malek S: RAS-targeted therapies: Is the undruggable drugged? Nat Rev Drug Discov 19: 533-552, 2020.
20. Punekar SR, Velcheti V, Neel BG and Wong KK: The current state of the art and future trends in RAS-targeted cancer therapies. Nat Rev Clin Oncol 19: 637-655, 2022.
21. Tria SM, Burge ME and Whitehall VLJ: The therapeutic landscape for *KRAS*-mutated colorectal cancers. Cancers (Basel) 15: 2375, 2023.
22. Carracedo A, Ma L, Teruya-Feldstein J, Rojo F, Salmena L, Alimonti A, Egia A, Sasaki AT, Thomas G, Kozma SC, *et al*: Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. J Clin Invest 118: 3065-3074, 2008.
23. Chandarlapaty S, Sawai A, Scaltriti M, Rodrik-Outmezguine V, Grbovic-Huezo O, Serra V, Majumder PK, Baselga J and Rosen N: AKT inhibition relieves feedback suppression of receptor tyrosine kinase expression and activity. Cancer Cell 19: 58-71, 2011.
24. Ostrem JM, Peters U, Sos ML, Wells JA and Shokat KM: K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature 503: 548-551, 2013.
25. Siegel RL, Miller KD, Sauer AG, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA and Jemal A: Colorectal cancer statistics, 2020. CA Cancer J Clin 70: 145-164, 2020.
26. Chinese Society of Clinical Oncology (CSCO). Colorectal cancer diagnosis and treatment guidelines. Beijing: CSCO Press; 2023.
27. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon Cancer. Version 2.2023. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2023. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (Accessed 2024 Jul 20)
28. National Comprehensive Cancer Network. NCCN Guidelines®: Rectal Cancer. Version 4.2023; 2023. Available from: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (Accessed 2024 Jul 20).
29. Bteich F, Mohammadi M, Li T, Bhat MA, Sofianidi A, Wei N and Kuang C: Targeting KRAS in colorectal cancer: A bench to bedside review. Int J Mol Sci 24: 12030, 2023.
30. Infante JR, Fecher LA, Falchook GS, Nallapareddy S, Gordon MS, Becerra C, DeMarini DJ, Cox DS, Xu Y, Morris SR, *et al*: Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol 13: 773-781, 2012.
31. Rosen LS, LoRusso P, Ma WW, Goldman JW, Weise A, Colevas AD, Adjei A, Yazji S, Shen A, Johnston S, *et al*: A first-in-human phase I study to evaluate the MEK1/2 inhibitor, cobimetinib, administered daily in patients with advanced solid tumors. Invest New Drugs 34: 604-613, 2016.
32. Huijberts SCFA, van Geel RMJM, van Brummelen EMJ, Opdam FL, Marchetti S, Steeghs N, Pulleman S, Thijssen B, Rosing H, Monkhorst K, *et al*: Phase I study of lapatinib plus trametinib in patients with KRAS-mutant colorectal, non-small cell lung, and pancreatic cancer. Cancer Chemother Pharmacol 85: 917-930, 2020.
33. Deming DA, Cavalcante LL, Lubner SJ, Mulkerin DL, LoConte NK, Eickhoff JC, Kolesar JM, Fioravanti S, Greten TF, Compton K, *et al*: A phase I study of selumetinib (AZD6244/ARRY-142866), a MEK1/2 inhibitor, in combination with cetuximab in refractory solid tumors and KRAS mutant colorectal cancer. Invest New Drugs 34: 168-175, 2016.
34. Hochster HS, Uboha N, Messersmith W, Gold PJ, ONeil BH, Cohen D, Denlinger C, Cohen S, Leichman CG, Leichman L and Lenz HJ: Phase II study of selumetinib (AZD6244, ARRY-142886) plus irinotecan as second-line therapy in patients with K-RAS mutated colorectal cancer. Cancer Chemother Pharmacol 75: 17-23, 2015.
35. Bedard PL, Tabernero J, Janku F, Wainberg ZA, Paz-Ares L, Vansteenkiste J, Van Cutsem E, Pérez-García J, Stathis A, Britten CD, *et al*: A phase Ib dose-escalation study of the oral pan-PI3K inhibitor buparlisib (BKM120) in combination with the oral MEK1/2 inhibitor trametinib (GSK1120212) in patients with selected advanced solid tumors. Clin Cancer Res 21: 730-738, 2015.
