

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



Prof. Tony Mok
Department of Clinical Oncology
Chinese University of Hong Kong
Hong Kong

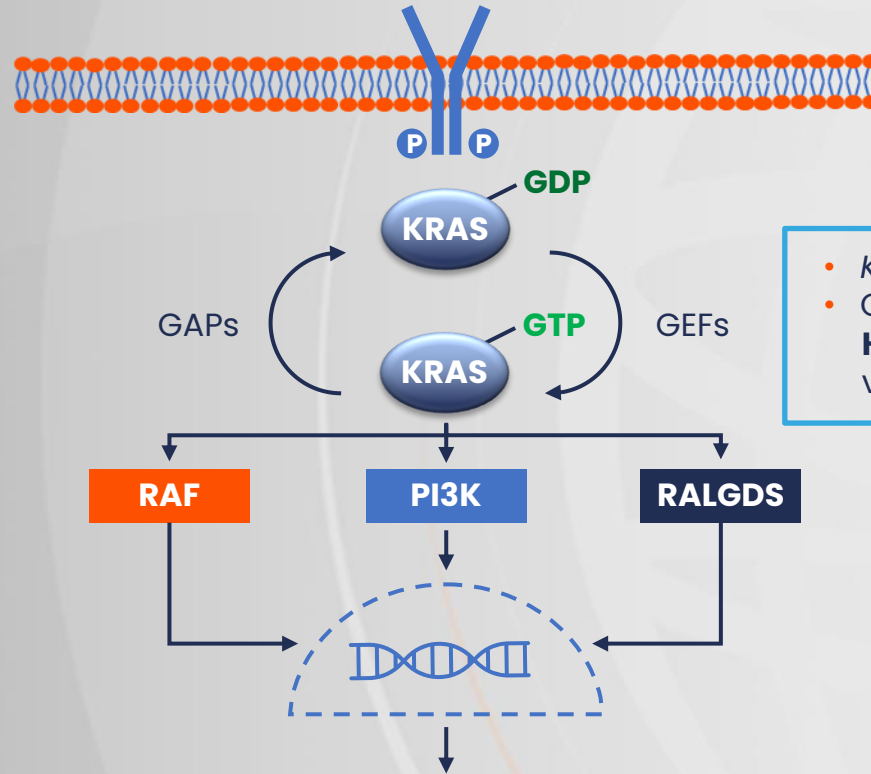
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Investigating the role of *KRAS* mutations in solid tumours

