Advances in Targeting KRAS G12C in Gastrointestinal Malignancies: Focus on KRAS G12C Inhibitors

Celine Hoyek,[1] Angelo Pirozzi,[1,2,3] Jeremy Jones,[4] Lorenza Rimassa,[2,3] Mohamad B Sonbol[1] and Tanios Bekaii-Saab[1]

1. Department of Hematology and Oncology, Mayo Clinic, Phoenix, AZ, USA; 2. Department of Biomedical Sciences, Humanitas University, Milano, Italy; 3. Medical Oncology and Hematology Unit, IRCCS Humanitas Research Hospital, Milano, Italy; 4. Department of Hematology and Oncology, Mayo Clinic, Jacksonville, FL, USA

Kirsten rat sarcoma virus (KRAS) gene mutations are amongst the most prevalent oncogenic mutations in gastrointestinal tumours. Attempts at targeting the KRAS protein have been unsuccessful for decades, mainly due to its challenging architecture that lacks small-molecule-binding sites. Recent breakthrough advances in crystallographic studies and related fields have led to the discovery of an allosteric binding pocket specific to the KRAS G12C protein, which inhibitors can selectively target through its cysteine residue. The development of KRAS G12C inhibitors, such as adagrasib and sotorasib, and their demonstrated clinical activity led to their regulatory approval, first for treating non-small-cell lung cancer, and more recently for pancreatic and colorectal cancers. Since then, several KRAS G12C inhibitors have emerged and are entering the clinic. However, a significant challenge currently faced by KRAS G12C inhibitors is the emergence of resistance. Understanding these mechanisms is essential to guide the development of future combination therapies, which include concurrent vertical inhibition of the receptor tyrosine kinase/rat sarcoma virus (RAS)/mitogen-activated protein kinase (MAPK) pathway, combinations with chemotherapy or immunotherapy and other innovations that target key players of RAS pathway activation, such as Src Homologous Protein 2 and Son of Sevenless 1, to prolong the survival of patients with limited treatment options.

Keywords

Combination therapies, garsorasib, gastrointestinal cancers, Kirsten rat sarcoma virus (KRAS) G12C, resistance mechanisms, sotorasib, targetable

Disclosures: Lorenza Rimassa consults, advises, is on the speakers' bureau and received grants from AstraZeneca, Eisai, Incyte, Ipsen and Roche. She consults, advises and is on the speakers' bureau for Bayer, Bristol Myers Squibb and Servier. She consults, advises and received grants from Eli Lilly, Exelixis, MSD, Nerviano Medical Sciences and Zymeworks. She consults and advises for Basilea, Genenta, Hengrui, IQVIA, Jazz Pharmaceuticals and Taiho Oncology. She is a member of the speakers' bureau for Gilead, Merck Serono and Sanofi. She received grants from Agios, BeiGene and Fibrogen. Mohamad B Sonbol has received consulting income from Novartis. Tanios Bekaii-Saab has received consulting income from Boehringer Ingelheim, Treos Bio, Sobi, Ipsen, Array Biopharma, Seattle Genetics, Bayer, Genentech, Incyte, Merck, Boston Biomedical, Bayer, Amgen, Merck, Celgene, Lilly, Ipsen, Clovis, Seattle Genetics, Array Biopharma, Genentech, Abgenomics and Incyte. Celine Hoyek, Angelo Pirozzi and Jeremy Jones have no financial or non-financial relationships or activities to declare in relation to this article.

Review Process: Double-blind peer review.

Compliance with ethics: This article involves a review of literature and does not report on new clinical data, or any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the writing of this article.

Authorship: All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Received: 9 July 2024

Accepted: 4 October 2024

Published online: 29 November 2024

Citation: *touchREVIEWS in Oncology & Haematology.* 2024;20(2):Online ahead of journal publication

Corresponding author: Dr Celine Hoyek, Department of Hematology and Oncology, Mayo Clinic, 5777 East Mayo Blvd, Phoenix, AZ 85054, USA. E: Hoyek.Celine@mayo.edu

Support: No funding was received for the publication of this article.

Rat sarcoma virus (RAS) proteins are a family of prototypical oncogenes frequently mutated in human cancers. Mutations in the *RAS* gene account for 19% of all pathogenic alterations and are the subject of extensive research in molecular and clinical oncology.[1] The RAS family consists of three major isoforms, namely the Harvey rat sarcoma virus (HRAS), the neuroblastoma RAS viral oncogene homologue (NRAS) and the Kirsten rat sarcoma virus (KRAS). Amongst these, KRAS is the most frequently mutated of the RAS isoforms, with a remarkably high mutational prevalence in gastrointestinal (GI) malignancies, including 90% of pancreatic ductal adenocarcinomas (PDAC) and 50% of colorectal cancers (CRC).[2] The high prevalence of KRAS aberrations in GI malignancies was crucial in promoting studies that identified KRAS's central role as an oncogenic driver and a critical factor in resistance against cytotoxic chemotherapy.[3] However, despite decades of research into its molecular configuration, efforts in targeting KRAS have been elusive for several reasons: the absence of deep pockets in the RAS protein, making it inaccessible to small-molecule inhibitors, the constant transition between two distinct conformational states with vastly different chemical behaviours and the high affinity for guanosine-5'-triphosphate (GTP), allowing the KRAS protein to function despite low GTP concentrations, have made the design of a targeted KRAS inhibitor particularly difficult.[4]

Nevertheless, advances in molecular biology and conformational biochemistry have profoundly changed our understanding of an anomalous mutant variant known as the Gly12Cys KRAS (KRAS G12C) mutant.[5] The successful development of KRAS G12C inhibitors is attributed to the distinct presence of the switch II pocket that allows covalent inhibition of the cysteine residue, as well as the high GTPase activity of KRAS G12C that likely results in an attenuated duration of rapidly accelerated fibrosarcoma (RAF) kinase activation, which is not fully present in other KRAS-mutant types.[6] Despite the ubiquity of KRAS mutations in solid tumours, the global prevalence of KRAS G12C

Table 1: Prevalence and distribution of Kirsten rat sarcoma virus G12 mutations across gastrointestinal cancer types[7,8]

	Colorectal (%)	Pancreas (%)	Gastric/Esophageal (%)	Gallbladder/cholangiocarcinoma (%)
KRAS G12C	7.0	1.3	5.9/7.6	0.5/1.2
KRAS G12D	29.9	41.8	27.0/33.0	33.6
KRAS G12V	20.0	31.6	18.0/13.0	27.2
KRAS G12R	1.1	16.1	3.9/0.8	9.6

KRAS = Kirsten rat sarcoma virus.

mutations is relatively low in PDAC and CRC, accounting for only 1.3 and 3.1% of the total mutational burden, respectively (*Table 1*).[9–11] Moreover, several studies in CRC and PDAC have found that KRAS mutations, particularly KRAS G12C, are associated with a poor response to cytotoxic chemotherapy.[12] Indeed, patients with KRAS G12C-mutated CRC had a median overall survival (mOS) of 16.1 (95% confidence interval [CI], 13.0–19.0) months compared with 18.3 (95% CI, 17.2–19.3) months for KRAS non-G12C-mutated tumours and 19.2 (18.5–19.8) months for the mCRC overall cohort .[13,14] In PDAC, mOS was 16.7 months in KRAS G12C-mutated tumours versus 24.9 months in KRAS non-G12C-mutated tumours.[15] This review aims to summarize the pleiotropic functions of the KRAS gene, highlight the unique features of the KRAS G12C protein concerning its biological role and targeted treatments, describe the main mechanisms of resistance of currently approved drugs and finally review the results from published clinical trials testing KRAS G12C inhibitors, as well as KRAS G12C downstream and upstream protein inhibitors, with a focus on the most promising ongoing trials.

