Investigating KRAS^{G12C} inhibitors: How might they improve outcomes for patients with solid tumours?

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Investigating the role of *KRAS* mutations in solid tumours

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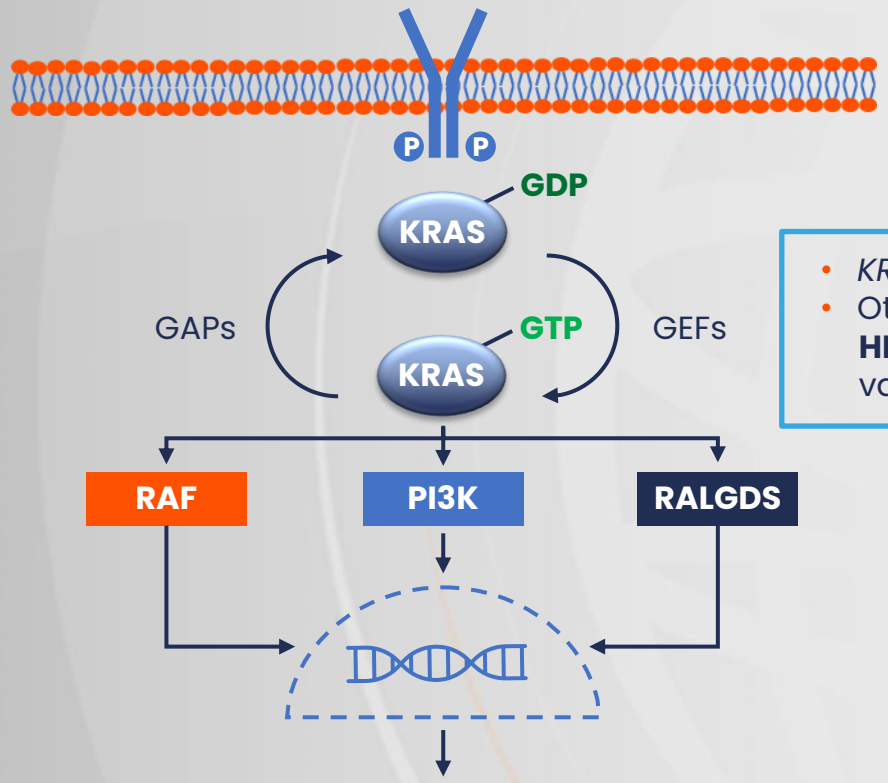
KRAS-mediated signalling

Kirsten RAt Sarcoma viral oncogene mechanism of action[1,2]



- *KRAS* is a proto-oncogene[3]
- Other RAS proteins include: **HRAS**, **NRAS**, and the splice variants **KRAS4A** and **KRAS4B**[4]

- Cell survival
- Cell-cycle progression
- Actin cytoskeletal organization
- Cell polarity and movement
- Vesicular and nuclear transport

GAP, GTPase activating proteins; GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GTP, guanosine triphosphate.
Figure adapted from: 1. Burns TF, et al. *J Clin Oncol*. 2020;38:4208–18; 2. Huang L, et al. *Signal Transduct Target Ther*. 2021;6:386.
3. Nagasaka M, et al. *Cancer Treat Rev*. 2021;101:102309; 4. Rásó E. *Cancer Metastasis Rev*. 2020;39:1039–49.

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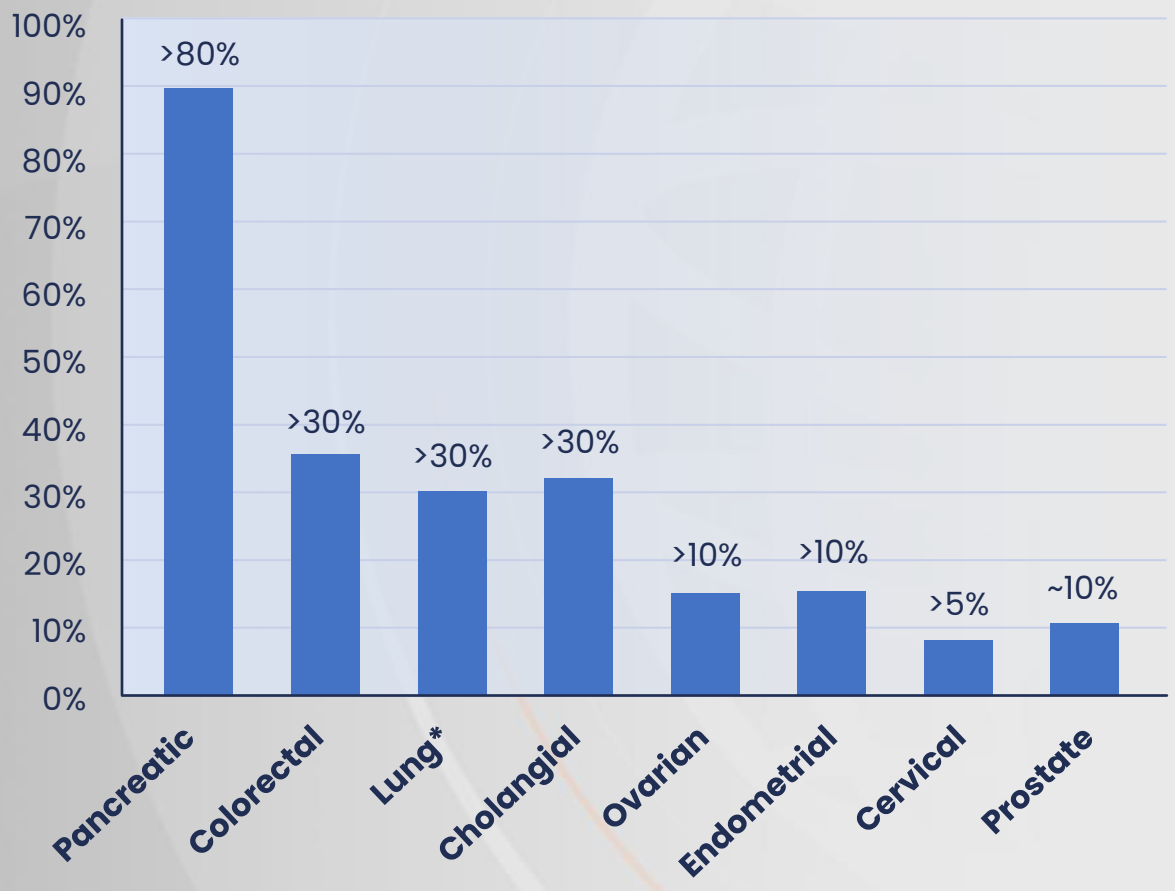
KRAS mutations in solid tumours

Mutation incidence in a range of solid tumours

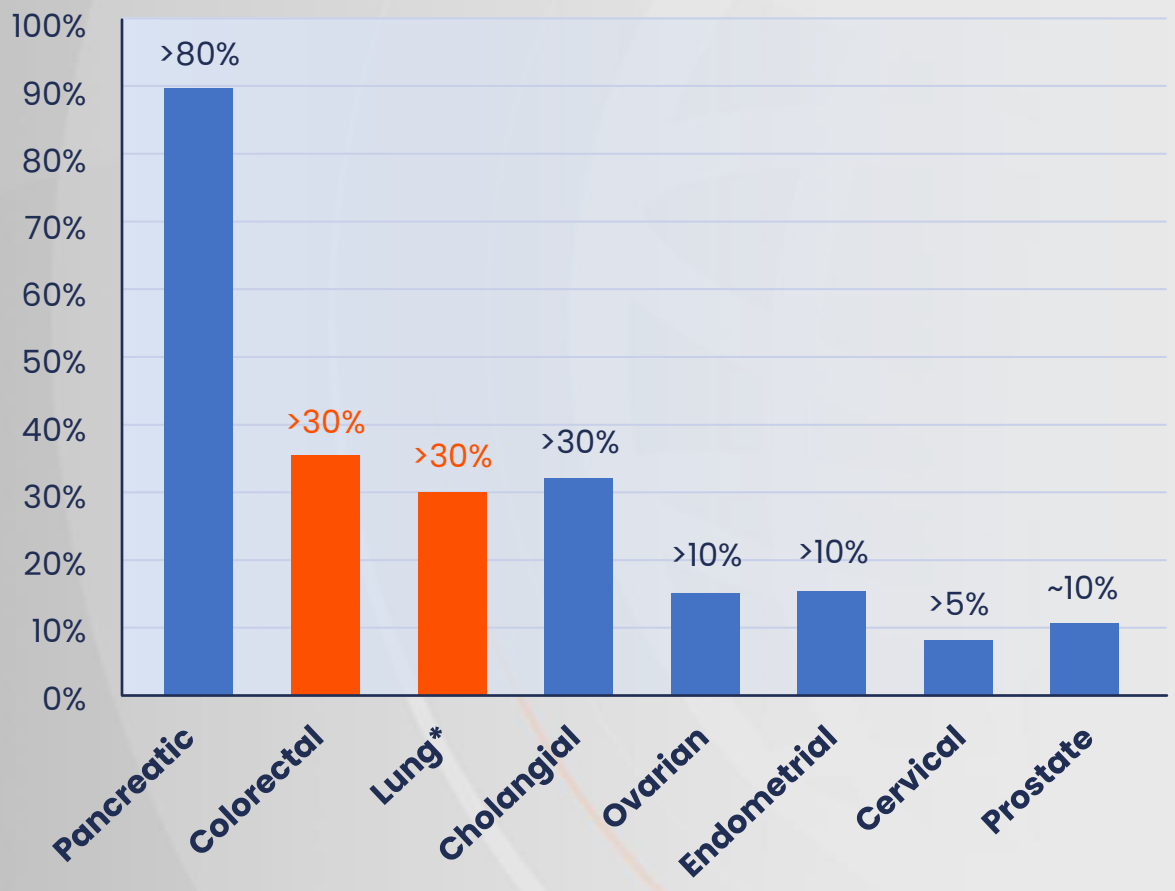


*Lung adenocarcinoma.

Timar J, Kashofer K. *Cancer Metastasis Rev*. 2020;39:1029–38.