KRAS-mediated signalling

Kirsten **RAT** Sarcoma viral oncogene mechanism of action^{1,2}

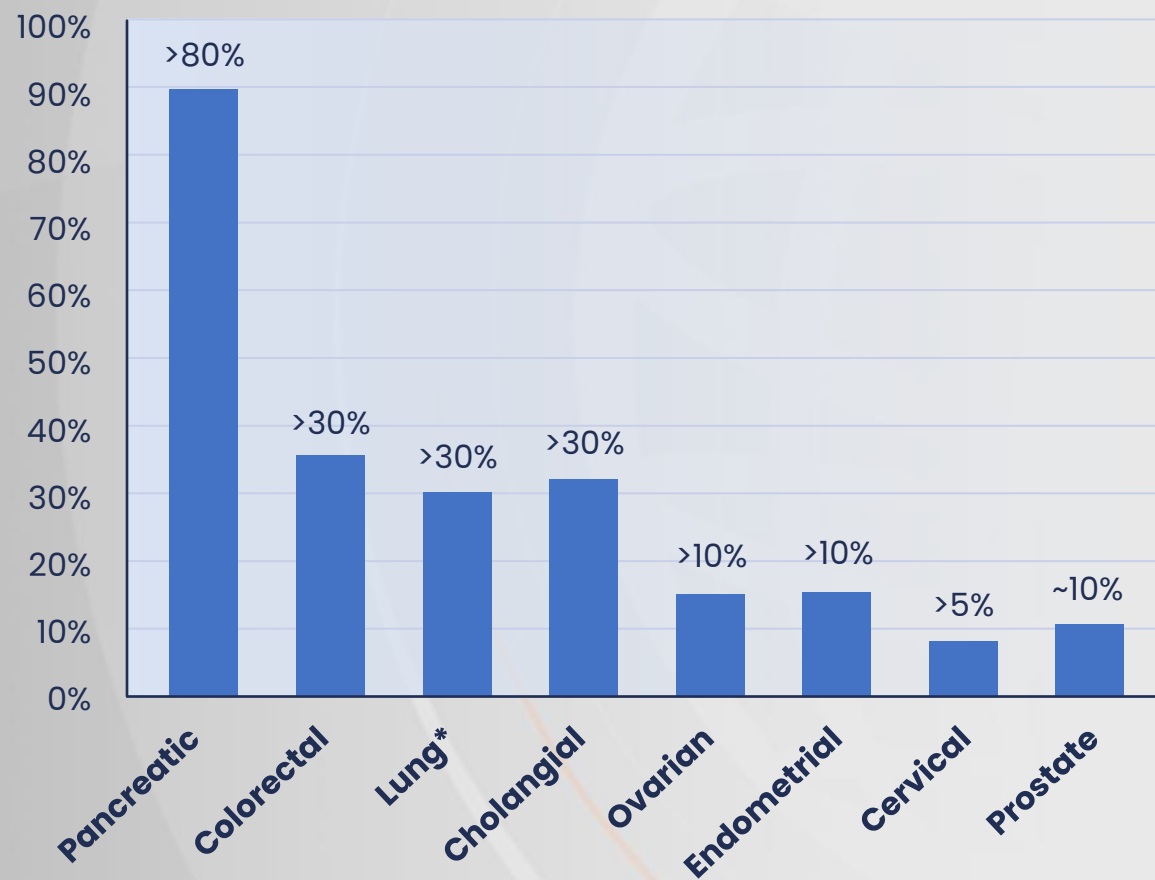


- KRAS is a proto-oncogene³
- Other RAS proteins include: **HRAS**, **NRAS**, and the splice variants **KRAS4A** and **KRAS4B**⁴

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

KRAS mutations in solid tumours

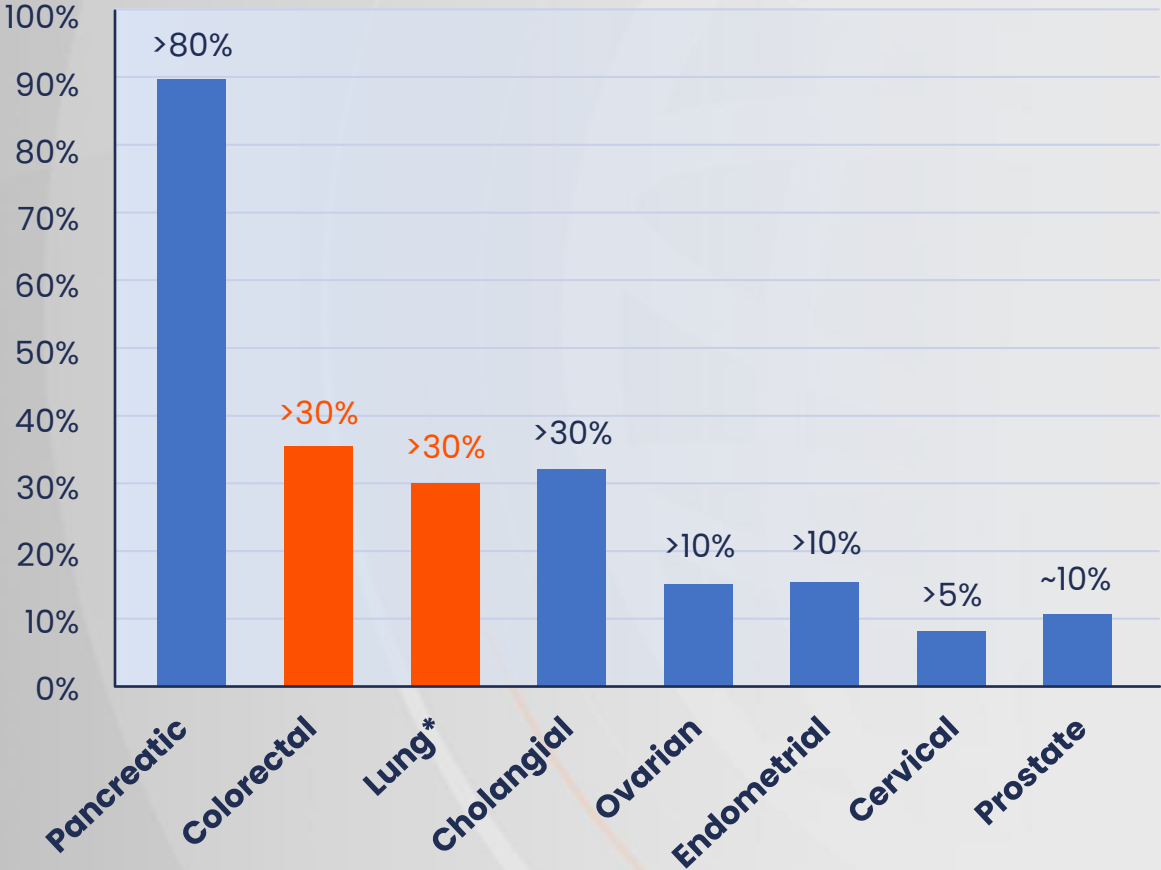
Mutation incidence in a range of solid tumours