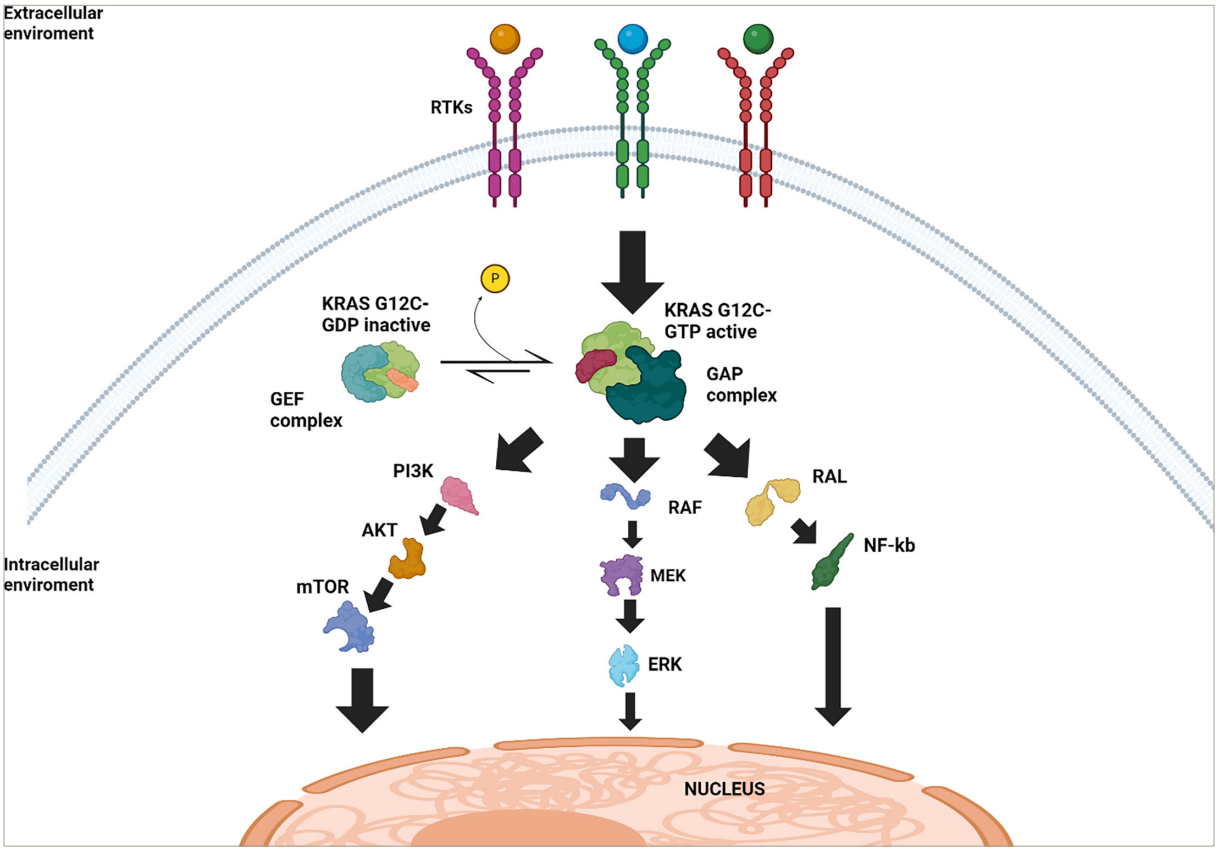
Kirsten rat sarcoma virus structure and effects of activating Kirsten rat sarcoma virus mutations

RAS proteins are small, membrane-bound guanine nucleotide-binding proteins. The major RAS isoforms are encoded by three genes, HRAS, NRAS and KRAS, producing four proteins, HRAS, NRAS, KRAS4A and KRAS4B, from a KRAS splice variant. The amino-terminal residues 1–165 of these proteins share 92–98% sequence similarity, and the remaining 23–24 carboxy-terminal residues diverge significantly. The structural domain of the RAS protein consists of the first 166–168 residues, forming the G domain, a structure featuring a mix of six-stranded β-sheet and five-α-helix fold, typical of α,β-nucleotide-binding proteins. Four main regions border the nucleotide-binding pocket: the phosphate-binding loop (P-loop, residues 10–17), switch I (residues 30–38), switch II (residues 60–76) and the base-binding loops (residues 116–120 and 145–147).[16] Similar to its RAS family counterparts, NRAS and HRAS, KRAS mediates downstream signalling via the activation of the RAF protein/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinases (ERK) cascade, the phosphoinositide-3-kinase complex/mammalian target of rapamycin (PI3K/mTOR) axis and ultimately the RAS-related protein/nuclear factor-κB (NF-κB) pathway, driving tumour onset, progression and distant spread.[17–19] KRAS constantly transitions between an inactive 'off' state when bound to guanosine diphosphate (GDP) and an active 'on' state when bound to GTP, a process facilitated by guanine nucleotide exchange factors (GEFs) such as Son of Sevenless (SOS) 1 and 2. In the GTP-bound state, threonine-35 (in the switch I region) and glycine-60 (in the switch II region) stabilize the active conformations of the switch I and switch II regions by anchoring to the γ-phosphate of GTP. Upon phosphate release during GTP hydrolysis, switch I and switch II recoil back into their inactive GDP conformations, such that these regions ultimately regulate all known nucleotide-dependent interactions between RAS and its binding partners.[16] The exchange of GDP for GTP results in the activation and dimerization of RAS proteins, ultimately leading to the propagation of signal transduction cascades. This transition is mainly regulated by a variety of upstream receptor tyrosine kinases (RTKs) such as the epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), human epidermal growth factor receptor 3 and fibroblast growth factor receptors (FGFRs).[20] Most KRAS-activating mutations trigger the conversion of KRAS-GDP into KRAS-GTP, further enhanced by inhibiting GTPase activity that locks KRAS in its 'on' state, leading to the constitutive activation of downstream signalling pathways (*Figure 1*).

Evolution of Kirsten rat sarcoma virus-targeting strategies

Targeting KRAS has been an important research challenge during the last 30 years when it was considered 'undruggable'. This challenge stemmed in part from the structure of KRAS, a small protein with a relatively smooth surface that lacks well-defined hydrophobic pockets (except for its GTP/GDP-binding pocket) suitable for small-molecule inhibitor binding, as well as from KRAS's ability to bind GTP with picomolar affinity in an environment with high intracellular GTP concentrations.[16,21–24] In addition, each *KRAS* mutation alters the structure of the GTP-binding pocket differently, which further complicates the design of an inhibitor that is effective against multiple *KRAS* alterations.[25–27] Strategies therefore focused on indirectly targeting KRAS by inhibiting downstream signalling effectors such as PI3K and MEK, modifying the epigenetic environment with telomerase inhibitors, and RNA interference or promoting synthetic lethality using cyclin-dependent kinase inhibitors, with limited tolerability and efficacy.[28–31] In the last decade, molecular studies of KRAS-mutated proteins highlighted the unique structure of the aberrant variant KRAS G12C, resulting from a missense mutation, causing the substitution of glycine with cysteine at codon 12 in exon 2. The presence of cysteine causes a steric block that prevents the arginine finger of GTPase-activating proteins from binding to the GTPase site of RAS, inhibiting the hydrolysis of GTP to GDP, thus maintaining KRAS in a constitutively active state.[32] However, a distinguishing feature of the KRAS G12C protein, discovered by Shokat's laboratory in 2013, is the presence of an allosteric pocket below the switch II region of the mutated cysteine residue, called the switch II pocket, which is susceptible to inhibition through covalent binding.[20] Unlike other KRAS mutations, KRAS G12C does not significantly alter the intrinsic GTPase activity, allowing KRAS to remain in the GDP-bound or inactive state for a longer period.[33] These biochemical and functional properties paved the way for the development of the first KRAS G12C-targeted therapies: sotorasib and adagrasib. Both drugs irreversibly bind the cysteine residue in the switch II pocket of KRAS G12C, locking it in its inactive GDP-bound state and inhibiting downstream signalling.[16,34] While adagrasib has high selectivity for KRAS G12C, sotorasib inhibits NRAS G12C more potently compared with KRAS G12C or HRAS G12C. According to structural and reciprocal mutagenesis studies, differences in isoform-specific binding are mediated only by histidine-95 in KRAS and leucine-95 in NRAS.[35] A single patient with NRAS G12C CRC was reported to have had a marked tumour response after being treated with sotorasib and panitumumab,

Figure 1: Schematic representation of Kirsten rat sarcoma virus G12C signalling pathways and regulatory mechanisms



Simplified illustration of the signalling pathways downstream of KRAS G12C in its active and inactive states. Black arrows indicate upregulation or activation. At the cell membrane, RTKs initiate the activation of KRAS. In the inactive state, KRAS G12C is bound to GDP and undergoes activation through interaction with GEFs, which facilitate the exchange of GDP for GTP. Once bound to GTP, KRAS G12C transitions to its active state and promotes the activation of multiple downstream signalling pathways (RAF/MEK/ERK, PI3K/AKT/mTOR pathway and RAL/NF-κB). The GAPs promote the hydrolysis of GTP to GDP, inactivating KRAS G12C and returning it to the inactive GDP-bound state. These signalling pathways ultimately converge at the nucleus, regulating cellular processes such as proliferation, survival and tumour progression.
AKT = protein kinase B; ERK = extracellular signal-regulated kinase; GAP = GTPase-activating protein; GDP = guanosine diphosphate; GEF = guanine nucleotide exchange factors; GTP = guanosine-5'-triphosphate; KRAS = Kirsten rat sarcoma virus; MEK = mitogen-activated protein kinase kinase; mTOR = mammalian target of rapamycin; NF-kB = nuclear factor-κB; PI3K = phosphoinositide3-kinase complex; RAF = rapidly accelerated fibrosarcoma; RAL = RAS-related protein; RTKs = receptor tyrosine kinase.

