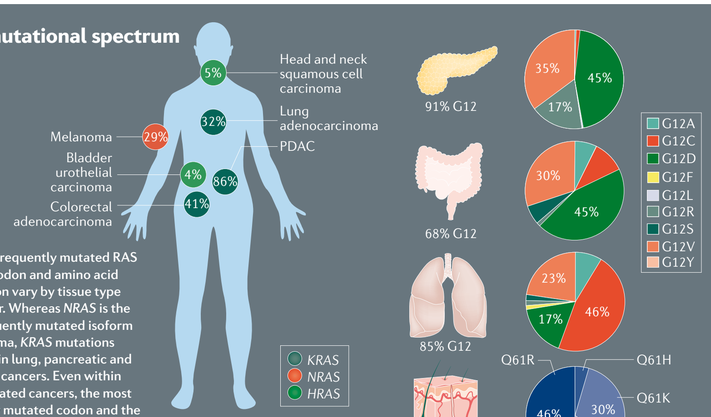
nature reviews
drug discovery

RAS-targeted therapies

Amanda R. Moore, Scott C. Rosenberg, Frank McCormick & Shiva Malek

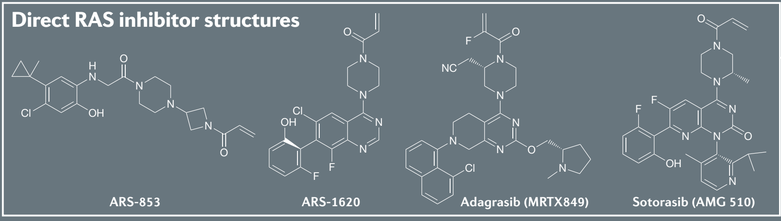
The RAS (*KRAS*, *NRAS* and *HRAS*) family is the most frequently mutated gene family in cancers, and, consequently, investigators have sought an effective RAS inhibitor for more than three decades. Now, allele-specific covalent inhibitors against the most frequently mutated version of RAS in NSCLC, KRAS-G12C, are in late-stage clinical trials, and other strategies to inhibit this pathway are being investigated. Such strategies include inhibition of SOS1 and SHP2, which promote RAS activation, and inhibition of pathways downstream of RAS. Many of these potential therapies are being tried in combinations with RAS inhibitors. Mutation-specific biochemical properties, the spectrum of co-mutations, and the tissue of origin are likely to affect the effectiveness of such treatments.

RAS mutational spectrum



The most frequently mutated RAS isoform, codon and amino acid substitution vary by tissue type and cancer. Whereas *NRAS* is the most frequently mutated isoform in melanoma, *KRAS* mutations dominate in lung, pancreatic and colorectal cancers. Even within *KRAS*-mutated cancers, the most frequently mutated codon and the distributions of amino acid substitutions at those mutated codons (12 or 61) are different for each tissue type, as shown in pie charts beside the relevant organ. Data from TCGA and AACR Project GENIE.

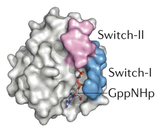
Direct RAS inhibitor structures



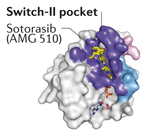
ARS-853 | ARS-1620 | Adagrasib (MRTX849) | Sotorasib (AMG 510)

Regions of RAS that could or are being targeted by therapeutics

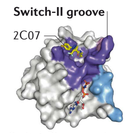
Regions targeted by clinical compounds



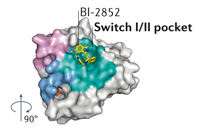
HRAS bound to GppNHp, a non-hydrolysable nucleotide, as a reference for orientation (PDB: 5P21).



Switch-II pocket (purple) of KRAS-G12C bound to sotorasib (AMG 510), a covalent RAS inhibitor (PDB: 6OIM; compound identifier: MOV).



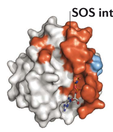
Switch-II groove (purple) bound to 2C07, the first covalent RAS inhibitor (PDB: 5VBZ; compound identifier: 92V).

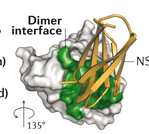


Switch I/II pocket of KRAS-G12D (teal) bound to BI-2852, which disrupts the RAS–SOS1 interaction (PDB: 6GJ8).