KRAS mutations in solid tumours

Mutation incidence in a range of solid tumours

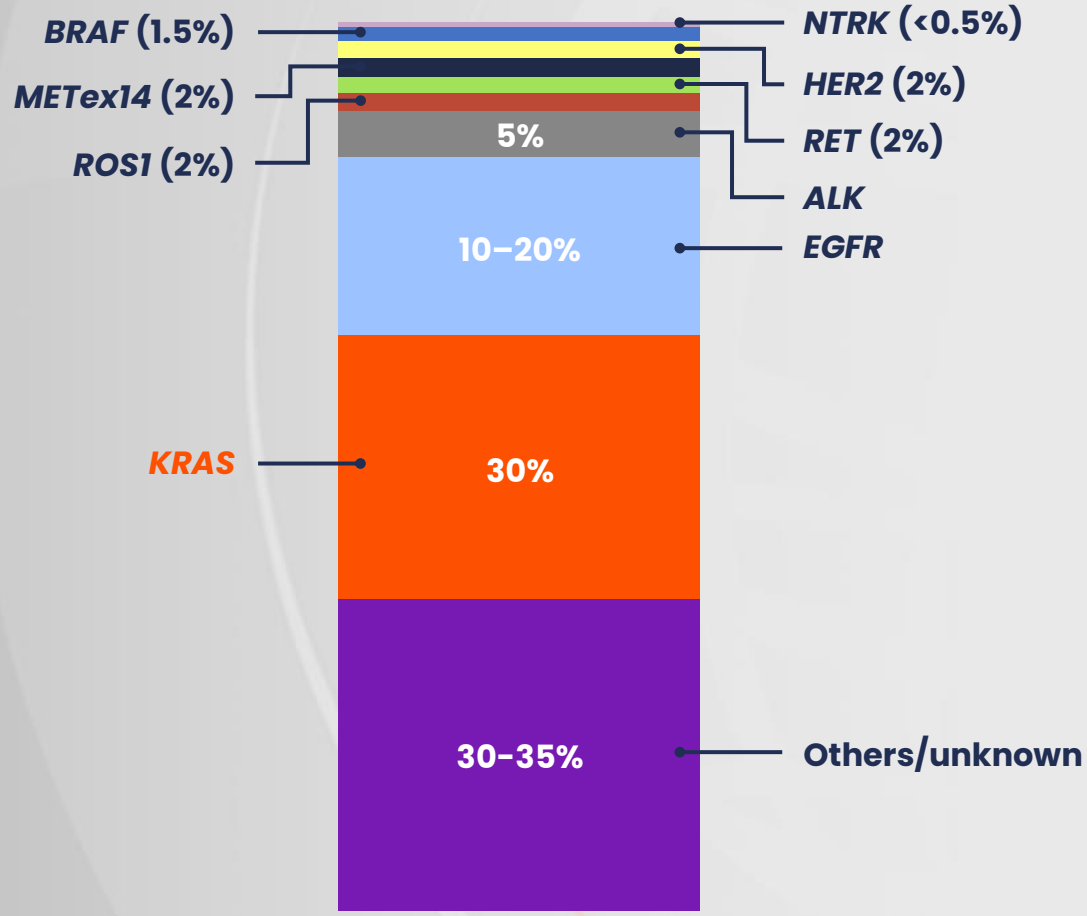


*Lung adenocarcinoma.

Timar J, Kashofer K. *Cancer Metastasis Rev*. 2020;39:1029–38.

Potential targetable mutations in lung carcinomas

Spectrum of actionable mutations in lung carcinomas globally



ex14, exon 14 skipping mutation.
Aleksakhina SN, Imyanitov EN. *Int J Mol Sci*. 2021;22:10931.

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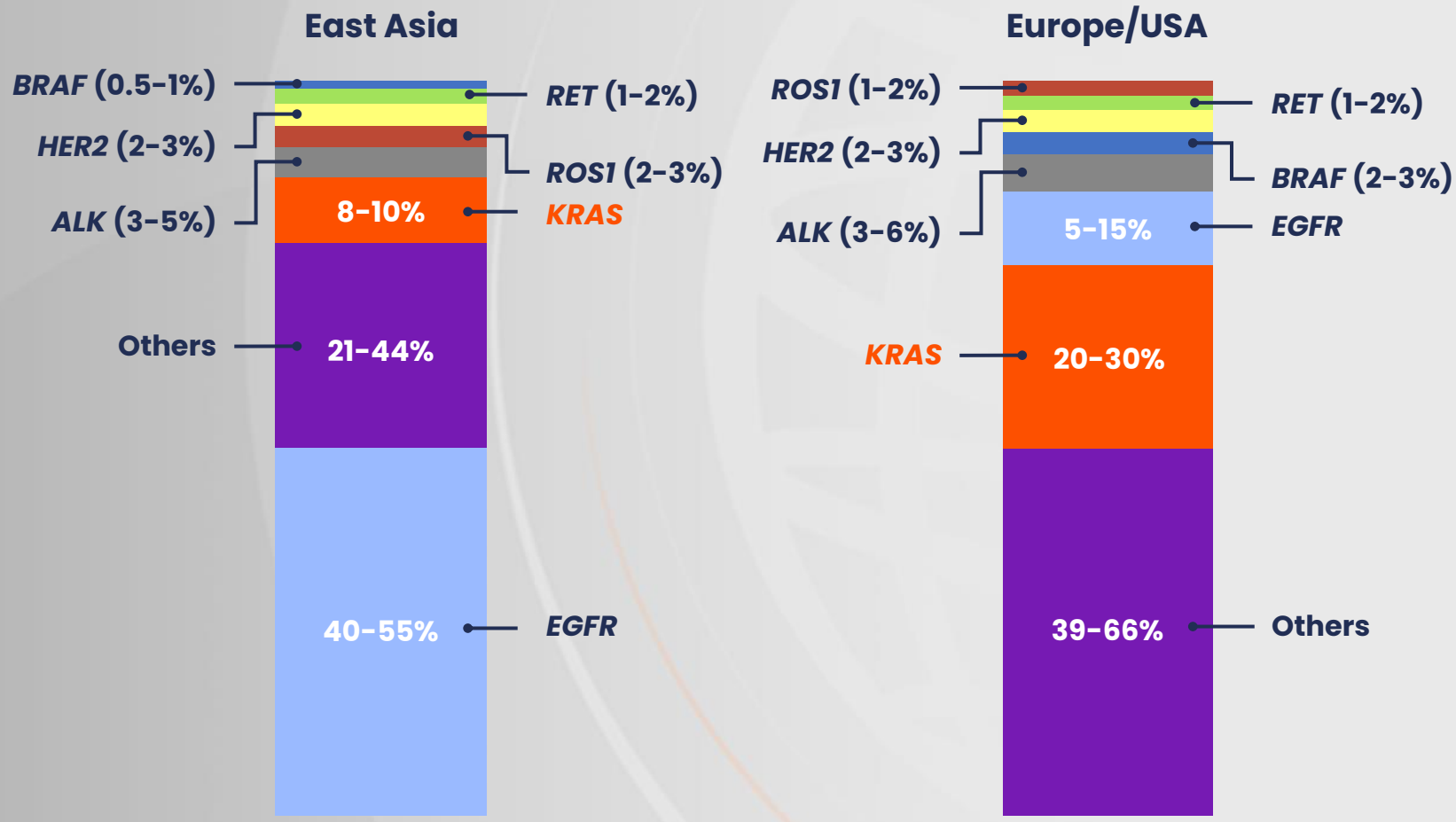
Potential targetable mutations in lung adenocarcinoma

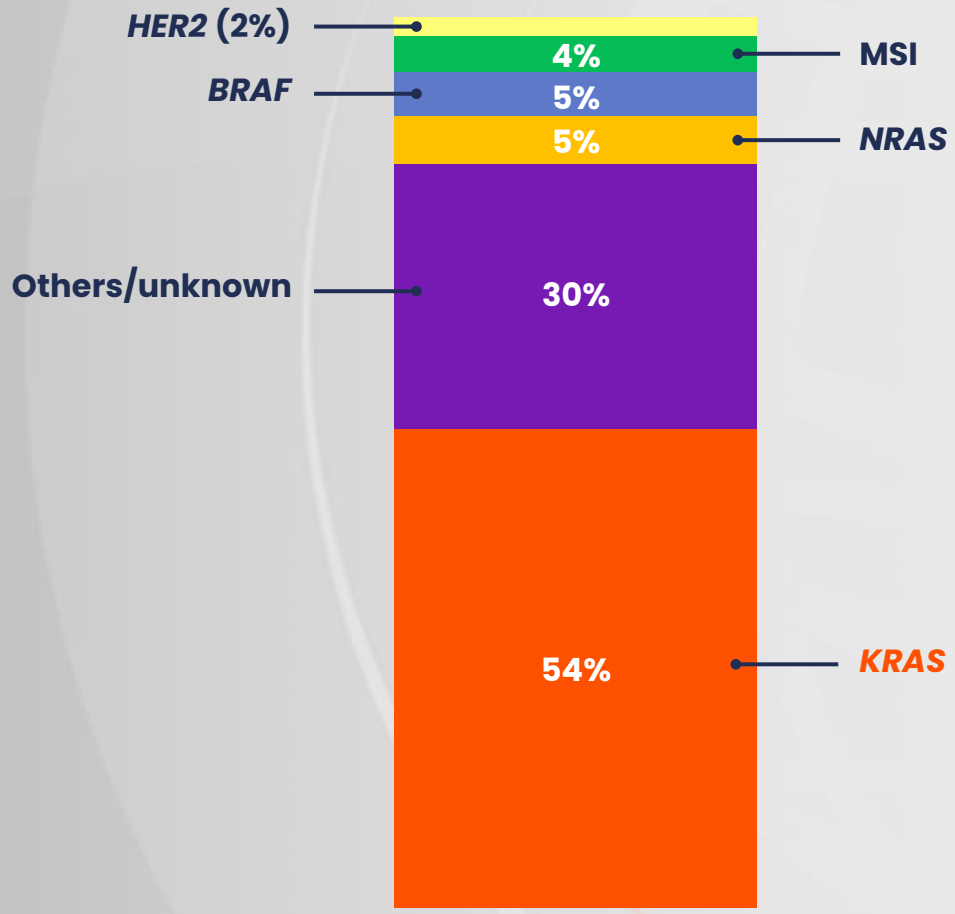
Spectrum of actionable mutations in East Asia and Western populations



Kohno T, et al. *Transl Lung Cancer Res.* 2015;4:156–64.

Potential targetable mutations in CRC

Spectrum of actionable mutations in CRC globally



CRC, colorectal cancer; MSI, microsatellite instability.
Aleksakhina SN, Imyanitov EN. *Int J Mol Sci*. 2021;22:10931.

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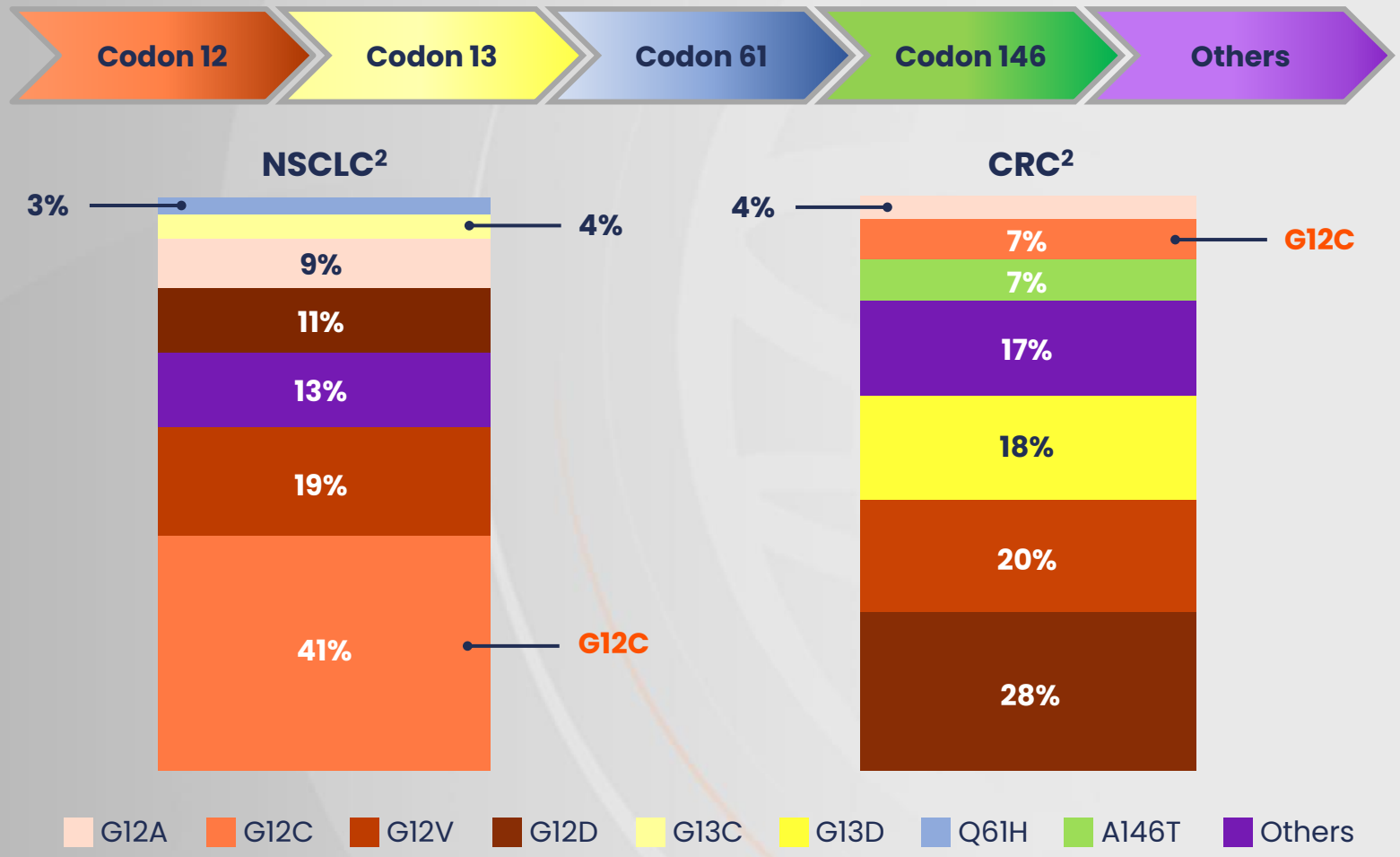
Activating *KRAS* mutations