suggesting that sotorasib can be clinically effective in NRAS G12C-mutated tumours.[35] Regardless, the clinical application of single-agent sotorasib was studied in 2021 to treat advanced KRAS G12C-mutated non-small-cell lung cancer (NSCLC) in the CodeBreaK 100 trial (A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Sotorasib [AMG 510] Monotherapy in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation and Sotorasib [AMG 510] Combination Therapy in Subjects With Advanced NSCLC With KRAS p.G12C Mutation; ClinicalTrials.gov identifier: NCT03600883).[36] This phase II trial enrolled 126 patients (pts) with previously treated KRAS G12C-mutated NSCLC who received sotorasib. The overall response rate (ORR) was 37.1% (95% CI, 28.6–46.2), disease control rate (DCR) was 80.6% (95% CI, 72.6–87.2), median progression-free survival (mPFS) was 6.8 months (95% CI, 5.1–8.2) and mOS was 12.5 months.[36] The CodeBreaK 100 trial has been considered a landmark trial based on these results, and sotorasib was granted accelerated approval by the US Food and Drug Administration (FDA) in May 2021 for the treatment of locally advanced or metastatic KRAS G12C-mutated NSCLC pts who have failed one or more systemic therapies.[37] Comparable findings were observed with adagrasib monotherapy in a similar population, prompting its approval by the US FDA in December 2022.[38] Sotorasib and adagrasib have also shown encouraging but varied results in GI cancers. The initial findings from the CodeBreaK 100 trial included a cohort of 12 pts with KRAS G12C-mutated PDAC who received sotorasib monotherapy, amongst whom one achieved a partial response (PR).[39] When the trial was expanded to include 38 pts with KRAS G12C-mutated PDAC, mPFS was 4.0 months and mOS was 6.9 months. In addition, 21% of pts achieved a PR, with a DCR of 84%.[40] In the phase I–II KRYSTAL-1 trial (ClinicalTrials.gov identifier: NCT03785249), adagrasib monotherapy demonstrated comparable outcomes to sotorasib: for 21 pts with metastatic PDAC receiving adagrasib, mPFS was 5.4 months (95% CI, 3.9–8.2) and mOS was 8.0 months (95% CI, 5.2–11.8). ORR was 33% and DCR was 49%.[41] So far, both adagrasib and sotorasib have been adopted as single-agent therapeutic options by the National Comprehensive Cancer Network guidelines for advanced KRAS G12C-mutated PDAC and biliary tract cancers (BTC).[41] While single-agent KRAS G12C inhibitors have shown promising results in PDAC, their efficacy appears less pronounced in CRC. On the other hand, improved results were observed testing sotorasib and adagrasib in combination with EGFR inhibitors. The analysis of CodeBreaK 101, a phase Ib study of pts with chemorefractory KRAS G12C-mutated CRC receiving sotorasib alone or in combination with EGFR inhibitors, showed an ORR of 30% with sotorasib–panitumumab compared with 9.7% with sotorasib monotherapy.[42,43] Subsequently, the CodeBreaK 300 trial evaluated two doses of sotorasib (960 mg once daily and 240 mg once daily) in combination with panitumumab versus standard-of-care trifluridine/tipiracil in chemorefractory metastatic CRC (mCRC) and showed an mPFS of 5.6 and 3.9 months in the 960 mg sotorasib–panitumumab group and 240 mg in the sotorasib–panitumumab group compared with 2.2 months in the standard-care group. ORR was 26.4, 5.7 and 0% for the 960 mg sotorasib–panitumumab, 240 mg sotorasib–panitumumab and

standard-care groups, respectively.[42] Of note, the phase I–II KRYSTAL-1 trial assessed adagrasib ± cetuximab in the same setting, showing an ORR of 34% (95% CI, 24.6–44.5) versus 21.4% (95% CI, 10.3–36.8) in favour of the combination treatment with a similar DCR (85.1 versus 86.2%) between the two arms. The combination confirmed its superiority in all the other efficacy outcomes, with an mPFS of 6.9 months (95% CI, 5.7–7.4) versus 4.1 months (95% CI, 2.8–6.5). mOS was 15.0 months (95% CI, 11.8–18.8) versus 12.2 months (95% CI, 8.1–15.2). Interestingly, the combination was more tolerated with 27% of grade 3–4 treatment-related adverse events (TRAEs) versus 34%, respectively.[44] Fuelled by these positive results, the KRYSTAL-10 (ClinicalTrials.gov identifier: NCT04793958), a global, open-label, randomized phase III study, evaluates adagrasib and cetuximab against chemotherapy in the same patient cohort.[45] On the other hand, the use of KRAS G12C inhibitors remains limited in other GI cancers. The prevalence of KRAS G12C varies across GI malignancies: it is limited in BTC, accounting for only 1% of mutations, and is slightly more prevalent in appendiceal cancers (3–4%).[10] A cohort of KRYSTAL-1 focusing on non-CRC GI cancers evaluated 57 pts, amongst whom 12 had BTC and 16 had other GI tumours (nine pts had appendiceal cancer, four had gastro-oesophageal junction/oesophageal cancer and three had small bowel cancer). Updated results published in May 2023 demonstrated an ORR of 35.1%, a DCR of 86.0% and a median duration of response of 5.3 months (95% CI, 2.8–7.3). mPFS was 7.4 months (95% CI, 5.3–8.6) and mOS was 14.0 months (95% CI, 8.5–18.6). Interestingly, in pts with BTC, ORR was 41.7%, DCR was 91.7%, mPFS was 8.6 months (95% CI, 2.7–11.3) and mOS was 15.1 months (95% CI, 8.6–not estimable).[41]

Emergence of resistance

Despite the initial clinical responses achieved with KRAS G12C inhibitors, treatment failure eventually occurs due to the emergence of resistance. Resistance mechanisms can be divided into genetic when a mutation is identified in genes involved in RAS-dependent molecular pathways and adaptive when reactivation of upstream proteins occurs. According to paired plasma sample analyses, genetically acquired mutations have been detected in 90% of mCRC pts treated with the new KRAS G12C inhibitor divarasib with or without cetuximab.[46] The most common on- and off-target alterations detected include new activating KRAS mutations, upstream RTKs hyperactive alterations (EGFR and FGFRs) and aberrations associated with downstream proteins (PIK3CA, RAF and MEK). Similarly, pts treated with adagrasib with or without cetuximab, for whom genomic-acquired mechanisms of resistance were detectable in more than 70% of pts, the newly acquired mutations affected both downstream signalling proteins, such as mitogen-activated protein kinase (MAPK) and PI3K, and upstream RTKs.[47] Adaptive resistance most commonly manifests through the reactivation of upstream RTKs in response to KRAS G12C inhibition, limiting the efficacy of targeted drug therapies.[48] Mutant KRAS G12C suppresses the activation of upstream RTKs and other wild-type RAS isoforms through ERK-mediated feedback inhibition. Therefore, using an agent stabilizing KRAS G12C protein in its 'off' state relieves this suppression with a consequent upregulation of RTKs, ultimately leading to the activation of wild-type RAS isoforms. This circuit was demonstrated in two studies by Ryan et al., where treatment with KRAS G12C inhibitors resulted in a rapid rebound increase in MAPK signalling as a result of the increased expression of multiple upstream RTKs, including EGFR, HER2 and FGFR.[49,50] Uncovering these resistance mechanisms has fuelled the development of novel targeted therapeutic agents, which are under clinical investigation as both single-agent and combined strategies with other agents. Several promising therapies are currently undergoing preclinical or early-phase trials within multicohort studies, with the most relevant highlighted in *Table 2*.p[28,36,51–65]

New direct inhibitors of Kirsten rat sarcoma virus G12C

Since the FDA approved adagrasib and sotorasib, several KRAS G12C inhibitors with different safety profiles are entering clinical trials. Divarasib is a KRAS G12C inhibitor that binds to the KRAS G12C protein in its 'off' state. It is, however, up to 50 times more selective and 5–20 times more potent than sotorasib and adagrasib according to *in vitro* studies.[33] Divarasib monotherapy was evaluated in a phase I trial enrolling 137 pts, 55 of whom had mCRC.[32] No dose-limiting toxicity occurred across concentrations ranging from 50 to 400 mg, and grade ≥3 TRAEs were observed in 12% of pts, leading to treatment discontinuation in 3% of cases. Amongst patients in the CRC cohort treated with divarasib 400 mg daily, 35.9% had a confirmed response (complete response [CR] or PR) and an mPFS of 6.9 months. More recently, the combination of divarasib with cetuximab achieved an improved ORR of 62.5% (95% CI, 40.6–81.2%) and an mPFS of 8.1 months (95% CI, 5.5–12.3) in pts with mCRC enrolled in a phase Ib trial (A Phase Ia/Ib Dose-escalation and Dose-expansion Study Evaluating the Safety, Pharmacokinetics, and Activity of GDC-6036 as a Single Agent and in Combination with Other Anti-cancer Therapies in Patients with Advanced or Metastatic Solid Tumors with a KRAS G12C Mutation; ClinicalTrials.gov identifier: NCT04449874).[67] In a limited PDAC cohort containing seven pts receiving divarasib, three achieved PR, while four had stable disease (SD). Similarly, amongst seven pts with BTC, one patient had a PR, four had SD and one had progressive disease (PD).[46] Therefore, further assessment of divarasib in PDAC and BTC is warranted in more extensive randomized trials. Divarasib is under evaluation in two phase I basket trials (ClinicalTrials.gov identifiers: NCT04449874 and NCT04929223), exploring its efficacy in combination with cetuximab with or without cytotoxic chemotherapy.[68,69] Garsorasib is another orally bioavailable small-molecule inhibitor of KRAS G12C shown to be highly potent *in vivo* using cell line-derived and patient-derived xenograft tumour models, as well as in PDAC and CRC *in vitro* cell lines. In CRC patient-derived xenografts models, single-agent demonstrated tumour growth inhibition ranging from 60.9 to 105.7%, with three out of nine models showing tumour regression.[70] Combining garsorasib with other anti-cancer agents, such as MEK inhibitors, tyrosine phosphatase-2 (Src Homologous Protein 2 [SHP2]) inhibitors and chemotherapy, increased its anti-tumoural activity and enhanced tumour regression.[71] The efficacy of garsorasib was evaluated in combination with cetuximab in an ongoing phase II trial (ClinicalTrials.gov identifier: NCT04585035) in pts with refractory mCRC. Preliminary results demonstrated an ORR of 45% and a DCR of 95%. However, data on overall survival are still pending.[70–72] Similarly, amongst 10 pts with advanced PDAC who received garsorasib, ORR was 50%, including one CR, DCR was 80% and mPFS was 8.54 months.[73] It is essential to mention that in this trial, only 40% of pts received two or more lines of therapy.