36. Grilley-Olson JE, Bedard PL, Fasolo A, Cornfeld M, Cartee L, Razak AR, Stayner LA, Wu Y, Greenwood R, Singh R, *et al*: A phase Ib dose-escalation study of the MEK inhibitor trametinib in combination with the PI3K/mTOR inhibitor GSK2126458 in patients with advanced solid tumors. Invest New Drugs 34: 740-749, 2016.
37. Ramanathan RK, Von Hoff DD, Eskens F, Blumenschein G Jr, Richards D, Genvresse I, Reschke S, Granvil C, Skubala A, Peña C and Mross K: Phase Ib trial of the PI3K inhibitor copanlisib combined with the allosteric MEK inhibitor refametinib in patients with advanced cancer. Target Oncol 15: 163-174, 2020.

38. Shapiro GI, LoRusso P, Cho DC, Musib L, Yan Y, Wongchenko M, Chang I, Patel P, Chan IT, Sanabria-Bohorquez S, *et al*: A phase Ib open-label dose escalation study of the safety, pharmacokinetics, and pharmacodynamics of cobimetinib (GDC-0973) and ipatasertib (GDC-0068) in patients with locally advanced or metastatic solid tumors. Invest New Drugs 39: 163-174, 2021.
39. Do K, Speranza G, Bishop R, Khin S, Rubinstein L, Kinders RJ, Datiles M, Eugeni M, Lam MH, Doyle LA, *et al*: Biomarker-driven phase 2 study of MK-2206 and selumetinib (AZD6244, ARRY-142886) in patients with colorectal cancer. Invest New Drugs 33: 720-728, 2015.
40. Pant S, Bendell JC, Sullivan RJ, Shapiro G, Millward M, Mi G, Yuen E, Willard MD, Wang D, Joseph S, *et al*: A phase I dose-escalation study of ERK inhibitor LY3214996 in advanced cancer patients. J Clin Oncol 37(15_suppl): S3001, 2019
41. O'Hara MH, Edmonds C, Farwell M, Perini RF, Pryma DA, Teitelbaum UR, Giantonio BJ, Damjanov N, Lal P, Feldman MD, *et al*: Phase II pharmacodynamics trial of palbociclib in patients with KRAS mutant colorectal cancer. J Clin Oncol 33: 626-630, 2015.
42. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, Italiano A, Schuler M, Borghaei H, Barlesi F, *et al*: Sotorasib for lung cancers with *KRAS* p.G12C mutation. N Engl J Med 384: 2371-2381, 2021.
43. Nakajima EC, Drezner N, Li X, Mishra-Kalyani PS, Liu Y, Zhao H, Bi Y, Liu J, Rahman A, Wearne E, *et al*: FDA approval summary: Sotorasib for KRAS G12C-mutated metastatic NSCLC. Clin Cancer Res 28: 1482-1486, 2022.
44. Fakih MG, Kopetz S, Kuboki Y, Kim TW, Munster PN, Krauss JC, Falchook GS, Han SW, Heinemann V, Muro K, *et al*: Sotorasib for previously treated colorectal cancers with $KRAS^{G12C}$ mutation (CodeBreaK100): A prespecified analysis of a single-arm, phase 2 trial. Lancet Oncol 23: 115-124, 2022.
45. Yaeger R, Weiss J, Pelster MS, Spira AI, Barve M, Ou SI, Leal TA, Bekaii-Saab TS, Paweletz CP, Heavey GA, *et al*: Adagrasib with or without cetuximab in colorectal cancer with mutated *KRAS* G12C. N Engl J Med 388: 44-54, 2023.
46. Jacobio Pharma. Clinical results of Glecirasib in colorectal cancer (Internet). 2023 (cited 2024 Jul 20). Available from: http://www.jacobiopharma.com/en/news/Jacobio_Pharma_Presents_Clinical_Results_of_Glecirasib_in_Colorectal_Cancer
47. Zhao MH and Wu AW: Targeting *KRAS G12C* mutations in colorectal cancer. Gastroenterol Rep (Oxf) 11: goac083, 2022.
48. Zhao Y, Murciano-Goroff YR, Xue JY, Ang A, Lucas J, Mai TT, Da Cruz Paula AF, Saiki AY, Mohn D, Achanta P, *et al*: Diverse alterations associated with resistance to KRAS(G12C) inhibition. Nature 599: 679-683, 2021.