KRAS 'hotspot' codons[1]



CRC, colorectal cancer; NSCLC, non-small cell lung cancer.

1. Cook JH, et al. *Nat Commun*. 2021;12:1808; 2. Huang L, et al. *Signal Transduct Target Ther*. 2021;6:386.

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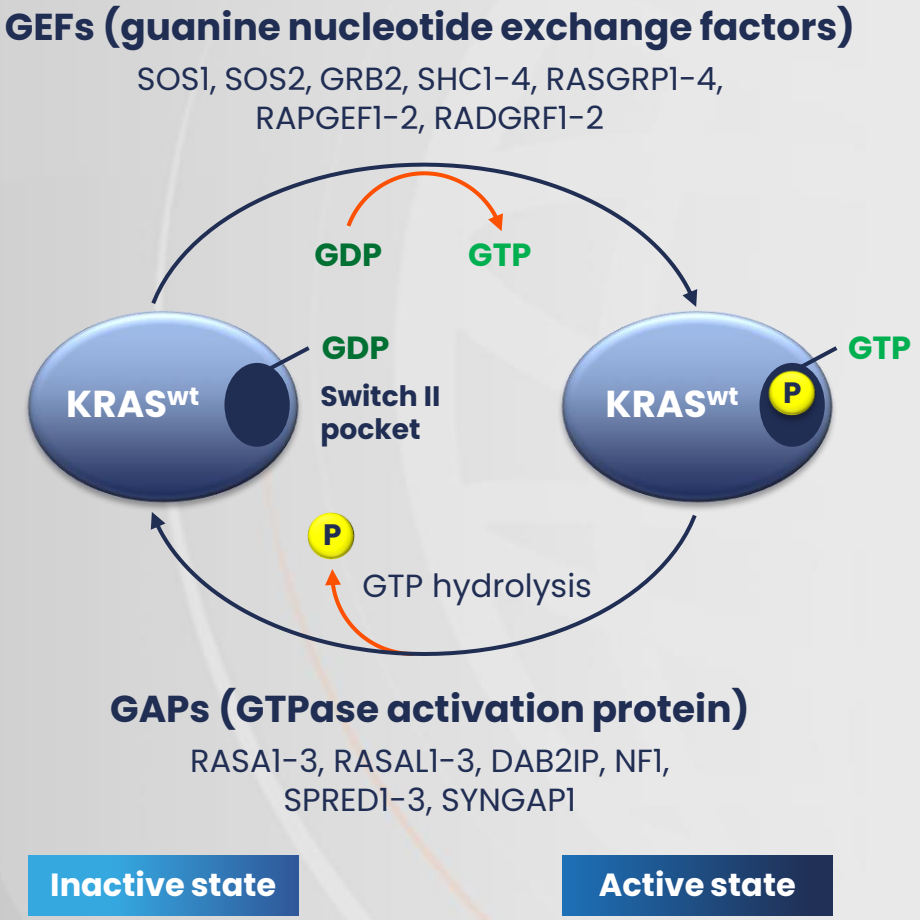
KRAS GTPase activity

GEFs and GAPs control KRAS activation and inactivation

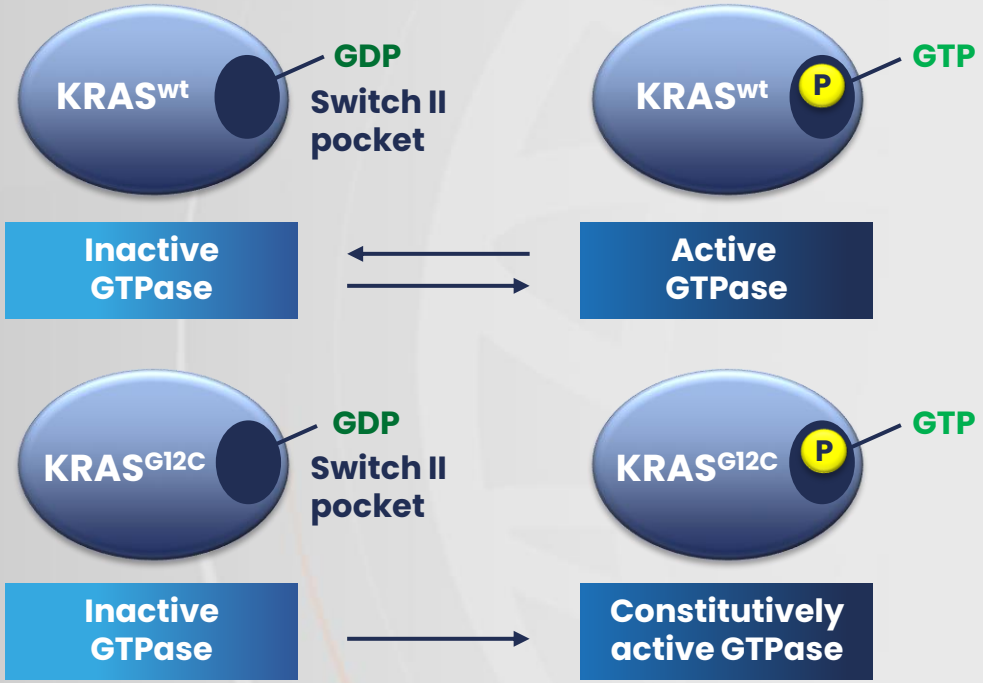


GAP, GTPase activation protein; GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GTP, guanosine triphosphate; wt, wild type.

1. Simanshu DK, et al. *Cell*. 2017;170:17–33; 2. Vetter IR, Wittinghofer V. *Science*. 2001;294:1299–304.

The *KRAS*^{G12C} mutation

Signal transduction through the KRAS^{G12C} protein



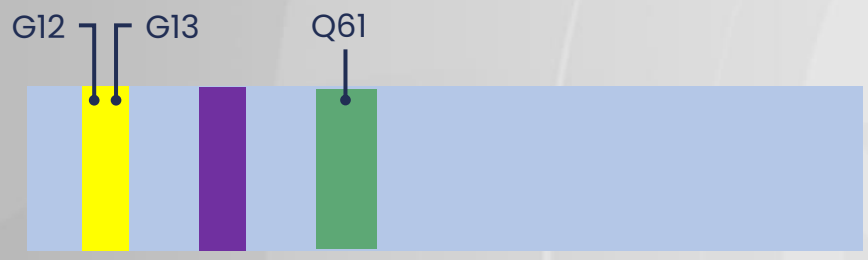
- Cysteine 12 (C12) mutation impairs intrinsic GTPase activity and locks KRAS in the GTP-bound state[1,2]
- Constitutive activation of KRAS^{G12C} enhances cell survival and proliferation and results in immune escape[2]

GDP, guanosine diphosphate; GTP, guanosine triphosphate; wt, wild type.

1. Liu J, et al. *Cancer Gene Ther*. 2021; doi: 10.1038/s41417-021-00383-9; 2. Huang L, et al. *Signal Transduct Target Ther*. 2021;6:386.

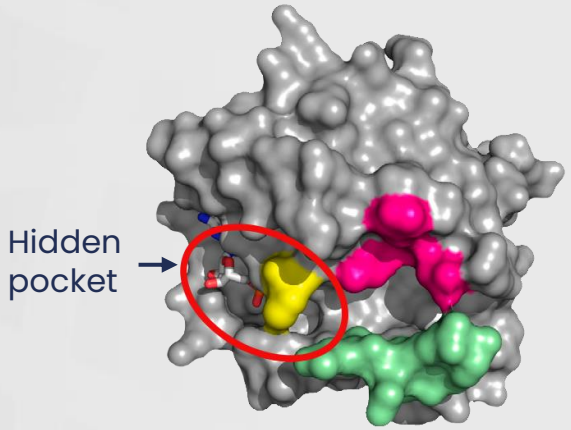
Not all *KRAS* mutations are the same

Key *KRAS* mutations at codons 12, 13 and 61 affect KRAS GTP binding[1]



- GTP binding
- Switch I: Effector/GAP interaction
- Switch II: GEF interaction

- Point mutations at codons 12, 13 or 61 in *KRAS*, *HRAS* or *NRAS* prevent GTP hydrolysis by inhibiting the arginine finger of GAPs from entering the GTPase site[2]



- Phosphate binding loop
- Switch II and helix 2
- Helix 3

- Covalent binding of small molecules prevents the conversion of mutant KRAS to its active state[3]

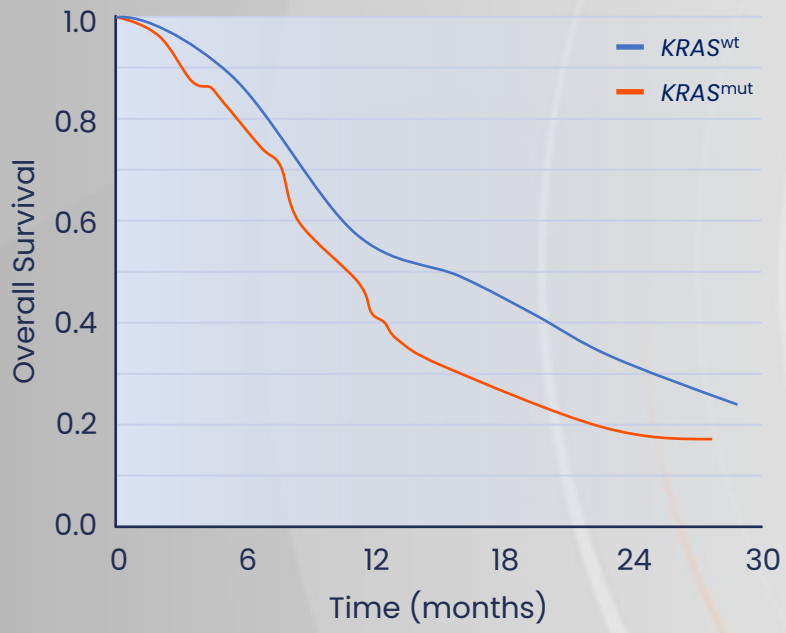
GAP, GTPase activation protein; GEF, guanine nucleotide exchange factor; GTP, guanosine triphosphate.