Son of Sevenless 1 and Src Homologous Protein 2 inhibitors

Son of Sevenless 1 (SOS1) and SHP2 are signalling intermediates activated by RTKs that act as central nodes in the RAS signalling pathway. SOS1 is a GEF protein that binds inactive KRAS–GDP complex and mediates GTP exchange. SHP2, an adaptive phosphatase, links directly to SOS1, further facilitating GTP exchange. Therefore, inhibiting both SOS1 and SHP2 blocks RTK-positive molecular signalling to KRAS, maintaining it in its inactive GDP state. Published data demonstrated that co-inhibition of SHP2 and KRAS G12C overturns feedback reactivation across different RTKs and that combined KRAS G12C–SHP2 inhibition maintains RAS pathway suppression with improved efficacy both *in vitro* and *in vivo*.[49,50] Since new activating RTK alterations were also commonly detected in liquid

Table 2: Comprehensive list of new Kirsten rat sarcoma virus G12C 'off' inhibitors and their treatment-related adverse events[28,36,51–65]

Agent	Pharmaceutical company	Clinical trial and identifier	Incidence of grade ≥3 TRAEs	Most commonly reported grade ≥3 TRAEs
LY3537982[51]	Eli Lilly and Company	Phase I (NCT04956640)	NA	Diarrhoea, constipation, fatigue, peripheral oedema, nausea and neutropenia
GDC-6036[28]	Genentech	Phase I (NCT04449874)	12%	Increased ALT, increased AST, nausea, vomiting and fatigue
D-1553[52]	InventisBio	Phase I/II (NCT04585035)	22%	Increased AST and ALT, diarrhoea, hypertension, hypokalaemia and nausea
HBI-2438[53]	Huyabio International	Phase I (NCT05485974)	Pending	Pending
JDQ443[54]	Novartis	Phase Ib/II (NCT04699188)	7.1%	Neutropenia, increased ALT and AST and myalgia
JAB-21822[55]	Jacobio Pharma	Phase I/II (NCT05009329)	0%	NA
HS-10370[36]	Jiangsu Hansoh Pharmaceutical Company	Phase I/II (NCT05367778)	27.3%	Increased AST and ALT, anaemia, diarrhoea, weight gain, decreased appetite, hypoproteinaemia, nausea, fatigue and rash
IBI-351 (GFH925)[56]	Innovent Biologics Inc.	Phase I/II (NCT05005234)	20%	Anaemia, leukopaenia, increased ALT and pruritus
BI-1823911[57]	Boehringer Ingelheim	Phase I (NCT04973163)	30%	Nausea, diarrhoea, vomiting, fatigue and decreased appetite
JNJ-74699157[58]	Johnson & Johnson	Phase I (NCT04006301)	55%	Increased blood CPK
GFH925[56]	GenFleet	Pooled analysis of two phase I studies (NCT05005234 and NCT05497336)	20%	Anaemia, decreased white blood cell count, increased ALT and pruritus
YL-15293[59]	Shanghai Yingli	Phase I (NCT05173805)	NA	NA
BPI0421286[60]	Belta	Phase I (NCT05315180)	Pending	Pending
GH35[61]	Suzhou Genhouse Bio	Phase I (NCT05010694)	Pending	Pending
GEC255[62]	GenEros Biopharma	Phase I	6.7%	Diarrhoea, increased ALT, rash and anaemia
MK-1084[63]	Merck	Phase I (NCT05067283)	Pending	Pending
D3S-001[64]	D3 Bio	Phase I	14.6%	NA
HBI-2438[66]	Huyabio	Phase I (NCT05485974)	Pending	Pending
SY-5933[65]	Shouyao Holdings	Phase I (NCT06006793)	Pending	Pending

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = blood creatinine phosphokinase; NA = not available; TRAEs = treatment-related adverse events.

biopsies at the time of radiological treatment progression, approaches that target KRAS activation via SOS1 or SHP2 inhibitors represent a compelling avenue for intervention. The combination of glecirasib with JAB-3312, an SHP2 inhibitor, in pts with NSCLC with no prior exposure to KRAS G12C inhibitors demonstrated an ORR of 50% and a DCR of 100%, albeit with increased toxicity.[74] RMC-4630 is another SHP2 inhibitor being examined with sotorasib in the CodeBreaK 101 trial.[75] In a cohort of six pts, five (83%) achieved disease control; however, no responses were observed.

Downstream mitogen-activated protein kinase blockade

As mentioned previously, adaptive and acquired resistance mechanisms may involve upregulation of the RTK/RAS/MAPK downstream signalling pathway, hence the rationale behind using RAS downstream inhibitors. A well-described example is the upregulation of EGFR that occurs with B-Raf murine sarcoma viral oncogene homologue B (BRAF) inhibition in BRAF-mutated CRC, necessitating the addition of EGFR inhibitors to counteract drug resistance. Another example is the compensatory activation of the mTOR pathway, which has been documented in KRAS G12C inhibitor-resistant CRC cell lines.[76] Currently, mTOR inhibitors such as everolimus are being explored in combination with sotorasib in NSCLC, while relevant phase I basket trials are investigating combinations such as adagrasib with nab-sirolimus (ClinicalTrials.gov identifier: NCT05840510) and divarasib with the PI3K inhibitor inavolisib (ClinicalTrials.gov identifier: NCT04449874) in pts with various solid tumours, including CRC.[68,77] Moreover, the addition of MEK inhibitors to G12C inhibitors is being tested in the CodeBreaK 101 study as a new alternative, based on preclinical studies showing that sotorasib and trametinib (MEK inhibitor) combination has a synergistic anti-tumour effect on NSCLC tumour cell lines *in vitro* compared with either of the single agents alone.[78] In this context, sotorasib and trametinib (MEK inhibitor) were evaluated in 36 pts, 18 of whom have KRAS G12C-mutant CRC, achieving a remarkable DCR of 86%.[79] It is worth noting that some pts had prior exposure to KRAS G12C inhibitors, and upon receiving the maximum tolerated dose of 2 mg trametinib and 960 mg sotorasib, all pts had radiological SD. These results, albeit reported in a limited number of pts, indicate a clinically significant therapeutic benefit associated with the addition of trametinib to sotorasib. Of note, this trial reported 34% of pts with grade ≥3 toxicity, leading to therapy discontinuation in 24% of cases.

Combination with immunotherapy

The tumour microenvironment (TME) in PDAC is a complex and dynamic cell network involving immune, stromal and cancer cells, facilitating tumour progression and response to therapy. KRAS mutations have been widely shown to foster anti-inflammatory and pro-inflammatory effects on the TME. Some studies underpinned that KRAS mutations promote an immunosuppressive TME through several mechanisms

Table 3: Summary of clinical trials testing Kirsten rat sarcoma virus G12C inhibitors as monotherapy or in combination with other agents in gastrointestinal cancers[40–42,44–46,51,56–58,67,69,72,74,75,79,88–107]

Target	Drugs	Trial name and identifier	Phase	GI malignancy	Number of pts in the trial, if applicable	Clinical efficacy
KRAS G12C 'off' inhibitors	Adagrasib[41]	KRYSTAL-1 (NCT03785249)	I/II	PDAC	21	ORR: 33% DCR: 49% mPFS: 5.4 months mOS: 8.0 months
				CRC	43	ORR: 19% DCR: 86% mPFS: 5.6 months mOS: 19.8 months
				BTC	12	ORR: 42% DCR: 92%
				Appendiceal adenocarcinoma	7	ORR: 0% DCR: 86%
				GEA	3	ORR: 33% DCR: 66%
	Adagrasib+cetuximab[44,45]	NCT05634525	I	PDAC	Pending	Pending
		KRYSTAL-1 (NCT03785249)	I/II	CRC	28	ORR: 46% DCR: 100% mPFS: 6.9 months mOS: 13.4 months
	Adagrasib+cetuximab+irinotecan[88]	NCT05722327	I	CRC	Pending	Pending
	Adagrasib+cetuximab versus chemotherapy[89]	KRYSTAL-10 (NCT04793958)	III	CRC, second line	Pending	Pending
	Adagrasib+TNO155[90]	KRYSTAL-2 (NCT04330664)	I/II	CRC	Pending	Pending
	Adagrasib+BI 1701963[91]	KRYSTAL-14 (NCT04975256)	I	CRC	Pending	Pending
	Adagrasib+MRTX0902[92]	NCT05578092	I/II	NA	Pending	Pending
	Adagrasib+durvalumab[93]	NCT05848843	I	CRC	Pending	Pending
	Adagrasib+INCB099280[94]	NCT06039384	I	CRC	Pending	Pending
	Sotorasib[40,42]	CodeBreaK 100 (NCT03600883)	I/II	PDAC	38	ORR: 21% DCR: 84% mPFS: 4.0 months mOS: 6.9 months
				CRC	62	ORR = 9.7% DCR = 82%
	Sotorasib+panitumumab[95]	CodeBreaK 101 (NCT04185883)	I/II	CRC	40	ORR: 30% DCR: 93% mPFS: 5.7 months
	Sotorasib+panitumumab+FOLFIRI[96]	CodeBreaK 101 (NCT04185883)	I/II	CRC	31	ORR: 58.1%
	Sotorasib+trametinib[79]	CodeBreaK 101 (NCT04185883)	I/II	CRC	18	ORR: 11.1% DCR: 83.3%
	Sotorasib+panitumumab versus standard of care[97]	CodeBreaK 300 (NCT05198934)	III	CRC		ORR: 26.4 versus 0% (SOC) DCR: 71.7 versus 46.3% (SOC) mPFS: 5.6 versus 2.2 months (SOC)
	Sotorasib+BI 1701963[98]	CodeBreaK 101 (NCT04185883)	I/II	NA	Pending	Pending
	Sotorasib+RMC-4630[75]	CodeBreaK 101 (NCT04185883)	I/II	CRC	6	ORR: 0% DCR: 83.3%
	Sotorasib+BBP-398[99]	NCT05480865	I/II	NA	Pending	Pending
	BI1823911 monotherapy+BI 1701963[57]	NCT04973163	I	NA	Pending	Pending
	Divarasib[46]	NCT04449874	I	CRC	55	ORR: 29% DCR: 85% mPFS: 5.6 months
				PDAC	7	ORR: 43% DCR: 100%
				BTC	5	ORR: 0% DCR: 80%
	Divarasib+cetuximab[67]	NCT04449874	I	CRC	29	ORR: 62.5%
	Divarasib+cetuximab+FOLFOX or FOLFIRI[69]	INTRINSIC (NCT04929223)	I	CRC	Pending	Pending
	Fulzerasib[56]	Pooled analysis of NCT05005234 and NCT05497336	I	CRC	45	ORR 43.8% DCR 87.5%
	Garsorasib[72]	NCT04585035	I/II	CRC	24	ORR: 21% DCR 95.8% mPFS: 7.6 months
	Garsorasib[72]	NCT04585035	I/II	PDAC	10	ORR: 50% DCR: 80% mPFS: 8.5 months
	Garsorasib+cetuximab[72]	NCT04585035	I/II	CRC	40	ORR: 45% DCR: 95% mPFS 7.6 months