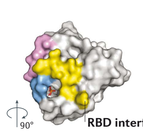
Other potentially targetable regions

SOS binding interface (red) of HRAS (PDB: 1BKD).





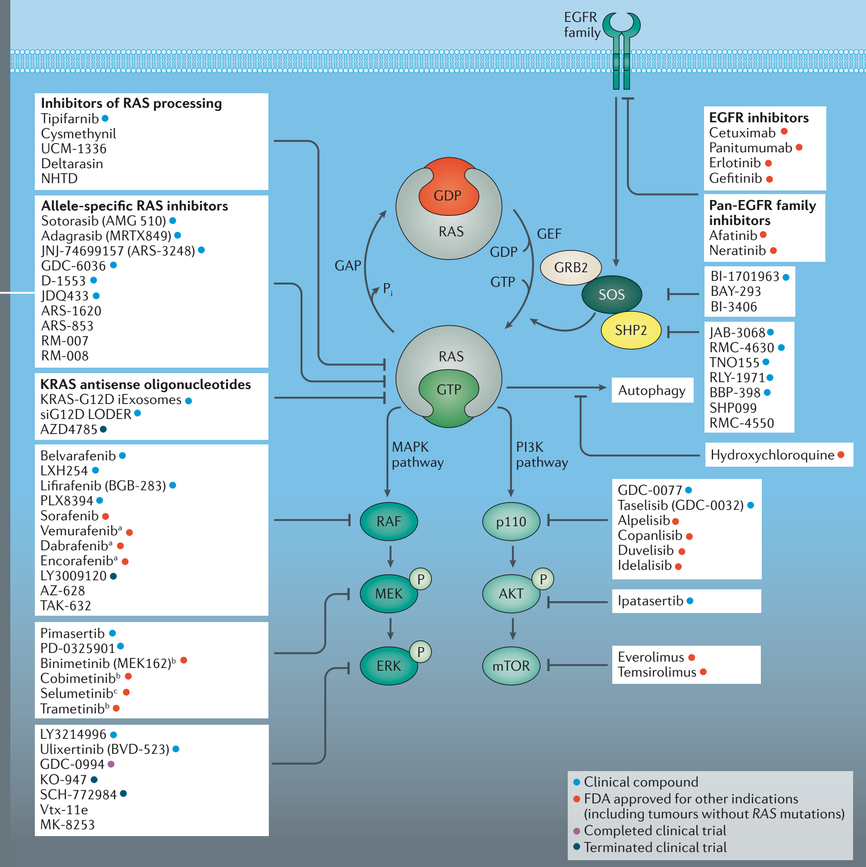
Proposed HRAS dimerization interface (green) bound by NS1 monobody (gold) (PDB: 5E95).



RAF–RAS–RBD binding interface (yellow) of HRAS (PDB: 4G0N).

Clinical development of potential therapies for RAS-mutant tumours

Activation of receptor tyrosine kinases, such as members of the EGFR family, leads to a cascade of events at the membrane inner leaflet culminating in the activation of RAS. Inhibition at various levels — such as EGFR, SOS or SHP2 — decreases the rate at which inactive KRAS–GDP becomes active KRAS–GTP and reduces the GTP-bound RAS population. Mutant RAS proteins accumulate in the GTP-bound state. A number of approaches have been developed to directly inhibit RAS, including covalent allele-specific inhibitors that bind to KRAS-G12C. GTP-bound RAS activates downstream signalling by binding to the RAS-binding domain of effector proteins, such as RAF and p110, to activate the MAPK and PI3K signalling cascades, respectively. Both the MAPK and PI3K signalling cascades can be inhibited at each kinase tier. Data compiled from ClinicalTrials.gov and AccessData.FDA.gov. [a]Only effective against monomeric BRAF (BRAF-V600E/K). [b]Approved for the treatment of BRAF-mutant melanoma. [c]Approved for the treatment of paediatric patients with *NF1* mutations.