1. Wicki A, et al. *Swiss Med Wkly.* 2010;140:w13112; 2. Simanshu DK, et al. *Cell.* 2017;170:17–33; 3. Burns TF, et al. *J Clin Oncol.* 2020;38:4208–18.

KRAS mutations as a prognostic factor in NSCLC and CRC

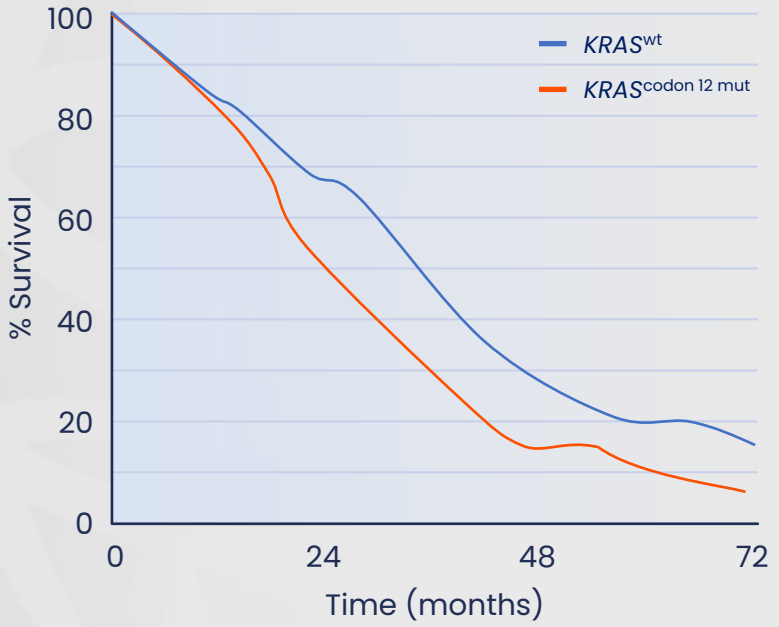
Prognostic effect of *KRAS* mutations relative to wt

Advanced NSCLC[1]
TAILOR Italian trial (NCT00637910)



- **Significantly worse OS** (unadjusted HR=1.41, p=0.03; adjusted HR=1.39, p=0.05)[1]

Advanced CRC[2]
UK study



- **Significantly worse OS** associated with *KRAS*^{G12C} and *KRAS*^{G12V} mutations vs *KRAS*^{wt} (p=0.01 and p=0.02)[2]

CRC, colorectal cancer; HR, hazard ratio; mut, mutant; NSCLC, non-small cell lung cancer; OS, overall survival; wt, wild type.
Data are approximate and adapted from: 1. Marabese M, et al. *Oncotarget*. 2015;6:34014–22; 2. Jones RP, et al. *Br J Cancer*. 2017;116:923–9.

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Predictive biomarker testing in advanced NSCLC

ESMO, JLCS and NCCN guideline recommendations

Molecular subtyping is necessary for therapeutic decision making[1–3]

Systematic testing of *EGFR* and *BRAF* mutations; analysis of *ALK*, *ROS1* and *NTRK* rearrangements; and determination of PD-L1 expression[1–3]

Testing for emerging biomarkers: *KRAS*, *MET*, *RET* and *ERBB2*/*HER2*[1]

ESMO, European Society of Medical Oncology; JLCS, Japanese Lung Cancer Society; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.

1. NCCN. NCCN Guidelines: Non-small cell lung cancer. Version 2.2022. Available at: www.nccn.org/guidelines/category_1 (accessed 10 May 2022);
2. Planchard D, et al. *Ann Oncol*. 2018;29:iv192–237; 3. Akamatsu H, et al. *Int J Clin Oncol*. 2019;24:731–70.

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Predictive biomarker testing in mCRC

ESMO, JLCS and NCCN guideline recommendations

Molecular subtyping is necessary for therapeutic decision making[1,2]

Systematic testing of *KRAS*/*NRAS* and *BRAF* mutations, and MMR/MSI status[1,2]

Testing for emerging biomarkers: *HER2* amplification/overexpression and *NTRK*[1]

ESMO, European Society for Medical Oncology; JLCS, Japanese Lung Cancer Society; mCRC, metastatic colorectal cancer; MMR, mismatch repair; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network.

1. NCCN. NCCN Guidelines: Colon cancer. Version 1.2022. Available at: www.nccn.org/guidelines/category_1 (accessed 10 May 2022);
2. Yoshino T, et al. *Ann Oncol*. 2018;29:44–70.

Testing for *KRAS* mutations

Recommended methodologies

DNA or RNA is extracted from tissue specimens[1]

Plasma samples can be used when tumour tissue is insufficient or unobtainable[1]

	PCR[1,2]	NGS[1]
+	• Turnaround time 1-2 days* • Low limits of detection ~1% • Less-costly equipment and infrastructure • Reduced hands-on time	• Provides comprehensive molecular profiling – Codons 12, 13, and 61 routinely detected • High accuracy of 98%
−	• May not identify specific mutations	• Time-consuming and long reporting times • Not accessible to all[3]

*Allele-specific PCR.
PCR, polymerase chain reaction; NGS, next-generation sequencing.
1. Veluswamy R, et al. *J Mol Diagn*. 2021;23:507–20; 2. Kerr KM, et al. *Lung Cancer*. 2021;154:161-75; 3. Pereira R, et al. *J Clin Med*. 2020;9:132.

Guideline recommendations for *KRAS* mutation testing

Recommendations from ESMO, EMA and JSMO

NSCLC[1,2]

ESMO guidelines:

- NGS is an emerging technology rapidly being adopted as the standard approach to screening adenocarcinomas for oncogenic targets

EMA:

- The presence of *KRAS*^{G12C} mutation must be confirmed prior to initiation of KRAS^{G12C} inhibitors

CRC[3]

JSMO–ESMO guidelines:

- *RAS* testing to confirm *RAS*^{wt} status is mandatory before treatment with cetuximab and panitumumab
- IHC testing for MMR proteins or PCR tests for MSI is recommended; NGS testing is not mentioned

CRC, colorectal cancer; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; IHC, immunohistochemistry; JSMO, Japanese Society of Medical Oncology; MMR, mismatch repair; MSI, microsatellite instability; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; wt, wildtype.

1. Kerr KM, et al. *Lung Cancer*. 2021;154:161-75; 2. Planchard D, et al. *Ann Oncol*. 2018;29:iv192–237; 3. Yoshino T, et al. *Ann Oncol*. 2018;29:44–70.

Conclusions

***KRAS* mutations are common in NSCLC and CRC** and occur in four hotspot codons: 12, 13, 61 or 146[1]

***KRAS*^{G12C} mutations** result in hyperactivation of downstream signalling and **uncontrolled proliferation**[1,2]

Molecular subtyping is recommended in NSCLC and CRC and **informs treatment decisions**, however only the **NCCN** recommend testing for ***KRAS* mutations**[3–7]

Molecular subtyping recommendations may evolve as novel KRAS-targeted treatments become available

CRC, colorectal cancer; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.

1. Huang L, et al. *Signal Transduct Target Ther*. 2021;6:386; 2. Liu J, et al. *Cancer Gene Ther*. 2021; doi: 10.1038/s41417-021-00383-9; 3. NCCN. NCCN Guidelines: Non-small cell lung cancer. Version 2.2022. Available at: https://www.nccn.org/guidelines/category_1 (accessed 10 May 2022); 4. Planchard D, et al. *Ann Oncol*. 2018;29:iv192–237; 5. Akamatsu H, et al. *Int J Clin Oncol*. 2019;24:731-70; 6. NCCN. NCCN Guidelines: Colon cancer. Version 1.2022. Available at: https://www.nccn.org/guidelines/category_1 (accessed 10 May 2022); 7. Yoshino T, et al. *Ann Oncol*. 2018;29:44–70.

Targeting the *KRAS*^{G12C} mutation in clinical practice

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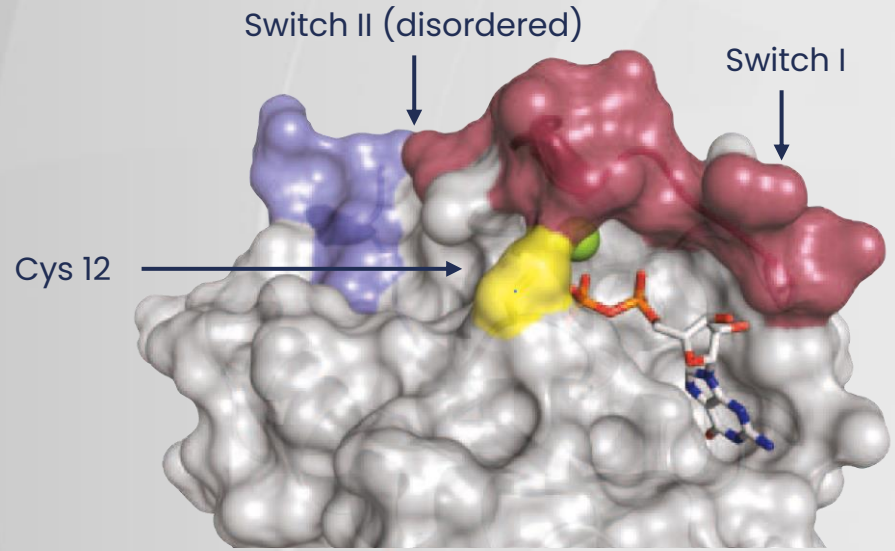
$KRAS^{G12C}$ crystal structure

Switch II pocket[1]

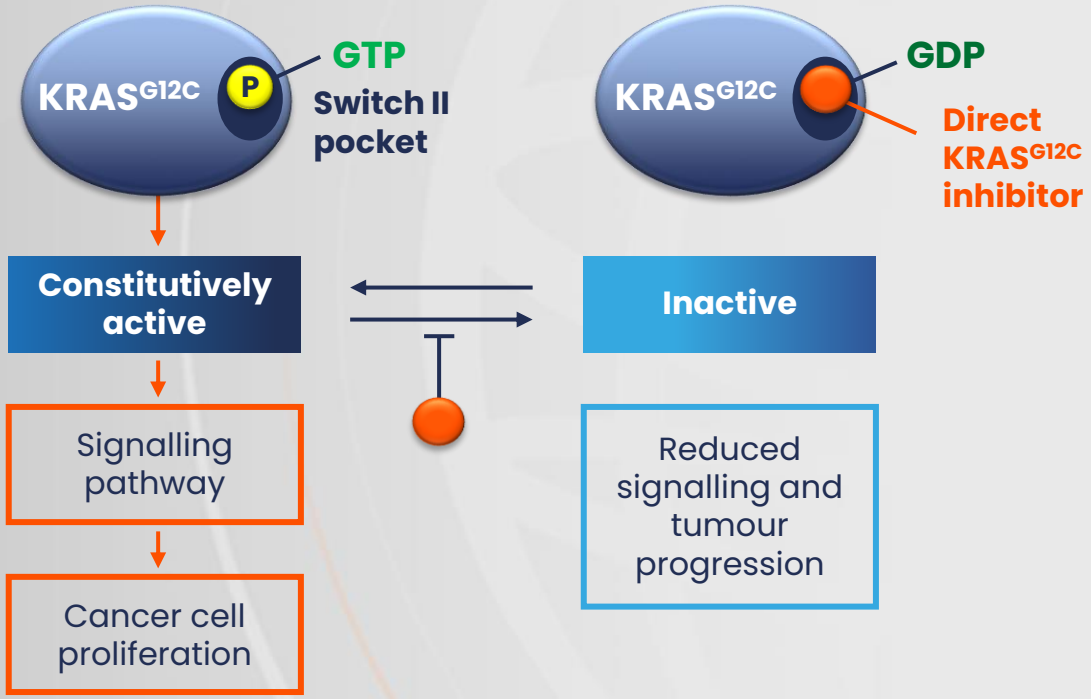


- Switch regions form the binding interface for effector proteins and regulators (GAPs and GEFs)[2]
- Cys 12 is in close proximity to both the nucleotide pocket and the switch regions[1]

GAP, GTPase activation protein; GEF, guanine nucleotide exchange factor; GTP, guanosine triphosphate.
1. Ostrem JM, et al. *Nature*. 2013;503:548–51; 2. Pantsar T. *Comput Struct Biotechnol J*. 2019;18:189–98.