Continued

Table 3: Continued

Target	Drugs	Trial name and identifier	Phase	GI malignancy	Number of pts in the trial, if applicable	Clinical efficacy
	Glecirasib[101]	NCT05009329 and NCT05002270	I/II	PDAC, biliary tract, gastric, small bowel, appendiceal, hepatocellular, peritoneal	PDAC = 28 Others = 19	ORR: 46.4% DCR: 96.4% mPFS: 5.5 months
	Glecirasib+cetuximab[102]	NCT05002270 and NCT05194995	I/II	CRC, small bowel and appendiceal adenocarcinoma	43	ORR: 62.8% DCR: 93% mPFS: Not reached
	Glecirasib[103]	NCT06008288	II	PDAC	Pending	Pending
	Glecirasib+JAB-3312[74]	NCT05288205	I/II	CRC and PDAC	Pending	Pending
	JDQ443 monotherapy+TNO155 or +tislelizumab[104]	KontRASt-01 (NCT04699188)	I/II	CRC	Pending	Pending
	JDQ443+trametinib+ribociclib or + cetuximab[105]	KontRASt-03 (NCT05358249)	I/II	CRC	Pending	Pending
	JNJ-74699157[58]	NCT04006301	I	CRC		Withdrawn from market
	LY3537982[51]	LOXO-RAS-20001 (NCT04956640)	I/II	PDAC	12	ORR: 42% DCR: 92%
				CRC	20	ORR: 10% DCR: 90%
				Others	21	ORR: 52% DCR: 95%
	LY3537982+cetuximab[51]	LOXO-RAS-20001 (NCT04956640)	I/II	CRC	11	ORR: 45% DCR: 100%
KRAS G12C 'on' inhibitors	BBO-8520[106]	Preclinical				
	RMC-6291[107]	NCT05462717	I	CRC	20	ORR = 40% DCR = 80%

BTC = biliary tract cancer; CRC = colorectal cancer; DCR = disease control rate; FOLFIRI = leucovorin calcium (folinic acid)–fluorouracil–irinotecan hydrochloride; FOLFOX = leucovorin calcium (folinic acid)–fluorouracil–oxaliplatin; GEA = gastro-oesophageal cancer; GI = gastrointestinal; KRAS = Kirsten rat sarcoma virus; mOS = median overall survival; mPFS = median progression-free survival; NA = not available; ORR = overall response rate; PDAC = pancreatic ductal adenocarcinoma; pts = patients; SOC = standard of care.

such as tumour cell expression of inhibitory cytokines interleukin (IL)-10 and transforming growth factor-β, recruitment of myeloid-derived suppressor cells, regulatory T-cell (T-reg cell) activation and suppression of cluster of differentiation 8 (CD8) T-cell activity.[21,80] Other studies suggest that KRAS mutations could also interfere with the secretion of pro-inflammatory cytokines, such as intercellular adhesion molecule-1, tumour necrosis factor-α, IL-1β, IL-6 and IL-18, through the induction of NF-κB.[81–83] On the other hand, adagrasib and sotorasib were found to induce a pro-inflammatory microenvironment and modulate the TME by recruiting macrophages, dendritic cells and CD8 T-cells, promoting anti-tumour immune response in NSCLC. These findings suggest a potential synergistic interaction between these agents and immune checkpoint inhibitors (ICIs).[84,85] However, conflicting data have emerged regarding the efficacy and tolerability of these combined regimens. Early data from the CodeBreaK 101 study, in which pts with NSCLC received sotorasib plus pembrolizumab or atezolizumab, showed a high incidence of liver toxicity, with an ORR of 29% and a DCR of 83%.[86] However, results from the KRYSTAL-7 (ClinicalTrials.gov identifier: NCT04613596) study combining adagrasib and pembrolizumab in pts with NSCLC who had programmed death-ligand 1 expression >50% demonstrated an ORR of 63% and a DCR of 84%, with limited high-grade toxicity (10%).[87] The combination of KRAS G12C inhibitors with ICIs and other target therapies is currently being assessed in several clinical trials across other KRAS G12C-mutant solid tumours, PDAC and CRC (*Table 3*).[40–42,44–46,51,56–58,67,69,72,74,75,79,88–107]

Conclusion

Since the first demonstration of sotorasib efficacy with the published results from the CodeBreaK 100 trial in 2019, the current landscape of RAS targeting strategy has shifted from undruggable to druggable. Fuelled by the successful implementation of adagrasib and sotorasib as standard treatment options in PDAC, and recently in BTC and CRC, more than a dozen small-molecule inhibitors targeting KRAS G12C and related upstream and downstream molecules have emerged. They are actively investigating, with many of them already advanced to clinical trials for evaluation in GI cancers. However, despite the crucial development and relative success of KRAS G12C inhibitors in treating GI cancers, clinical research must still prioritize strategies to overcome primary and acquired resistance, primarily through vertical inhibition with RTK/RAS/MAPK pathway inhibitors and combination with immunotherapy or standard chemotherapy. In addition, more data about toxicity management and quality of life are awaited to ensure the safety of new drugs and combinations under evaluation. Other important considerations will be integrating KRAS G12C inhibitors in earlier phases of treatment, such as in the neoadjuvant and adjuvant settings. These strategies may expand the population of pts with GI cancers, benefitting from the inhibition of KRAS G12C. Undoubtedly, we are in a new and promising era of cancer treatment, pushing the boundaries of KRAS target therapy. ❑

1. Prior IA, Hood FE, Hartley JL. The frequency of Ras mutations in cancer. *Cancer Res*. 2020;80:2969–74. DOI: 10.1158/0008-5472.CAN-19-3682.
2. Cancer Genome Atlas N. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012;487:330–7. DOI: 10.1038/nature11252.
3. Miyashita H, Kato S, Hong DS. KRAS G12C inhibitor combination therapies: Current evidence and challenge. *Front Oncol*. 2024;14:1380584. DOI: 10.3389/fonc.2024.1380584.
4. Singhal A, Li BT, O'Reilly EM. Targeting KRAS in cancer. *Nat Med*. 2024;30:969–83. DOI: 10.1038/s41591-024-02903-0.
5. Ros J, Vaghi C, Baraibar I, et al. Targeting KRAS G12C mutation in colorectal cancer, a review: New arrows in the quiver. *Int J Mol Sci*. 2024;25:3304. DOI: 10.3390/ijms25063304.
6. Hunter JC, Manandhar A, Carrasco MA, et al. Biochemical and structural analysis of common cancer-associated KRAS mutations. *Mol Cancer Res*. 2015;13:1325–35. DOI: 10.1158/1541-7786.MCR-15-0203.
7. Salem M, El-Refai S, Sha W, et al. O-3 characterization of KRAS mutation variants and prevalence of KRAS-G12C in gastrointestinal malignancies. *Ann Oncol*. 2021;32:S218. DOI: 10.1016/j.annonc.2021.05.007.
8. Lee JK, Sivakumar S, Schrock AB, et al. Comprehensive pan-cancer genomic landscape of KRAS altered cancers and real-world outcomes in solid tumors. *NPJ precision oncology*. 2022;6:91. DOI: 10.1038/s41698-022-00334-z.
9. Aaltonen LA, Abascal F, Abeshouse A, et al. Pan-cancer analysis of whole genomes. *Nature*. 2020;578:82–93. DOI: 10.1038/s41586-020-1969-6.
10. Salem ME, El-Refai SM, Sha W, et al. Landscape of KRAS(G12C), associated genomic alterations, and interrelation with immuno-oncology biomarkers in KRAS-mutated cancers. *JCO Precis Oncol*. 2022;6:e2100245. DOI: 10.1200/PO.21.00245.
11. Strickler JH, Yoshino T, Stevinson K, et al. Prevalence of KRAS G12C mutation and co-mutations and associated clinical outcomes in patients with colorectal cancer: A systematic literature review. *Oncologist*. 2023;28:e981–94. DOI: 10.1093/oncolo/oyad138.
12. Jones RP, Sutton PA, Evans JP, et al. Specific mutations in KRAS codon 12 are associated with worse overall survival in patients with advanced and recurrent colorectal cancer. *Br J Cancer*. 2017;116:923–9. DOI: 10.1038/bjc.2017.37.
13. Fakih M, Tu H, Hsu H, et al. Real-world study of characteristics and treatment outcomes among patients with KRAS p.G12C-mutated or other KRAS mutated metastatic colorectal cancer. *Oncologist*. 2022;27:663–74. DOI: 10.1093/oncolo/oyac077.