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

KRAS mutations in solid tumours

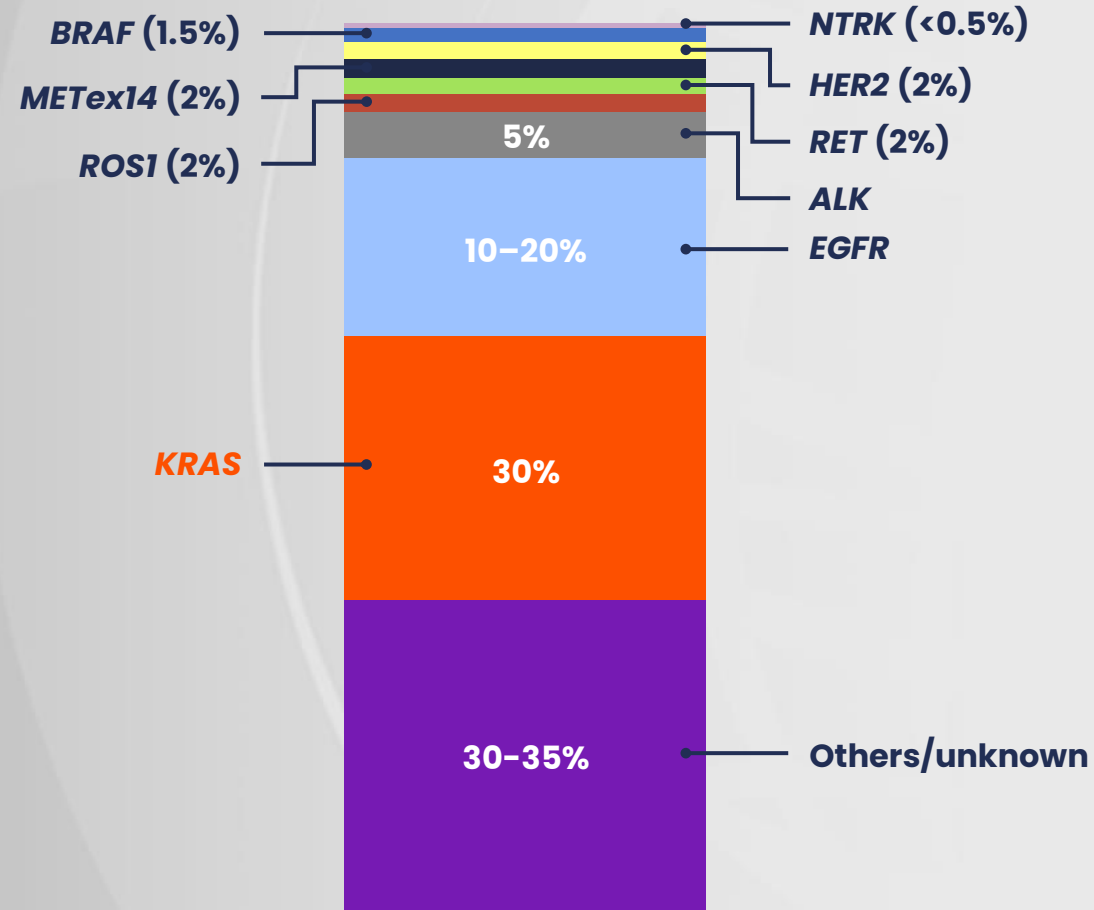
Mutation incidence in a range of solid tumours