Direct KRAS^{G12C} inhibitors: Mechanism of action

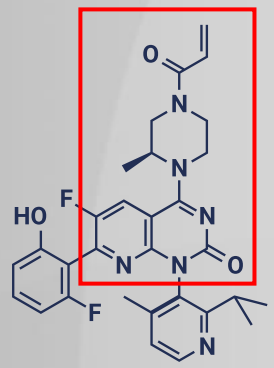
Targeting the switch II pocket



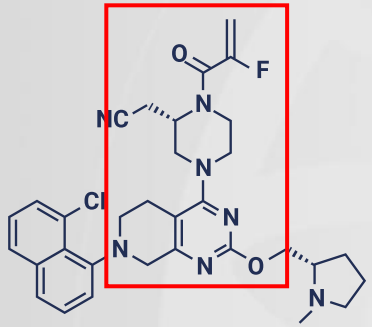
GDP, guanosine diphosphate; GTP, guanosine triphosphate.
Kwan AK, et al. *J Exp Clin Cancer Res*. 2022;41:27.

Direct KRAS^{G12C} inhibitors

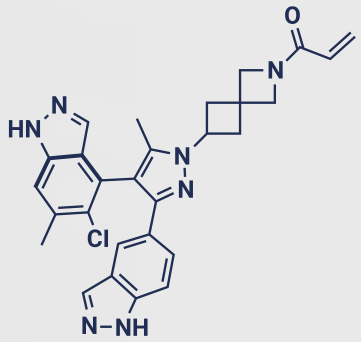
Chemical structures[1,2]



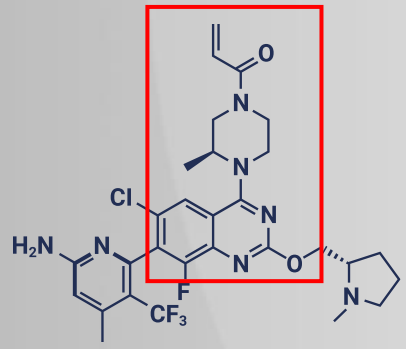
Sotorasib



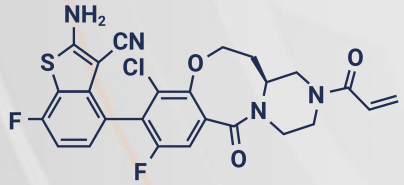
Adagrasib



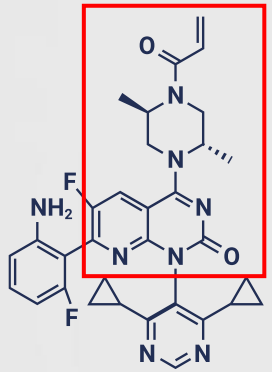
JDQ443



GDC-6036



LY3537982



D-1553

1. Christensen JG. AACR-NCI-EORTC Conference on Molecular Targets and Cancer Therapeutics. 2021; 2. Weiss A, et al. *Cancer Discov*. 2022;candisc.0158.2022.

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Direct KRAS^{G12C} inhibitors

Active clinical trials and approval status[1]

KRAS^{G12C} inhibitor	Ongoing clinical trials	Approval status
Sotorasib	CodeBreaK 100, 101, 105, 200, 201, Lung-MAP	Approved in the EU[2] and Japan[3] for ≥2L treatment of *KRAS*^{G12C}–mutated NSCLC, phase III
Adagrasib	KRYSTAL-1, -2, -7, -10, -12, -14	Investigational, phase III
JDQ443	KontRASt-01, -02, -03	Investigational, phase III
D-1553	NCT04585035	Investigational, phase I/II
GDC-6036	NCT04449874	Investigational, phase I
LY3537982	NCT04956640	Investigational, phase I
BI 1823911	NCT04973163	Investigational, phase I
JAB-21822	NCT05002270, NCT05194995	Investigational, phase I/II

2L, second line; NSCLC, non-small cell lung cancer; PMDA, Pharmaceuticals and Medical Devices Agency.

1. Kwan AK, et al. *J Exp Clin Cancer Res*. 2022;41:27; 2. Sotorasib SmPC. Available at: www.ema.europa.eu/en/documents/product-information/lumykras-epar-product-information_en.pdf (accessed 1 May 2022); 3. PMDA. Available at: www.pmda.go.jp/files/000245772.pdf (accessed 1 May 2022).

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Sotorasib	**CodeBreaK 100**, 101, 105, **200**, **201**, Lung-MAP	Approved in the EU[2] and Japan[3] for ≥2L treatment of *KRAS*^{G12C}–mutated NSCLC, phase III
Adagrasib	**KRYSTAL-1**, -2, -7, -10, **-12**, -14	Investigational, phase III
JDQ443	**KontRASt-01**, **-02**, -03	Investigational, phase III
D-1553	NCT04585035	Investigational, phase I/II
GDC-6036	NCT04449874	Investigational, phase I
LY3537982	NCT04956640	Investigational, phase I
BI 1823911	NCT04973163	Investigational, phase I
JAB-21822	NCT05002270, NCT05194995	Investigational, phase I/II

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1. Kwan AK, et al. *J Exp Clin Cancer Res*. 2022;41:27; 2. Sotorasib SmPC. Available at: www.ema.europa.eu/en/documents/product-information/lumykras-epar-product-information_en.pdf (accessed 1 May 2022); 3. PMDA. Available at: www.pmda.go.jp/files/000245772.pdf (accessed 1 May 2022).

Sotorasib monotherapy: Efficacy

CodeBreaK 100: Phase I/II open-label study in patients with *KRAS*^{G12C}-mutated solid tumours

- **Advanced NSCLC**: **phase II data** from 124 patients evaluated for response to sotorasib monotherapy[1]
  - ORR, 37.1%
  - mDOR, 11.1 months
  - mPFS, 6.8 months
  - mOS, 12.5 months

- **Advanced NSCLC**: **2-year data** from 174 patients evaluated for response to sotorasib monotherapy[2]
  - ORR, 40.7%
  - mDOR, 12.3 months
  - mPFS, 6.3 months
  - mOS, 12.5 months

- **Advanced CRC**: **phase II data** 62 patients evaluated for response to sotorasib monotherapy[3]
  - ORR, 9.7%
  - mDOR, 4.2 months
  - mPFS, 4.0 months
  - mOS, 10.6 months

CRC, colorectal cancer; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate.

1. Skoulidis F, et al. *N Engl J Med*. 2021;384:2371–81; 2. Dy GK, et al. AACR Annual Meeting. April 2022. Abstract CT008; 3. Fakih MG, et al. *Lancet Oncol*. 2022;23:115–24.

Sotorasib monotherapy: Safety

CodeBreaK 100: Phase I/II open-label study in patients with *KRAS*^{G12C}-mutated solid tumours

- **Phase I data**: 59 patients with **advanced NSCLC**, 42 patients with **advanced CRC** and 28 with other solid tumours, all treated with sotorasib monotherapy[1]
  - TRAEs, 56.6%
  - Grade 3 or 4 AEs, 11.6%
  - Most common AEs: diarrhoea (29.5%), fatigue (23.3%) and nausea (20.9%)

- **Advanced NSCLC**: **phase II data** from 126 patients treated with sotorasib monotherapy[2]
  - TRAEs, 69.8%
  - Grade 3 or 4 AEs, 20.1%
  - Most common AEs: diarrhoea (31.7%), nausea (19.0%), increase in ALT (15.1%) and increase in AST (15.1%)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; TRAE, treatment-related adverse event.

1. Hong DS, et al. *N Engl J Med*. 2020;383:1207–17; 2. Skoulidis F, et al. *N Engl J Med*. 2021;384:2371–81.

Sotorasib monotherapy: First-line in NSCLC

CodeBreaK 201: Phase II open-label study

*Patients who received adjuvant/neoadjuvant therapy are eligible if it was completed >12 months prior to the development of metastatic disease.
NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed death-ligand 1.
ClinicalTrials.gov. NCT04933695. Available at: www.clinicaltrials.gov/ct2/show/NCT04933695 (accessed 1 May 2022).

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Adagrasib monotherapy: Efficacy

KRYSTAL-1: Phase I/II open-label study

- **Advanced NSCLC**: **phase I/II data** from 116 patients evaluated for response to adagrasib monotherapy[1]
  - ORR, 43%
  - DCR, 80%
  - mDOR, 8.5 months
  - mPFS, 6.5 months
  - mOS, 12.6 months

- **Advanced CRC**: **phase I/II data** from 45 patients evaluated for response to adagrasib monotherapy[2]
  - Response rate, 22%
  - DCR, 87%
  - mDOR, 4.2 months
  - mPFS, 5.6 months

- **Advanced pancreatic and other GI cancers**:* **phase II data** from 27 previously treated patients evaluated for response to adagrasib monotherapy[3]
  - PR, 41%
  - DCR, 100%
  - mPFS†, 6.6 months

*Excluding NSCLC and CRC; †in patients with metastatic pancreatic cancer.
CRC, colorectal cancer; DCR, disease control rate; GI, gastrointestinal; mDOR, median duration of response; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate; mOS, median overall survival; PR, partial response.
1. Spira A, et al. *J Clin Oncol*. 2022;40(Suppl. 16):9002; 2. Weiss J, et al. *Ann Oncol*. 2021;32(S5):S1283–S346. LBA6; 3. Bekaii-Saab TS, et al. *J Clin Oncol*. 2022;40(Suppl. 4):519.