14. van de Haar J, Ma X, Ooft SN, et al. Codon-specific KRAS mutations predict survival benefit of trifluridine/tipiracil in metastatic colorectal cancer. *Nat Med*. 2023;29:605–14. DOI: 10.1038/s41591-023-02240-8.
15. Boilève A, Rousseau A, Hilmi M, et al. Codon-specific KRAS mutations predict survival in advanced pancreatic cancer. *ESMO Gastrointest Oncol*. 2024;3:100030. DOI: 10.1016/j.esmogo.2023.100030.
16. Ostrem JML, Shokat KM. Direct small-molecule inhibitors of KRAS: From structural insights to mechanism-based design. *Nat Rev Drug Discov*. 2016;15:771–85. DOI: 10.1038/nrd.2016.139.
17. Hymowitz SG, Malek S. Targeting the MAPK pathway in RAS mutant cancers. *Cold Spring Harb Perspect Med*. 2018;8:a031492. DOI: 10.1101/cshperspect.a031492.
18. Erijman A, Shifman JM. RAS/effector interactions from structural and biophysical perspective. *Mini Rev Med Chem*. 2016;16:370–5. DOI: 10.2174/1389557515666151001141838.
19. Glaviano A, Foo AS, Lam HY, et al. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. *Mol Cancer*. 2023;22:138.
20. Kim D, Xue JY, Lito P. Targeting KRAS(G12C): From inhibitory mechanism to modulation of antitumor effects in patients. *Cell*. 2020;183:850–9. DOI: 10.1016/j.cell.2020.09.044.
21. Liu P, Wang Y, Li X. Targeting the untargetable KRAS in cancer therapy. *Acta Pharmaceutica Sinica B*. 2019;9:871–9. DOI: 10.1016/j.apsb.2019.03.002.
22. Ryan MB, Corcoran RB. Therapeutic strategies to target RAS-mutant cancers. *Nat Rev Clin Oncol*. 2018;15:709–20.
23. Cox AD, Fesik SW, Kimmelman AC, et al. Drugging the undruggable RAS: Mission possible? *Nat Rev Drug Discov*. 2014;13:828–51. DOI: 10.1038/nrd4389.
24. Papke B, Der CJ, Drugging RAS. Know the enemy. *Science*. 2017;355:1158–63.
25. Lu S, Jang H, Nussinov R, Zhang J. The structural basis of oncogenic mutations G12, G13 and Q61 in small GTPase K-RAS4b. *Sci Rep*. 2016;6:21949. DOI: 10.1038/srep21949.
26. Traut TW. Physiological concentrations of purines and pyrimidines. *Mol Cell Biochem*. 1994;140:1–22. DOI: 10.1007/BF00928361.
27. John J, Sohmen R, Feuerstein J, et al. Kinetics of interaction of nucleotides with nucleotide-free H-RAS p21. *Biochemistry*. 1990;29:6058–65. DOI: 10.1021/bi00477a025.
28. Schram AM, Gandhi L, Mita MM, et al. A phase Ib dose-escalation and expansion study of the oral MEK inhibitor pimasertib and PI3K/mTOR inhibitor voxtalisib in patients with advanced solid tumours. *Br J Cancer*. 2018;119:1471–6. DOI: 10.1038/s41416-018-0322-4.
29. Liu W, Yin Y, Wang J, et al. KRAS mutations increase telomerase activity and targeting telomerase is a promising therapeutic strategy for KRAS-mutant NSCLC. *Oncotarget*. 2017;8:179–90. DOI: 10.18632/oncotarget.10162.
30. Srikar R, Suresh D, Zambre A, et al. Targeted nanoconjugate co-delivering siRNS and tyrosine kinase inhibitor to KRAS mutant NSCLC dissociates GAB1-SHP2 post oncogene knockdown. *Sci Rep*. 2016;6:30245. DOI: 10.1038/srep30245.
31. Puyol M, Martín A, Dubus P, et al. A synthetic lethal interaction between K-RAS oncogenes and CDK4 unveils a therapeutic strategy for non-small cell lung carcinoma. *Cancer Cell*. 2010;18:63–73. DOI: 10.1016/j.ccr.2010.05.025.
32. Dearden S, Stevens J, Wu Y-L, et al. Mutation incidence and coincidence in non small-cell lung cancer: Meta-analyses by ethnicity and histology (mutMap). *Ann Oncol*. 2013;24:2371–6. DOI: 10.1093/annonc/mdt205.
33. Purkey H. Abstract ND11: Discovery of GDC-6036, a clinical stage treatment for KRAS G12C-positive cancers. *Cancer Res*. 2022;82(Suppl.12):Abstr.ND11. DOI: 10.1158/1538-7445.AM2022-ND11.
34. Hallin J, Engstrom LD, Hargis L, et al. The KRAS^{G12C} inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients. *Cancer Discov*. 2020;10:54–71. DOI: 10.1158/2159-8290.CD-19-1167.
35. Rubinson DA, Tanaka N, Fece de la Cruz F, et al. Sotorasib is a pan-RASG12C inhibitor capable of driving clinical response in NRASG12C cancers. *Cancer Discov*. 2024;14:727–36. DOI: 10.1158/2159-8290.CD-23-1138.
36. Dong X, Meng X, Zhang Y, et al. Abstract CT119: Safety and efficacy of HS-10370 in KRAS G12C-mutated solid tumors including non-small cell lung cancer (NSCLC). *Cancer Res*. 2024;84(Suppl.):Abstr.CT119. DOI: 10.1158/1538-7445.AM2024-CT119.
37. US FDA. FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC. 2021. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sotorasib-kras-g12c-mutated-nsclc (accessed: 24 October 2024).
38. Janne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non-small-cell lung cancer harboring a KRAS(G12C) mutation. *N Engl J Med*. 2022;387:120–31.
39. Hong DS, Fakih MG, Strickler JH, et al. KRAS(G12C) inhibition with sotorasib in advanced solid tumors. *N Engl J Med*. 2020;383:1207–17. DOI: 10.1056/NEJMoa1917239.
40. Strickler JH, Satake H, George TJ, et al. Sotorasib in KRAS p.G12C–mutated advanced pancreatic cancer. *N Engl J Med*. 2023;388:33–43. DOI: 10.1056/NEJMoa2208470.
41. Pant S, Yaeger R, Spira AI, et al. KRYSTAL-1: activity and safety of adagrasib (MRTX849) in patients with advanced solid tumors harboring a KRAS ^{g12c} mutation. *J Clin Oncol*. 2023;41(Suppl.):Abstr.425082. DOI: 10.1200/JCO.2023.41.36_suppl.425082.
42. Fakih MG, Kopetz S, Kuboki Y, 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*. 2022;23:115–24. DOI: 10.1016/S1470-2045(21)00605-7.
43. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with KRAS pG12C mutation. *N Engl J Med*. 2021;384:2371–81. DOI: 10.1056/NEJMoa2103695.
44. Yaeger R, Uboha NV, Pelster MS, et al. Efficacy and safety of adagrasib plus cetuximab in patients with KRASG12C-mutated metastatic colorectal cancer. *Cancer Discov*. 2024;14:982–93. DOI: 10.1158/2159-8290.CD-24-0217.
45. Kopetz S. Dr Kopetz on the future utility of adagrasib/cetuximab in KRAS G12C–mutant CRC. 2024. Available at: www.onclive.com/view/dr-kopetz-on-the-future-utility-of-adagrasib-cetuximab-in-kras-g12c-mutant-crc (accessed: 24 October 2024).
46. Sacher A, LoRusso P, Patel MR, et al. Single-agent divarasib (GDC-6036) in solid tumors with a KRAS G12C mutation. *N Engl J Med*. 2023;389:710–21. DOI: 10.1056/NEJMoa2303810.
47. Awad MM, Liu S, Rybkin II, et al. Acquired resistance to KRAS(G12C) inhibition in cancer. *N Engl J Med*. 2021;384:2382–93.
48. Amodio V, Yaeger R, Arcella P, et al. EGFR blockade reverts resistance to KRAS^{G12C} inhibition in colorectal cancer. *Cancer Discov*. 2020;10:1129–39. DOI: 10.1158/2159-8290.CD-20-0187.
49. Ryan MB, Fece de la Cruz F, Phat S, et al. Vertical pathway inhibition overcomes adaptive feedback resistance to KRAS^{G12C} inhibition. *Clin Cancer Res*. 2020;26:1633–43. DOI: 10.1158/1078-0432.CCR-19-3523.
50. Ryan MB, Coker O, Sorokin A, et al. KRAS^{G12C}-independent feedback activation of wild-type RAS constrains KRAS^{G12C} inhibitor efficacy. *Cell Reports*. 2022;39:110993. DOI: 10.1016/j.celrep.2022.110993.
51. Hollebecque A, Kuboki Y, Murciano-Goroff YR, et al. Efficacy and safety of LY3537982, a potent and highly selective KRAS G12C inhibitor in KRAS G12C-mutant GI cancers: Results from a phase 1 study. *J Clin Oncol*. 2024;42(Suppl.3):Abstr.94. DOI: 10.1200/JCO.2024.42.3_suppl.94.
52. Ruan D, Lee MA, Deng Y, et al. Safety and efficacy of D-1553 in KRAS G12C-mutated colorectal cancer: Results from a phase I/II study. *J Clin Oncol*. 2023;41(Suppl.16):Abstr.3563. DOI: 10.1200/JCO.2023.41.16_suppl.3563.
53. ClinicalTrials.gov. A Dose Escalation Study of HBI-2438 in Patients With Solid Tumors Harboring KRAS G12C Mutation. ClinicalTrials.gov identifier: NCT05485974. Available at: www.clinicaltrials.gov/study/NCT05485974 (accessed: 22 November 2024).
54. Cassier PA, Dooms CA, Gazzah A, et al. KontRASt-01 update: Safety and efficacy of JDQ443 in KRAS *G12C*-mutated solid tumors including non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2023;41(Suppl.16):Abstr.9007. DOI: 10.1200/JCO.2023.41.16_suppl.9007.
55. Li J, Zhao J, Cao B, et al. A phase I/II study of first-in-human trial of JAB-21822 (KRAS G12C inhibitor) in advanced solid tumors. *J Clin Oncol*. 2022;40(Suppl.16):Abstr.3089. DOI: 10.1200/JCO.2022.40.16_suppl.3089.