Select single-agent inhibitors in clinical development for RAS-mutant tumours

Drug	Biomarker	Disease setting	Study phase	Clinical trial number
KRAS-G12C inhibitors				
Sotorasib (AMG 510)	$KRAS^{G12C}$ mutation	NSCLC	III	NCT04303780
Adagrasib (MRTX849)	$KRAS^{G12C}$ mutation	NSCLC	III	NCT04685135
JNJ-74699157 (ARS-3248)	$KRAS^{G12C}$ mutation	Advanced solid tumours	I	NCT04006301
GDC-6036	$KRAS^{G12C}$ mutation	Advanced solid tumours	I	NCT04449874
D-1553	$KRAS^{G12C}$ mutation	NSCLC, CRC	I	NCT04585035
JDQ433	$KRAS^{G12C}$ mutation	Advanced solid tumours	I/II	NCT04699188
SOS inhibitors				
BI-1701963	*KRAS* mutations	Advanced or metastatic solid tumours	I	NCT04111458
SHP2 inhibitors				
RMC-4630	Mutations that hyperactivate the MAPK pathway	Relapsed or refractory solid tumours	I	NCT03634982
TNO155	*EGFR* or $KRAS^{G12C}$ mutations	Advanced solid tumours	I	NCT03114319
BBP-398	Mutations that hyperactivate the MAPK pathway	Advanced solid tumours	I	NCT04528836
Farnesyltransferase inhibitors				
Tipifarnib	*HRAS* mutations	HNSCC, NSCLC	II	NCT02383927, NCT03496766
RAF inhibitors				
Belvarafenib	*NRAS* mutations	Advanced melanoma	I	NCT04835805
LXH254	MAPK pathway mutation	Advanced solid tumours	I	NCT02607813
MEK inhibitors				
Binimetinib (MEK162)	*NRAS* mutation	Unresectable or metastatic melanoma	III	NCT01763164
ERK inhibitors				
LY3214996	*BRAF* or *NRAS* mutations	Metastatic melanoma and NSCLC	I	NCT02857270
Adoptive cell therapies				
Anti-RAS-G12D mTCR	HLA-A*11:01 RAS^{G12D} mutation	Advanced solid tumours	I/II	NCT03745326
Anti-RAS-G12V mTCR	HLA-A*11:01 RAS^{G12V} mutation	Advanced solid tumours	I/II	NCT03190941
Anti-RAS-G12V TCR	HLA-A*11:01 RAS^{G12V} mutation	Advanced solid tumours	I/II	NCT04146298
siRNA strategies				
KRAS-G12D iExosomes	$KRAS^{G12D}$ mutation	PDAC	I	NCT03608631
Cancer vaccines				
mRNA-5671	HLA-A*11:01 and/or HLA-C*08:02; $KRAS^{G12C}$, $KRAS^{G12D}$, $KRAS^{G12V}$ or $KRAS^{G13D}$ mutations	NSCLC, non-MSI-H CRC, PDAC	I	NCT03948763