Adagrasib monotherapy: Safety

KRYSTAL-1: Phase I/II open-label study

- **Advanced solid tumours**: **phase I/Ib** dose-finding study in 25 patients[1]
  - RP2D determined as 600 mg BID based on safety, tolerability and pharmacokinetics
  - TRAEs, 92%
  - Grade 3 or 4 AEs, 36%
  - Most common AEs: nausea (80%), diarrhoea (70%), vomiting (50%) and fatigue (45%)

- **Advanced NSCLC**: **phase I/II data** from 116 patients evaluated for response to adagrasib monotherapy[2]
  - TRAEs, 97%
  - Grade 3 or 4 AEs, 43%
  - Most common AEs: diarrhoea (63%), nausea (62%), vomiting (47%) and fatigue (41%)

- **Advanced pancreatic and other GI cancers**:* **Phase II data** from 42 patients treated with adagrasib monotherapy[3]
  - TRAEs, 91%
  - Grade 3 or 4 AEs, 21%
  - Most common AEs: nausea (48%), diarrhoea (43%), vomiting (43%) and fatigue (29%)

*Excluding NSCLC and CRC.
AE, adverse event; BID, twice daily; GI, gastrointestinal; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse event.
1. Ou SHI, et al. *J Clin Oncol*. 2022:JCO2102752; 2. Spira A, et al. *J Clin Oncol*. 2022;40(Suppl. 16):9002; 3. Bekaii-Saab TS, et al. *J Clin Oncol*. 2022;40(Suppl. 4):519.

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JDQ443 monotherapy: Efficacy and safety

KontRASt-01: Phase Ib/II open-label study

- Dose escalation study: 20 patients with **advanced NSCLC** and 16 with **advanced CRC**
  - RP2D determined as 200 mg BID
  - ORR for NSCLC, 57% at RP2D
  - Most common TRAEs: fatigue (30.8%), nausea (17.9%), oedema (15.4%), diarrhoea (12.8%) and vomiting (12.8%)

BID, twice daily; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; ORR, objective response rate; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse event.
Tan DS, et al. AACR Annual Meeting. April 2022. Abstract CT033.

Phase III trials with KRAS^{G12C} inhibitors in previously treated NSCLC

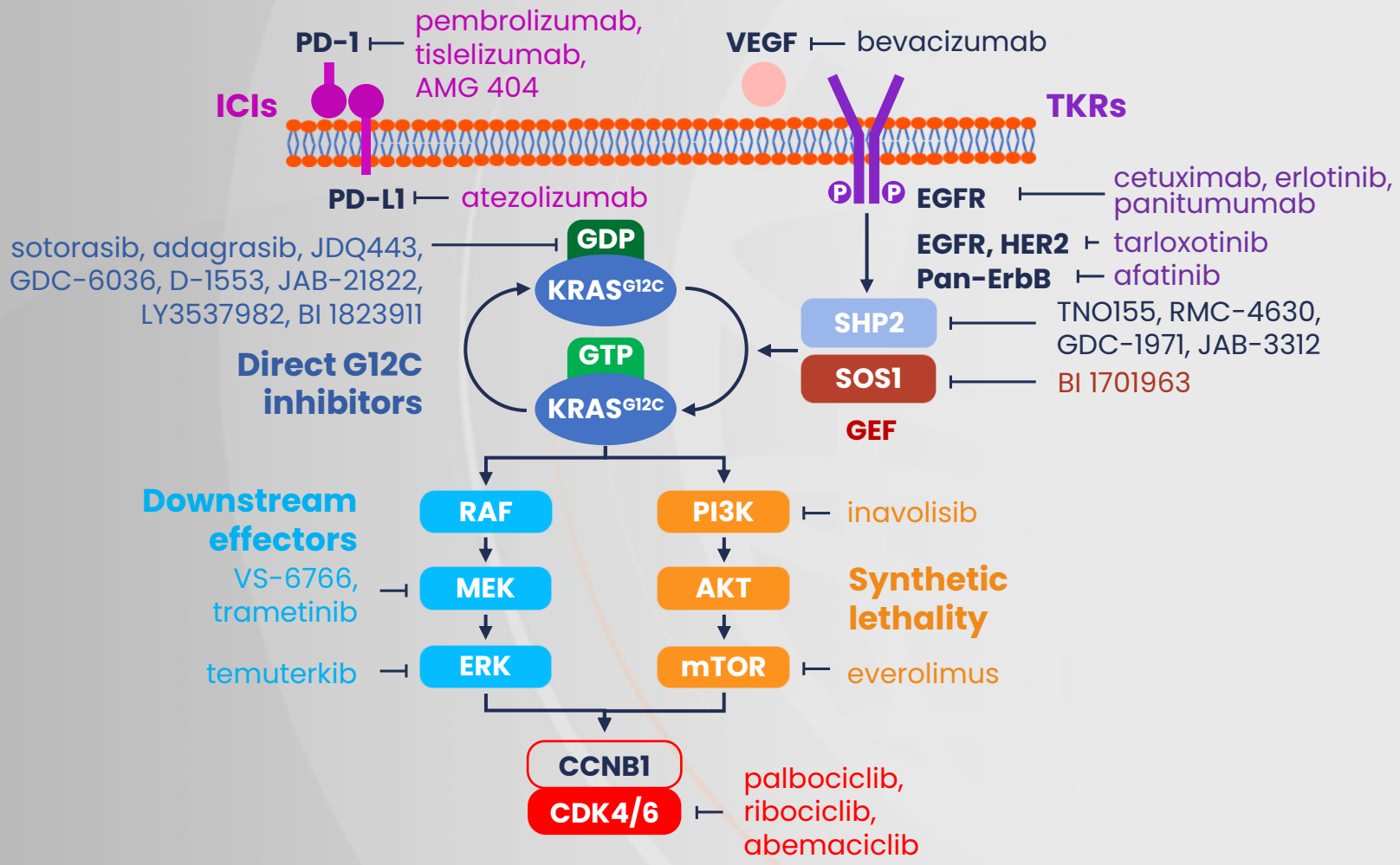
KRAS^{G12C} inhibitors vs docetaxel

	Sotorasib CodeBreaK 200 (NCT04303780)	**Adagrasib** KRYSTAL-12 (NCT04685135)	**JDQ443** KontRASt-02 (NCT05132075)
Estimated primary completion	July 2022	August 2023	August 2024
Patient eligibility	Locally advanced and unresectable or metastatic NSCLC with *KRAS*^{G12C} mutation	Metastatic NSCLC with *KRAS*^{G12C} mutation	Locally advanced and unresectable or metastatic NSCLC with *KRAS*^{G12C} mutation
Primary outcome measure	PFS	PFS	PFS

NSCLC, non-small cell lung cancer; PFS, progression-free survival.
All clinical trial information can be accessed at www.clinicaltrials.gov using the study identifier (accessed 1 May 2022).

Potential combination strategies

Adding on to direct KRAS^{G12C} inhibitors to overcome resistance[1–3]



GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GTP, guanosine triphosphate; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TKR, tyrosine kinase receptor.

Figure adapted from: 1. Palma G, et al. *NPJ Precis Oncol*. 2021;5:98; 2. Dunnett-Kane V, et al. *Cancers*. 2021;13:151; 3. Negri F, et al. *Int J Mol Sci*. 2022;23.4120.

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Conclusions

Multiple **KRAS^{G12C} inhibitors** are in development, with sotorasib being approved for previously treated NSCLC, and others showing promising results in both NSCLC and CRC[1–5]

Several **direct KRAS^{G12C} inhibitors** (sotorasib, adagrasib and JDQ443) are in **phase III development** vs docetaxel for previously treated **advanced NSCLC**[6–8]

Direct KRAS^{G12C} inhibitors in combination with cell signalling inhibitors, ICIs and pan-KRAS inhibitors are being intensively studied to further improve outcomes in patients with solid tumours[9]

CRC, colorectal cancer; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer.

All clinical trial information can be accessed at www.clinicaltrials.gov using the study identifier (accessed 1 May 2022). 1. Hong DS, et al. *N Engl J Med*. 2020;383:1207–17; 2. Dy GK, et al. AACR Annual Meeting. April 2022. Abstract CT008; 3. Fakih MG, et al. *Lancet Oncol*. 2022;23:115–24; 4. Jänne PA, et al. *Eur J Cancer*. 2020;138(S2):S1–2; 5. Weiss J, et al. *Ann Oncol*. 2021;32(S5):S1283–S346. LBA6; 6. NCT04303780; 7. NCT04685135; 8. NCT05132075; 9. Kwan AK, et al. *J Exp Clin Cancer Res*. 2022;41:27.

Tackling resistance to KRAS-targeted therapies

KRAS^{G12C} inhibitors

Ongoing challenges with resistance

Intrinsic and **acquired resistance** is a major challenge with direct KRAS^{G12C} inhibitor treatment, limiting responses and driving disease progression[1]

Response

- ~50% of patients in clinical trials with sotorasib/adagrasib do not experience significant tumour shrinkage[1]

Disease progression

- ~10% of patients experience primary disease progression
- All patients who initially experience an objective response or stable disease will eventually progress[1]

Intrinsic resistance

Secondary *KRAS* mutations mean another effector perpetuates the signalling[2]

Acquired resistance

Driven by the selective pressure of the therapy[1]

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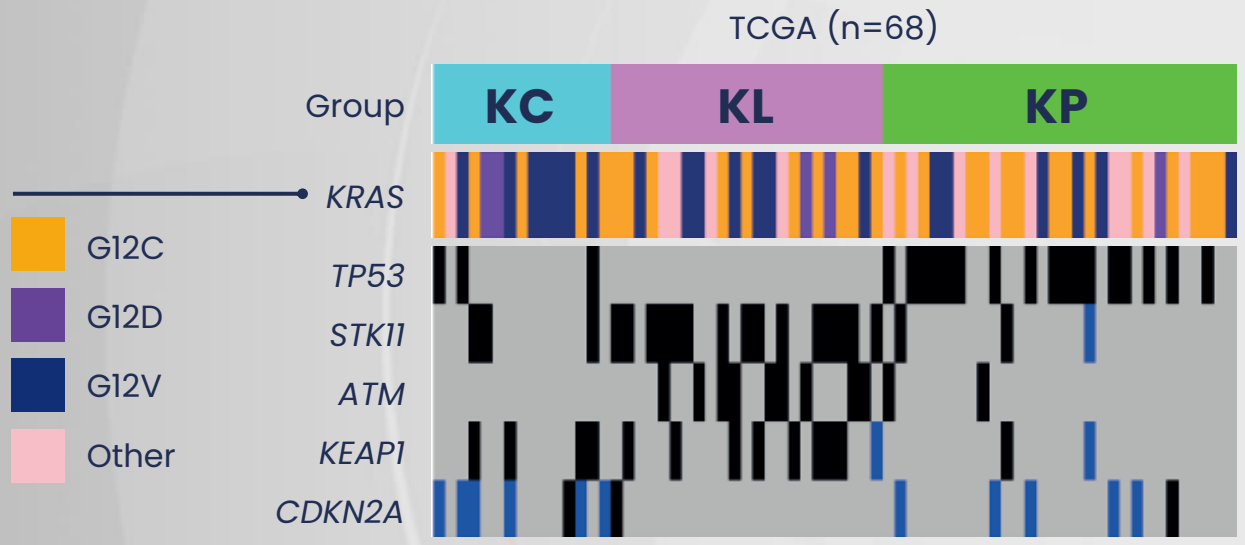
1. Blaquier JB, et al. *Front Oncol*. 2021;11:787585; 2. Addeo A, et al. *Cancers (Basel)*. 2021;13:2541.