56. Yuan Y, Deng Y, Jin Y, et al. Efficacy and safety of IBI351 (GFH925) monotherapy in metastatic colorectal cancer harboring KRAS ^{g12c} mutation: preliminary results from a pooled analysis of two phase I studies. *J Clin Oncol*. 2023;41(Suppl.16):Abstr.3586. DOI: 10.1200/JCO.2023.41.16_suppl.3586.
57. ClinicalTrials.gov. A Study to Test Different Doses of BI 1823911 Alone and Combined With Other Medicines in People With Different Types of Advanced Cancer With KRAS Mutation. ClinicalTrials.Gov Identifier: NCT04973163. Available at: https://clinicaltrials.gov/study/NCT04973163 (accessed: 22 November 2024).
58. Wang J, Martin-Romano P, Cassier P, et al. Phase I study of JNJ-74699157 in patients with advanced solid tumors harboring the KRAS G12C mutation. *Oncologist*. 2022;27:536–e553. DOI: 10.1093/oncolo/oyab080.
59. ClinicalTrials.gov. Phase I Clinical Study of YL-15293 in Patients With Advanced Solid Tumor With KRAS Mutation. ClinicalTrials.gov identifier: NCT05173805. Available at: www.clinicaltrials.gov/study/NCT05173805 (accessed: 22 November 2024).
60. ClinicalTrials.gov. A Phase 1, Open-label Study of BPI-421286 in Subjects With Advanced Solid Tumors. ClinicalTrials.gov identifier: NCT05315180. Available at: www.clinicaltrials.gov/study/NCT05315180 (accessed: 22 November 2024).
61. ClinicalTrials.gov. GH35 Tablets for Advanced Solid Tumors: A Study on Safety and Early Results. ClinicalTrials.gov identifier: NCT05010694. Available at: https://clinicaltrials.gov/study/NCT05010694 (accessed: 22 November 2024).
62. Zhang Y, Zhou L, Gong Y, et al. Phase 1 study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of GEC255, a novel KRAS ^{g12c} inhibitor, in advanced solid tumors. *J Clin Oncol*. 2023;41(Suppl.16):Abstr.9112. DOI: 10.1200/JCO.2023.41.16_suppl.9112.
63. ClinicalTrials.gov. A Study of MK-1084 in KRAS Mutant Advanced Solid Tumors (MK-1084-001). ClinicalTrials.gov identifier: NCT05067283. Available at: https://clinicaltrials.gov/study/NCT05067283 (accessed: 22 November 2024).
64. Cho BC, Lu S, Lee MA, et al. Abstract CT117: A phase 1 study of D3S-001, A second-generation GDP-bound KRAS G12C inhibitor, as monotherapy in patients with KRAS G12C-mutated solid tumors. *Cancer Res*. 2024;84(Suppl.7):Abstr.CT117. DOI: 10.1158/1538-7445.AM2024-CT117.
65. ClinicalTrials.gov. A Study of SY-5933 in Patients With Advanced Solid Tumors Harboring the KRAS p.G12C Mutation. ClinicalTrials.gov identifier: NCT06006793. Available at: https://clinicaltrials.gov/study/NCT06006793 (accessed: 22 November 2024).
66. ClinicalTrials.gov. A Dose Escalation Study of HBI-2438 in Patients With Solid Tumors Harboring KRAS G12C Mutation. ClinicalTrials.gov identifier: NCT05485974. Available at: https://clinicaltrials.gov/study/NCT05485974 (accessed: 1 August 2022).
67. Desai J, Alonso G, Kim SH, et al. Divarasib plus cetuximab in KRAS G12C-positive colorectal cancer: A phase 1b trial. *Nat Med*. 2024;30:271–8. DOI: 10.1038/s41591-023-02696-8.
68. ClinicalTrials.gov. A Study to Evaluate the Safety, Pharmacokinetics, and Activity of GDC-6036 Alone or in Combination in Participants With Advanced or Metastatic Solid Tumors With A KRAS G12C Mutation. ClinicalTrials.gov identifier: NCT04449874. Available at: https://clinicaltrials.gov/study/NCT04449874 (accessed: 22 November 2024).
69. ClinicalTrials.gov. A Study Evaluating the Safety and Efficacy of Targeted Therapies in Subpopulations of Patients With Metastatic Colorectal Cancer (INTRINSIC). ClinicalTrials.gov identifier: NCT04929223. Available at: https://clinicaltrials.gov/study/NCT04929223 (accessed: 22 November 2024).
70. Shi Z, Weng J, Fan X, et al. Abstract 932: Discovery of D-1553, a novel and selective KRAS-G12C inhibitor with potent anti-tumor activity in a broad spectrum of tumor cell lines and xenograft models. *Cancer Res*. 2021;81(Suppl.13):Abstr.932. DOI: 10.1158/1538-7445.AM2021-932.
71. Shi Z, Weng J, Fan X, et al. Abstract 1056: potent in vivo anti-tumor activity of D-1553 as a single agent and in combination with targeted therapeutics in a broad spectrum of patient-derived xenograft tumor models with KRAS G12C mutation. *Cancer Res*. 2021;81(Suppl.13):Abstr.1056. DOI: 10.1158/1538-7445.AM2021-1056.
72. Xu R-H, Xu Y, Yan D, et al. 550O Safety and efficacy of D-1553 in combination with cetuximab in KRAS G12C mutated colorectal cancer (CRC): A phase II study. *Ann Oncol*. 2023;34(Suppl.2):S410–1. DOI: 10.1016/j.annonc.2023.09.1741.
73. Kondo S, Yan D, Ganju V, et al. 1622P D-1553 in patients with KRAS G12C mutated advanced pancreatic cancer (PCA). *Ann Oncol*. 2023;34(Suppl.2):S898–9. DOI: 10.1016/j.annonc.2023.09.2571.
74. Wang J, Zhao J, Zhong J, et al. 653O Glecirasib (KRAS G12C inhibitor) in combination with JAB-3312 (SHP2 inhibitor) in patients with KRAS p.G12C mutated solid tumors. *Ann Oncol*. 2023;34(Suppl.2):S459. DOI: 10.1016/j.annonc.2023.09.1839.
75. Falchook G, Li BT, Marrone KA, et al. OA03.03 Sotorasib in combination with RMC-4630, a SHP2 inhibitor, in KRAS p.G12C-mutated NSCLC and other solid tumors. *J Thorac Oncol*. 2022;17(Suppl.):S8. DOI: 10.1016/j.jtho.2022.07.022.
76. Yaeger R, Mezzadra R, Sinopoli J, et al. Molecular characterization of acquired resistance to KRASG12C-EGFR inhibition in colorectal cancer. *Cancer Discov*. 2023;13:41–55. DOI: 10.1158/2159-8290.CD-22-0405.
77. ClinicalTrials.gov. Adagrasib in Combination With Nab-Sirolimus in Patients With Advanced Solid Tumors and Non-Small Cell Lung Cancer With a KRAS G12C Mutation (KRYSTAL-19). ClinicalTrials.gov identifier: NCT05840510. Available at: https://clinicaltrials.gov/study/NCT05840510 (accessed: 22 November 2024).
78. Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature*. 2019;575:217–23. DOI: 10.1038/s41586-019-1694-1.
79. Ramalingam S, Fakih M, Strickler J, et al. Abstract P05-01: A phase 1b study evaluating the safety and efficacy of sotorasib: A KRASG12C inhibitor, in combination with trametinib, a MEK inhibitor, in *KRAS* p.G12C-mutated solid tumors. *Mol Cancer Ther*. 2021;20(Suppl.12):P05–01. DOI: 10.1158/1535-7163.TARG-21-P05-01.
80. Zdanov S, Mandapathil M, Abu Eid R, et al. Mutant *KRAS* conversion of conventional T cells into regulatory T cells. *Cancer Immunol Res*. 2016;4:354–65. DOI: 10.1158/2326-6066.CIR-15-0241.
81. Hamarsheh S, Groß O, Brummer T, Zeiser R. Immune modulatory effects of oncogenic KRAS in cancer. *Nat Commun*. 2020;11:5439. DOI: 10.1038/s41467-020-19288-6.
82. Liou G-Y, Döppler H, Necela B, et al. Mutant *KRAS*-induced expression of ICAM-1 in pancreatic acinar cells causes attraction of macrophages to expedite the formation of precancerous lesions. *Cancer Discov*. 2015;5:52–63. DOI: 10.1158/2159-8290.CD-14-0474.
83. Baud V, Karin M. Is NF-kappab a good target for cancer therapy? Hopes and pitfalls. *Nat Rev Drug Discov*. 2009;8:33–40. DOI: 10.1038/nrd2781.
84. Salgia R, Pharaon R, Mambetsariev I, et al. The improbable targeted therapy: *KRAS* as an emerging target in non-small cell lung cancer (NSCLC). *Cell Rep Med*. 2021;2:100186. DOI: 10.1016/j.xcrm.2020.100186.
85. Ghimessy A, Radeczky P, Laszlo V, et al. Current therapy of KRAS-mutant lung cancer. *Cancer Metastasis Rev*. 2020;39:1159–77. DOI: 10.1007/s10555-020-09903-9.
86. Li BT, Falchook GS, Durm GA, et al. OA03.06 CodeBreaK 100/101: First report of safety/efficacy of sotorasib in combination with pembrolizumab or atezolizumab in advanced KRAS p.g12c NSCLC. *J Thorac Oncol*. 2022;17(Suppl.):S10–1. DOI: 10.1016/j.jtho.2022.07.025.
87. ClinicalTrials.gov. Phase 2 Trial of Adagrasib Monotherapy and in Combination With Pembrolizumab and a Phase 3 Trial of Adagrasib in Combination in Patients With a KRAS G12C Mutation KRYSTAL-7. ClinicalTrials.gov identifier: NCT04613596. Available at: https://clinicaltrials.gov/study/NCT04613596 (accessed: 22 November 2024).
88. ClinicalTrials.gov. Phase I Trial of Adagrasib (MRTX849) in Combination With Cetuximab and Irinotecan in Patients With Colorectal Cancer. ClinicalTrials.gov identifier: NCT05722327.