Select combination therapies in clinical development for RAS-mutant cancers

Drugs	Biomarker	Disease setting	Study phase	Clinical trial number
KRAS-G12C combinations				
Sotorasib and antibodies to PD1 or PDL1	$KRAS^{G12C}$ mutation	Advanced NSCLC	II	NCT03600883
Adagrasib and TNO155	$KRAS^{G12C}$ mutation	Advanced or metastatic solid tumours	I/II	NCT04330664
JDQ433 and TNO155	$KRAS^{G12C}$ mutation	Advanced solid tumours	I/II	NCT04699188
GDC-6036 and atezolizumab, cetuximab, bevacizumab or erlotinib	$KRAS^{G12C}$ mutation	Advanced or metastatic solid tumours	I	NCT04449874
SOS inhibitor combinations				
BI-1701963 and trametinib	*KRAS* mutation	Advanced or metastatic solid tumours	I	NCT04111458
BI-1701963 and irinotecan	*KRAS* mutation	Metastatic CRC	I	NCT04627142
SHP2 inhibitor combinations				
TNO155 and spartalizumab	*EGFR* or *ALK* WT NSCLC	Advanced solid tumours	Ib	NCT04000529
TNO155 and ribociclib	*EGFR* or *ALK* WT NCSLC, *KRAS*-mutant CRC or NSCLC	Advanced solid tumours	Ib	NCT04000529
RAF inhibitor combinations				
Belvarafenib and cobimetinib	*RAS* or *RAF* mutations	Locally advanced or metastatic tumours	Ib	NCT03284502
LXH254 and an antibody to PD1	*NRAS* (melanoma) or *KRAS* (NSCLC) mutations	Advanced solid tumours	I	NCT02607813
LXH254 and trametinib, LTT462 or ribociclib	*KRAS* or *BRAF* (NSCLC) or *NRAS* (melanoma) mutations	Advanced or metastatic solid tumours	Ib	NCT02974725
BGB-283 and PD-0325901	*KRAS*-mutant NSCLC or endometrial cancer	Advanced or refractory solid tumours	Ib	NCT03905148
MEK inhibitor combinations				
Cobimetinib and atezolizumab	*KRAS* mutation	Advanced and metastatic NSCLC	II	NCT03600701
Cobimetinib and RMC-4630	Mutations that hyperactivate the MAPK pathway	Relapsed or refractory solid tumours	Ib/II	NCT03989115
Selumetinib and MK-8353	*RAS* or *RAF* mutations	Advanced solid tumours	Ib	NCT03745989
Trametinib and ponatinib	*KRAS* mutation	Advanced NSCLC	I	NCT03704688
ERK inhibitor combinations				
LY3214996 and midazolam, abemaciclib, or nab-paclitaxel + gemcitabine	*BRAF* or *RAS* mutations	Advanced or metastatic solid tumours	I	NCT02857270
Cancer vaccine combinations				
mRNA-5671 and pembrolizumab	HLA-A*11:01 and/or HLA-C*08:02 $KRAS^{G12C}$, $KRAS^{G12D}$, $KRAS^{G12V}$ or $KRAS^{G13D}$ mutations	NSCLC, non-MSI-H CRC, PDAC	I	NCT03948763

Abbreviations

CRC, colorectal cancer; DCAI, 4,6-dichloro-2-methyl-3-aminoethyl-indole; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; MSI-H, microsatellite instability-high; mTCR, murine T cell receptor; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; NSCLC, non-small-cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; PDB, protein data bank; RBD, RAS-binding domain; SOS, Son of Sevenless; TCGA, the cancer genome atlas; WT, wild type.

References

1. Canon, J. et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature* **575**, 217–223 (2019).
2. Hallin, J. et al. The $KRAS^{G12C}$ inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients. *Cancer Discov.* **10**, 54–71 (2019)
3. Hong, D. S. et al. $KRAS^{G12C}$ Inhibition with sotorasib in advanced solid tumors. *N. Engl. J. Med.* **383**, 1207–1217 (2020).
4. Janes, M. R. et al. Targeting KRAS mutant cancers with a covalent G12C-specific inhibitor. *Cell* **172**, 578–589 (2018).
5. Moore, A. R., Rosenberg, S. C., McCormick, F. & Malek, S. RAS-targeted therapies: is the undruggable drugged? *Nat. Rev. Drug Discov.* **19**, 533–552 (2020).
6. Ostrem, J. M., Peters, U., Sos, M. L., Wells, J. A., & Shokat, K. M. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature* **503**, 548–551 (2013).
7. The AACR Project GENIE Consortium. AACR Project GENIE: Powering Precision Medicine through an International Consortium. *Cancer Discov.* **7**, 818–831 (2017).
8. Kessler, D. et al. Drugging an undruggable pocket on KRAS. *Proc. Natl Acad. Sci. U.S.A.* **116**, 15823–15829 (2019).

Affiliations

- Amanda R. Moore, Scott C. Rosenberg and Shiva Malek are at the Department of Discovery Oncology, Genentech Inc., South San Francisco, CA, USA.
- Frank McCormick is at Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA.

Competing interests statement

FMcC. is a consultant for the following companies: Amgen, Pfizer Inc., and Quanta Therapeutics; is a consultant and co-founder with ownership interest including stock options of BridgeBio Pharma, Inc; and is Scientific Director of the NCI Ras Initiative at Frederick National Laboratory for Cancer Research/Leidos Biomedical Research Inc. S.M. is an employee of Genentech/Roche. A.R.M. and S.C.R. are also post-doctoral fellows employed by Genentech/Roche.

The poster content is peer reviewed, editorially independent and the sole responsibility of Springer Nature Limited. Edited by Megan Cully; copyedited by George Booth; designed by Susanne Harris.

https://www.nature.com/articles/s41573-021-00220-6