KRAS and co-mutations

Identification of co-mutations in lung adenocarcinoma



- **KC subgroup**: *CDKN2A/B* inactivation plus low *TTF1*
- **KL subgroup**: *STK11/LKB1* mutation
- **KP subgroup**: *TP53* mutation

TCGA, The Cancer Genome Atlas.
Skoulidis F, et al. *Cancer Discov*. 2015;5:860–77.

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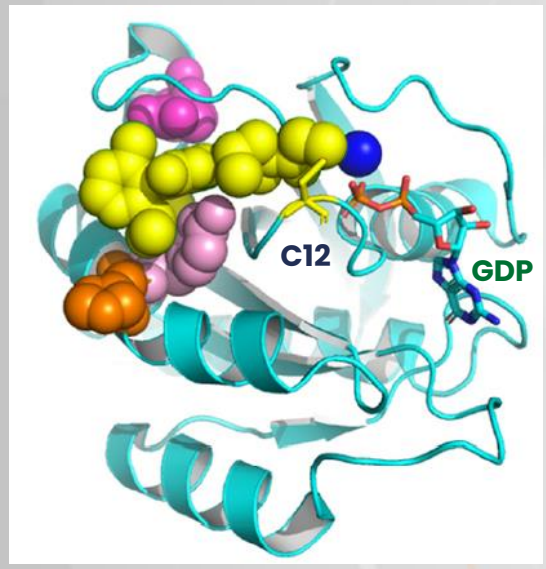
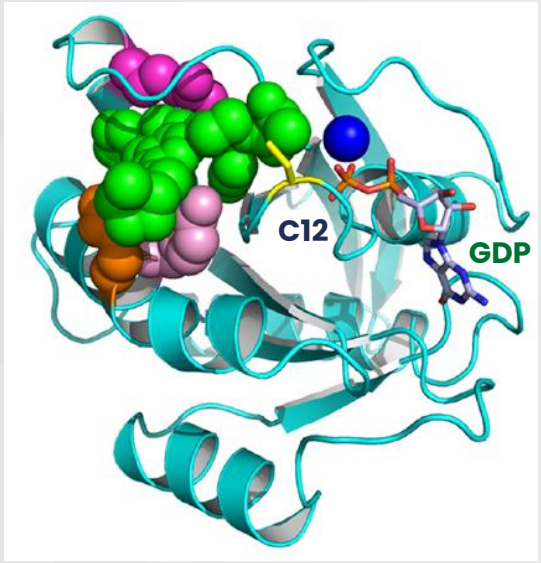
Resistance to direct KRAS^{G12C} inhibitors

Acquired missense mutation in KRAS^{G12C} inhibitor binding sites[1–2]



Sotorasib



Adagrasib

GDP, guanosine diphosphate.

1. Awad MM, et al. *N Engl J Med*. 2021;384:2382–93; 2. Zhang J, et al. *Pharmacol Ther*. 2022;229:108050.

Acquired resistance mechanisms

Adagrasib resistance in the KRYSTAL-1 study (N=38)

- NGS of tissue samples or ctDNA was analysed at the time of disease progression
- Patients: 27 with NSCLC, 10 with CRC, 1 with appendiceal cancer

38 patients experienced disease progression, with 17 having identifiable mechanisms of resistance

KRAS alterations

- Acquired mutations at R68, H95 and Y96 in the SIIP prevent adagrasib binding
- Activating mutations, e.g. G12D/V/R, G13D and Q61H
- High-level amplification of the $KRAS^{G12}$ allele

Bypass mechanisms

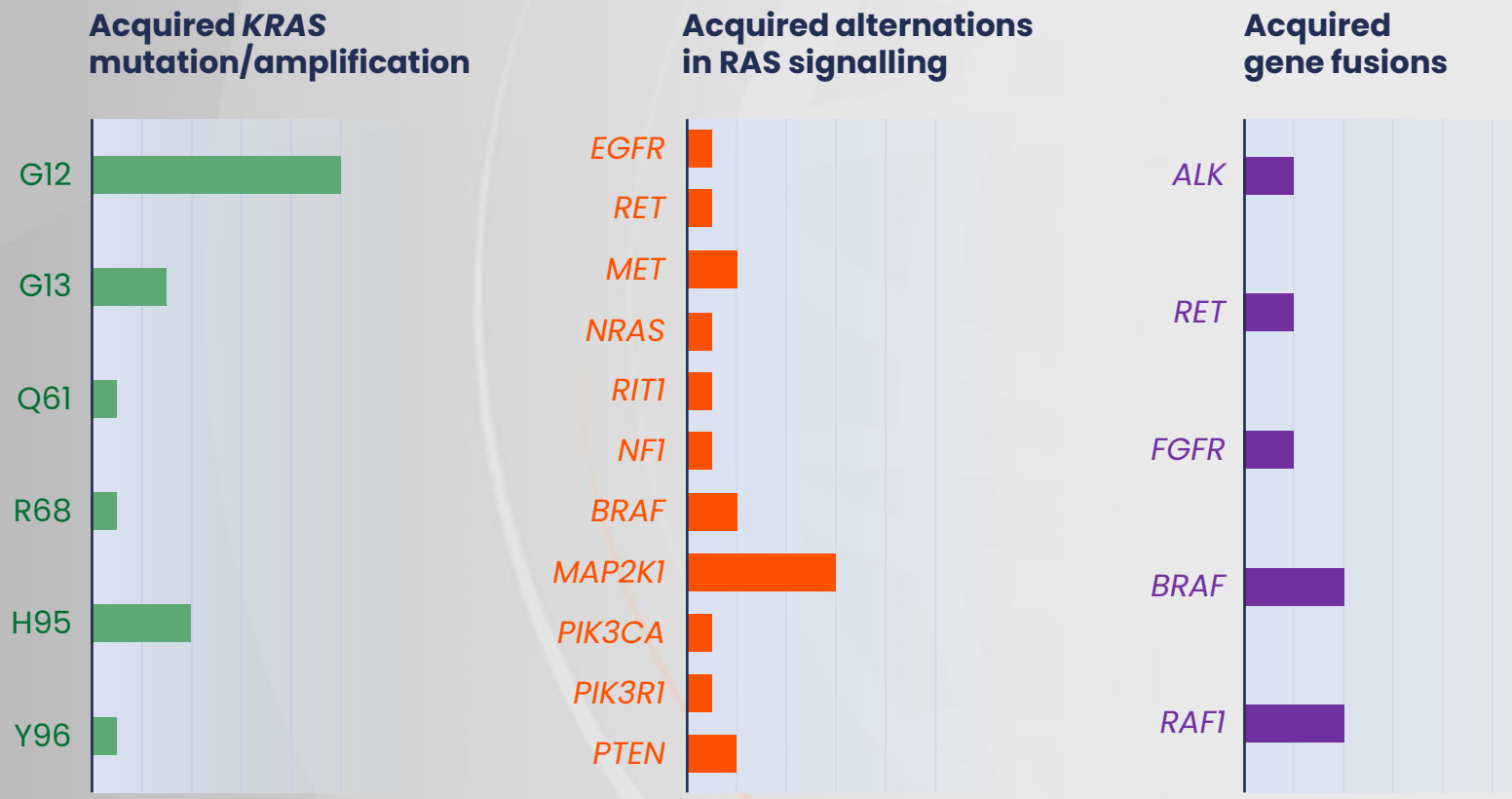
- *MET* amplification
- Activating mutations in *NRAS*, *BRAF*, *MAP2K1* and *RET*
- Oncogenic fusions, e.g. *ALK*, *RET*, *BRAF*, *RAF1* and *FGFR3*
- Loss-of-function mutations in *NF1* and *PTEN*

CRC, colorectal cancer; ctDNA, circulating tumour DNA; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; SIIP, switch 2 pocket.

Awad MM, et al. *N Engl J Med.* 2021;384:2382–93.

Resistance to direct KRAS^{G12C} inhibitors

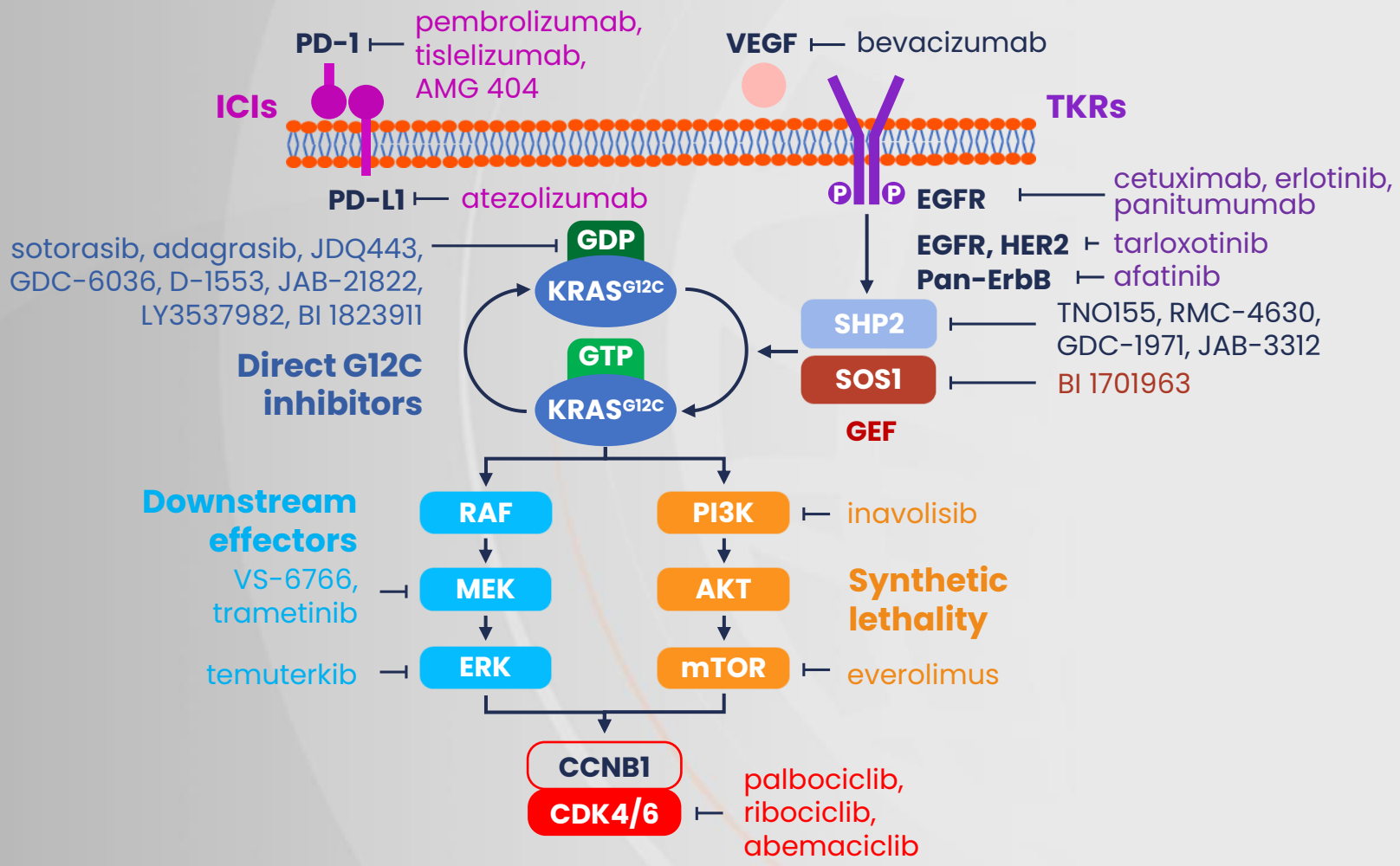
Resistance mechanisms identified in the KRYSTAL-1 study (n=17)



Awad MM, et al. *N Engl J Med*. 2021;384:2382–93.