Available at: https://clinicaltrials.gov/study/NCT05722327 (accessed: 22 November 2024).
89. ClinicalTrials.gov. Phase 3 Study of MRTX849 With Cetuximab vs Chemotherapy in Patients With Advanced Colorectal Cancer With KRAS G12C Mutation (KRYSTAL-10). ClinicalTrials.gov identifier: NCT04793958. Available at: https://clinicaltrials.gov/study/NCT04793958 (accessed: 22 November 2024).
90. ClinicalTrials.gov. Adagrasib in Combination With TNO155 in Patients With Cancer (KRYSTAL 2). ClinicalTrials.gov identifier: NCT04330664. Available at: https://clinicaltrials.gov/study/NCT04330664 (accessed: 22 November 2024).
91. ClinicalTrials.gov. Adagrasib in Combination With BI 1701963 in Patients With Cancer (KRYSTAL 14). ClinicalTrials.gov identifier: NCT04975256. Available at: https://clinicaltrials.gov/study/NCT04975256 (accessed: 22 November 2024).
92. ClinicalTrials.gov. A Phase 1/2 Study of MRTX0902 in Solid Tumors With Mutations in the KRAS MAPK Pathway. ClinicalTrials.gov identifier: NCT05578092. Available at: https://clinicaltrials.gov/study/NCT05578092 (accessed: 2 December 2022).
93. ClinicalTrials.gov. A Phase I Study of Adagrasib and Durvalumab for Treatment of Advanced Non-Small Cell Lung Cancers and Gastro-Intestinal Cancers Harboring KRAS G12C Mutations. ClinicalTrials.gov identifier: NCT05848843. Available at: https://clinicaltrials.gov/study/NCT05848843 (accessed: 25 April 2023).
94. ClinicalTrials.gov. A Study of INCB099280 in Combination With Adagrasib in Adults With Advanced Solid Tumors Harboring A KRASG12C Mutation. ClinicalTrials.gov identifier: NCT06039384. Available at: https://clinicaltrials.gov/study/NCT06039384 (accessed: 22 November 2024).
95. Yaeger R, Langer CJ, Ruffinelli JC, et al. A phase 1b study of sotorasib combined with panitumumab as second-line treatment of *kras* G12C - mutated colorectal cancer. *J Clin Oncol*. 2024;42:128–128. DOI: 10.1200/JCO.2024.42.3_suppl.128.
96. Hong DS, Kuboki Y, Strickler JH, 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*. 2023;41:3513–3513. DOI: 10.1200/JCO.2023.41.16_suppl.3513.
97. Pietrantonio F, Salvatore L, Esaki T, et al. LBA10 sotorasib plus panitumumab versus standard-of-care for chemorefractory KRAS G12C-mutated metastatic colorectal cancer (mcrc): codebreak 300 phase III study. *Ann Oncol*. 2023;34:S1266. DOI: 10.1016/j.annonc.2023.10.016.
98. ClinicalTrials.gov. Sotorasib Activity in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation (CodeBreak 101). ClinicalTrials.gov identifier: NCT04185883. Available at: https://clinicaltrials.gov/study/NCT04185883 (accessed: 22 November 2024).
99. ClinicalTrials.gov. SHP2 Inhibitor BBP-398 in Combination With Sotorasib in Patients With Advanced Solid Tumors and a KRAS-G12C Mutation (Argonaut). ClinicalTrials.gov identifier: NCT05480865. Available at: www.clinicaltrials.gov/study/NCT05480865 (accessed: 22 November 2024).
100. Kondo S, Yan D, Ganju V, et al. D-1553 (Garsorasib) in Patients with KRAS G12C mutated Advanced Pancreatic Cancer (PCa). Available at: www.cabrini.com.au/app/uploads/29.-Gary-Richardson-D-1553-in-patients-with-KRAS-G12C-mutated-advanced-pancreatic-cancer.pdf (accessed: 22 November 2024).
101. Li J, Shen L, Gu Y, et al. Preliminary activity and safety results of KRAS G12C inhibitor glecirasib (JAB-21822) in patients with pancreatic cancer and other solid tumors. *J Clin Oncol*. 2024;42:604–604. DOI: 10.1200/JCO.2024.42.3_suppl.604.
102. Jacobio. Jacobio Announces China CDE Clearance for Phase III Clinical Trial of KRAS G12C Inhibitor Glecirasib in Patients with Colorectal Cancer. 2024. Available at: www.jacobiopharma.com/en/news/Jacobio_Announces_China_CDE_Clearance_for_Phase_III_Clinical_Trial_of_KRAS_G12C_Inhibitor_Glecirasib_in_Patients_with_Colorectal_Cancer (accessed: 22 November 2024).
103. ClinicalTrials.gov. A Study of JAB-21822 in Patients With KRAS p.G12C Mutated Pancreatic Cancer. ClinicalTrials.gov: NCT06008288. Available at: https://clinicaltrials.gov/study/NCT06008288 (accessed: 22 November 2024).
104. ClinicalTrials.gov. Study of JDQ443 in Patients With Advanced Solid Tumors Harboring the KRAS G12C Mutation (KontRASt-01). ClinicalTrials.gov identifier: NCT04699188. Available at: https://clinicaltrials.gov/study/NCT04699188 (accessed: 22 November 2024).
105. ClinicalTrials.gov. Platform Study of JDQ443 in Combinations in Patients With Advanced Solid Tumors Harboring the KRAS G12C Mutation (KontRASt-03). ClinicalTrials.gov identifier: NCT05358249. Available at: https://clinicaltrials.gov/study/NCT05358249 (accessed: 22 November 2024).
106. Maciag AE, Stice J, Wang B, et al. Abstract ND07: BBO-8520, a first-in-class, direct inhibitor of KRASG12C (ON), locks GTP-bound KRASG12C in the state 1 conformation resulting in rapid and complete blockade of effector binding. *Cancer Res*. 2024;84:D07–ND07. DOI: 10.1158/1538-7445.AM2024-ND07.
107. Jänne PA, Bigot F, Papadopoulos K, et al. Abstract PR014: preliminary safety and anti-tumor activity of RMC-6291, a first-in-class, tri-complex KRASG12C(ON) inhibitor, in patients with or without prior KRASG12C(OFF) inhibitor treatment. *Mol Cancer Ther*. 2023;22:R014–PR014. DOI: 10.1158/1535-7163.TARG-23-PR014.