49. Awad MM, Liu S, Rybkin II, Arbour KC, Dilly J, Zhu VW, Johnson ML, Heist RS, Patil T, Riely GJ, *et al*: Acquired resistance to $KRAS^{G12C}$ Inhibition in Cancer. N Engl J Med 384: 2382-2393, 2021.
50. Hong DS, Kuboki Y, Strickler JH, Fakih M, Houssiau H, Price TJ, Elez E, Siena S, Chan E, Nolte-Hippenmeyer J, *et al*: Sotorasib (Soto) plus panitumumab (Pmab) and FOLFIRI for previously treated KRAS G12C-mutated metastatic colorectal cancer (mCRC): CodeBreaK 101 phase 1b safety and efficacy. J Clin Oncol 41 (16_Suppl): S3513, 2023.
51. Yuan Y, Deng YH, Jin YD, Pan Y, Wang C, Wang Z, Zhang Z, Meng X, Hu Y, Zhao M, *et al*: Efficacy and safety of IBI351 (GFH925) monotherapy in metastatic colorectal cancer harboring KRASG12C mutation: Preliminary results from a pooled analysis of two phase I studies. J Clin Oncol 41 (16_Suppl): S3586, 2023.
52. Desai J, Alonso G, Kim SH, Cervantes A, Karasic T, Medina L, Shacham-Shmueli E, Cosman R, Falcon A, Gort E, *et al*: Divarasib plus cetuximab in KRAS G12C-positive colorectal cancer: A phase 1b trial. Nat Med 30: 271-278, 2024.
53. Liu C, Lu H, Wang H, Loo A, Zhang X, Yang G, Kowal C, Delach S, Wang Y, Goldoni S, *et al*: Combinations with allosteric SHP2 inhibitor TNO155 to block receptor tyrosine kinase signaling. Clin Cancer Res 27: 342-354, 2021.
54. Kerr DL, Haderk F and Bivona TG: Allosteric SHP2 inhibitors in cancer: Targeting the intersection of RAS, resistance, and the immune microenvironment. Curr Opin Chem Biol 62: 1-12, 2021.
55. Hunter JC, Manandhar A, Carrasco MA, Gurbani D, Gondi S and Westover KD: Biochemical and structural analysis of common cancer-associated KRAS mutations. Mol Cancer Res 13: 1325-1335, 2015.
56. Kim D, Xue JY and Lito P: Targeting KRAS(G12C): From inhibitory mechanism to modulation of antitumor effects in patients. Cell 183: 850-859, 2020.
57. Kuboki Y, Yaeger R and Fakih M: Sotorasib in combination with panitumumab in refractory KRAS G12C-mutated colorectal cancer: Safety and efficacy for phase Ib full expansion cohort. Ann Oncol: 33 (Suppl 9) : S1445-S1453, 2022.
58. Desai J, Han S, Forster MD, Kim TW, Alonso Casal G, Shmueli ES, Bowyer SE, De Miguel MJ, Gonzalez AF, Jones RH, *et al*: Phase Ia study to evaluate GDC-6036 monotherapy in patients with colorectal cancer (CRC) with KRAS G12C mutation. Ann Oncol 33 (Suppl 7): S136-S196, 2022.
59. Liu RR, Qu XJ, Yang N, Chai XL and Xu JM: First-in-human study of ZG19018, targeting KRAS G12C, as monotherapy in patients with advanced solid tumors. J Clin Oncol 41 (Suppl 16): e15127, 2023.
60. Salvatore L, Fakih M, Kuboki Y, Hong DS, Modest DA, Taieb J, Price TJ, Cremolini C, Majer IM, Rehn M, *et al*: 59P Matching-adjusted indirect treatment comparisons (MAIC) of sotorasib 960mg plus panitumumab vs trifluridine/tipiracil plus bevacizumab in chemorefractory metastatic colorectal cancer Ann Oncol 35 (Suppl 1): S28-S29, 2024.
61. Ruan D, Lee MA, Deng Y, Lee KW, Millward M, Grewal JS, Gadgeel SM, Sanborn RE, Hou X, Wei S, *et al*: Safety and efficacy of D-1553 in KRAS G12C-mutated colorectal cancer: Results from a phase I/II study. J Clin Oncol 41: 3563, 2023.