Potential combination strategies

Adding on to direct KRAS^{G12C} inhibitors to overcome resistance[1–3]



GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GTP, guanosine triphosphate; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TKR, tyrosine kinase receptor.

Figure adapted from: 1. Palma G, et al. *NPJ Precis Oncol*. 2021;5:98; 2. Dunnett-Kane V, et al. *Cancers*. 2021;13:151; 3. Negri F, et al. *Int J Mol Sci*. 2022;23.4120.

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Direct KRAS^{G12C} inhibitor combinations

Sotorasib clinical trials

Trial details	Combination agent(s)	Results
CodeBreaK 101 NCT04185883 • Phase Ib/II • Solid tumours	• AMG 404 • Trametinib • RMC-4630 • Afatinib • Pembrolizumab • Panitumumab • Atezolizumab • Everolimus • Palbociclib • Bevacizumab • TNO155 • FOLFIRI, FOLFOX • Carboplatin-pemetrexed-docetaxel	**Sotorasib + afatinib (NSCLC)** • No new AEs observed • ORR 20.0–34.8%[1] **Sotorasib + trametinib (solid tumours)** • No new AEs observed • mDOR, 84 days[2] **Sotorasib + panitumumab (CRC)** • No new AEs observed • mDOR, 4.4 months[3] Primary completion: Aug 2024
NCT05054725 • Phase II • NSCLC	RMC-4630	Primary completion: Mar 2023
RAMP203 NCT05074810 • Phase I/II • NSCLC	VS-6766	Primary completion: Dec 2023
NCT05313009 • Phase I/II • NSCLC	Tarloxotinib	Primary completion: Dec 2023

AE, adverse event; CRC, colorectal cancer; mDOR, median duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate.
All clinical trial information can be accessed at www.clinicaltrials.gov using the study identifier (accessed 1 May 2022).
1. Gandara D, et al. *Mol Cancer Ther*. 2021;20(Suppl. 12):P05–02; 2. Ramalingam S, et al. *Mol Cancer Ther*. 2021;20(Suppl. 12):P05-01; 3. Fakih M, et al. *Ann Oncol*. 2021;32(Suppl. 5):S530–82.

Direct KRAS^{G12C} inhibitor combinations

Adagrasib clinical trials

Trial details	Combination agent(s)	Results
KRYSTAL-1 NCT03785249 • Phase I/II • Solid tumours	• Pembrolizumab • Cetuximab • Afatinib	**Adagrasib + cetuximab (CRC)** • TEAEs, 100%; grade 3/4 AEs, 16% • Response rate, 43%; DCR, 100%[1] Primary completion: Dec 2022
KRYSTAL-2 NCT04330664 • Phase I/II • CRC + NSCLC	TNO155	Primary completion: Sept 2022
KRYSTAL-7 NCT04613596 • Phase II • NSCLC	Pembrolizumab	Primary completion: Oct 2023
KRYSTAL-10 NCT04793958 • Phase III • CRC	Cetuximab vs mFOLFOX6 or FOLFIRI	Primary completion: Sept 2023
KRYSTAL-14 NCT04975256 • Phase I • CRC + NSCLC	BI 1701963	Primary completion: Nov 2023
KRYSTAL-16 NCT05178888 • Phase I • Solid tumours	Palbociclib	Primary completion: Dec 2023

AE, adverse event; CRC, colorectal cancer; DCR, disease control rate; NSCLC, non-small cell lung cancer; TEAE, treatment-emergent adverse event.
All clinical trial information can be accessed at www.clinicaltrials.gov using the study identifier (accessed 1 May 2022).
1. Weiss J, et al. *Ann Oncol*. 2021;32(Suppl. 5):S1283–S346.

Direct KRAS^{G12C} inhibitor combinations

JDQ443 clinical trials

Trial details	Combination agents	Results
KontRASt-01 NCT04699188 • Phase I/II • Solid tumours	• TNO155, • Tislelizumab	Primary completion: Aug 2024
KontRASt-03 NCT05358249 • Phase I/II • Solid tumours	• Trametinib • Ribociclib • Cetuximab	Study start: Jul 2022 Primary completion: Apr 2025

All clinical trial information can be accessed at www.clinicaltrials.gov using the study identifier (accessed 1 May 2022).

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Direct KRAS^{G12C} inhibitor combinations

JAB-21822, GDC-6036, LY3537982 and BI 1823911 clinical trials in solid tumours

Trial details	Combination agent(s)	Results
JAB-21822 NCT05002270 • Phase I/II	Cetuximab	Primary completion: Jul 2023
GDC-6036 NCT04449874 • Phase I	• Atezolizumab • Cetuximab • Bevacizumab • Erlotinib • GDC-1971 • Inavolisib	Primary completion: Aug 2023
LY3537982 NCT04956640 • Phase I	• Abemaciclib • Erlotinib • Pembrolizumab • Temuterkib • LY3295668 • Cetuximab • TNO155	Primary completion: Oct 2023
BI1823911 NCT04973163 • Phase I	BI 1701963	Primary completion: Jun 2024

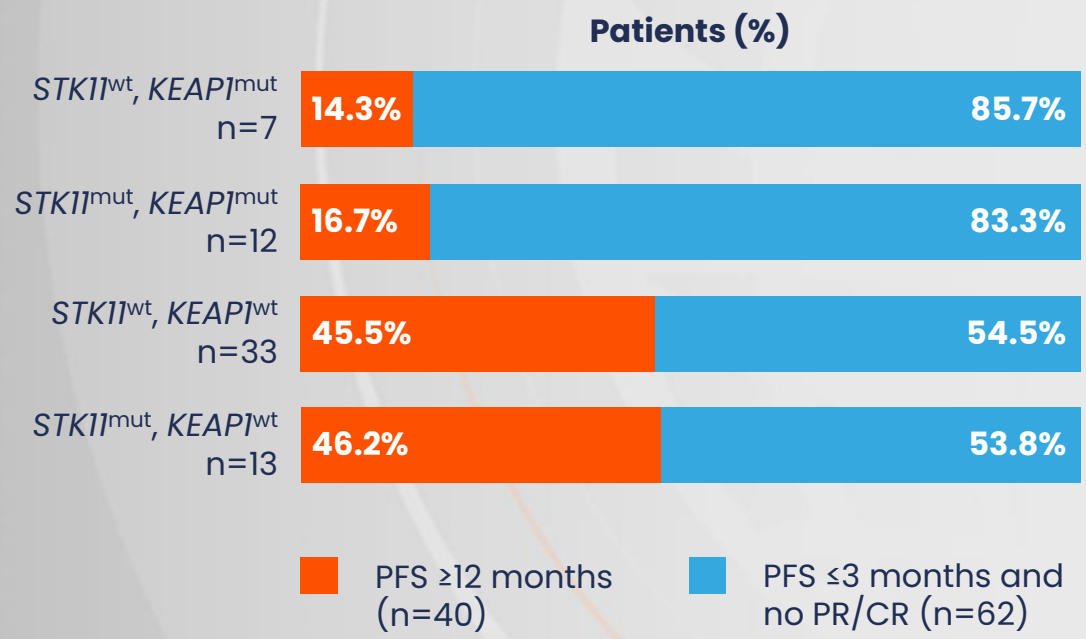
All clinical trial information can be accessed at www.clinicaltrials.gov using the study identifier (accessed 1 May 2022).

Biomarkers in patients with *KRAS*^{G12C} mutations

Can biomarkers help to optimize treatment outcomes?

Biomarker selection

What is the role of biomarkers such as PD-L1, TMB, TILs, *STK11, KEAP1*?



CR, complete response; mut, mutant; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; TIL, tumour-infiltrating lymphocyte; TMB, tumour mutational burden; wt, wild type.

Dy GK, et al. AACR Annual Meeting. April 2022. CT008.

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Novel approaches to targeting KRAS

Different target sites and mechanisms

GDP/GTP KRAS^{G12C} inhibitor[1]

- Binds SIIP of GTP/GDP KRAS^{G12C}
- Preclinical studies show anti-cancer activity in cell lines resistant to sotorasib/adagrasib

KRAS^{G12D} inhibitor[2,3]

- *KRAS*^{G12D} is the most common *KRAS* mutation in PC and CRC, and second most common in NSCLC
- **MRTX1133** is a noncovalent, potent selective KRAS^{G12D} inhibitor

SOS1::pan-KRAS inhibitor[4]

- **BI 1701963** targets SOS1 and prevents binding to KRAS-GDP, blocking active KRAS-GTP
- Undergoing clinical trials as monotherapy and in combination

pan-KRAS mRNA vaccine[5,6]

- **V941(mRNA-5671/V941)** targets KRAS^{G12C}, KRAS^{G12D}, KRAS^{G12V} and KRAS^{G13D}
- In phase I development as monotherapy and in combination with pembrolizumab

CRC, colorectal cancer; GDP, guanosine diphosphate; GTP, guanosine triphosphate; mRNA, messenger RNA; NSCLC, non-small cell lung cancer; PC, pancreatic cancer; SIIP, switch 2 pocket.

1. Calses P, et al. AACR Annual Meeting. April 2022. Abstract 3601; 2. Wang X, et al. *J Med Chem*. 2022;65:3123–33; 3. Huang L, et al. *Signal Transduct Target Ther*. 2021;6:386;
4. Gort E, et al. *J Clin Oncol*. 2020;38:TPS3651; 5. ClinicalTrials.gov. NCT03948763. Available at: https://clinicaltrials.gov/ct2/show/NCT03948763 (accessed 1 May 2022);
6. National Cancer Institute. Available at: www.cancer.gov/publications/dictionaries/cancer-drug/def/mrna-derived-kras-targeted-vaccine-v941 (accessed 1 May 2022).

Conclusions

Resistance to direct **KRAS^{G12C} inhibitors** may be caused by **co-mutations**, **acquired *KRAS* mutations** and **bypass mechanisms**[1]

An array of direct **KRAS^{G12C} inhibitor combinations** with upstream, downstream, cell cycle and immune checkpoint inhibitors **are being investigated to overcome resistance**[2]

New agents, such as KRAS^{G12C} GTP/GDP, KRAS^{G12D} and pan-KRAS inhibitors, are in the **early stages of clinical development**[3–8]

GDP, guanosine diphosphate; GTP, guanosine triphosphate.

1. Awad MM, et al. *N Engl J Med*. 2021;384:2382–93; 2. Kwan AK, et al. *J Exp Clin Cancer Res*. 2022;41:27; 3. Calses P, et al. AACR Annual Meeting. April 2022. Abstract 3601; 4. Wang X, et al. *J Med Chem*. 2022;65:3123–33; 5. Huang L, et al. *Signal Transduct Target Ther*. 2021;6:386; 6. Gort E, et al. *J Clin Orthod*. 2020;38:TPS3651; 7. ClinicalTrials.gov. NCT03948763. Available at: https://clinicaltrials.gov/ct2/show/NCT03948763 (accessed 1 May 2022); 8. National Cancer Institute. Available at: www.cancer.gov/publications/dictionaries/cancer-drug/def/mrna-derived-kras-targeted-vaccine-v941 (accessed 1 May 2022).