*Lung adenocarcinoma.
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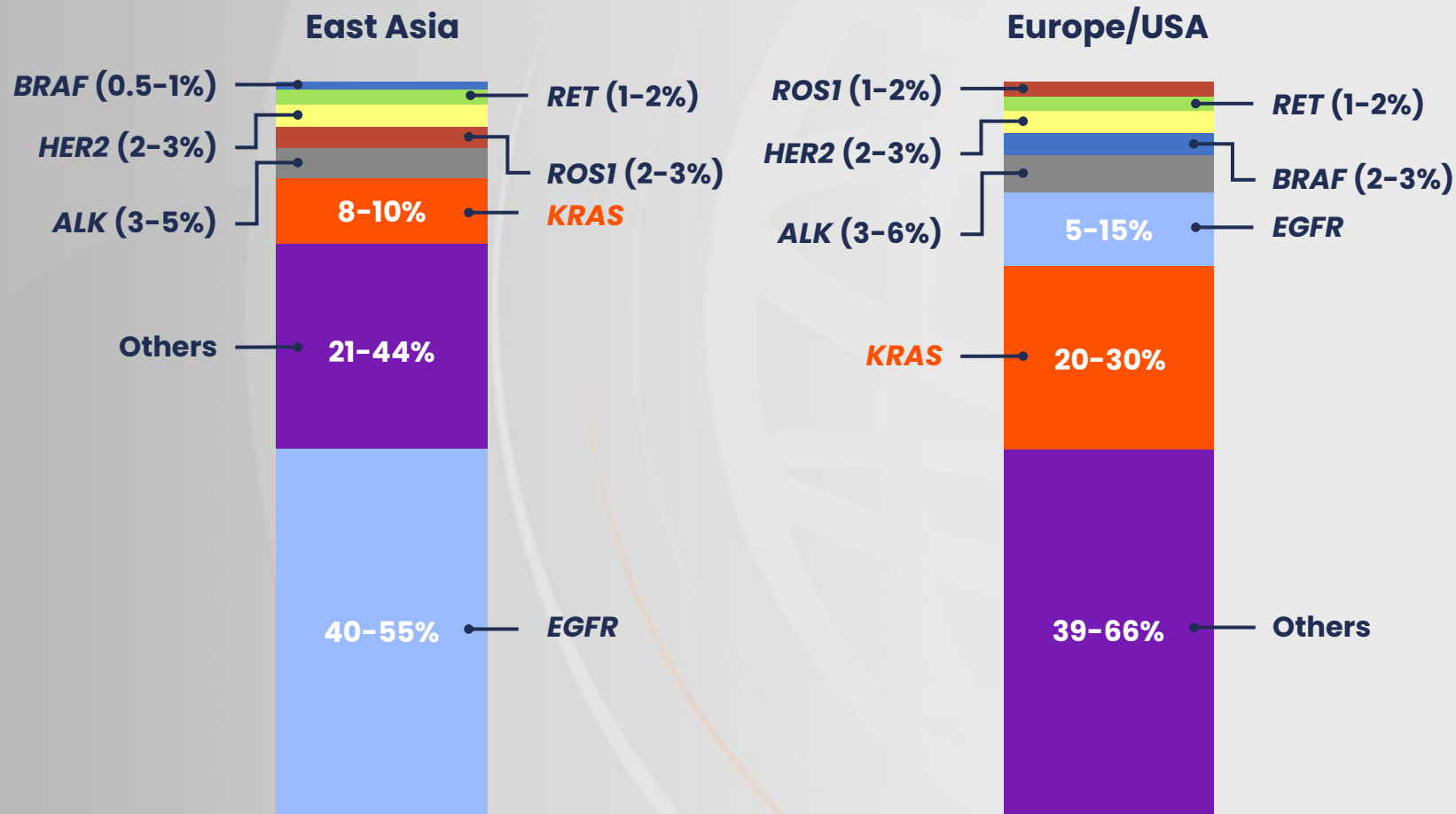
Potential targetable mutations in lung carcinomas

Spectrum of actionable mutations in lung carcinomas globally



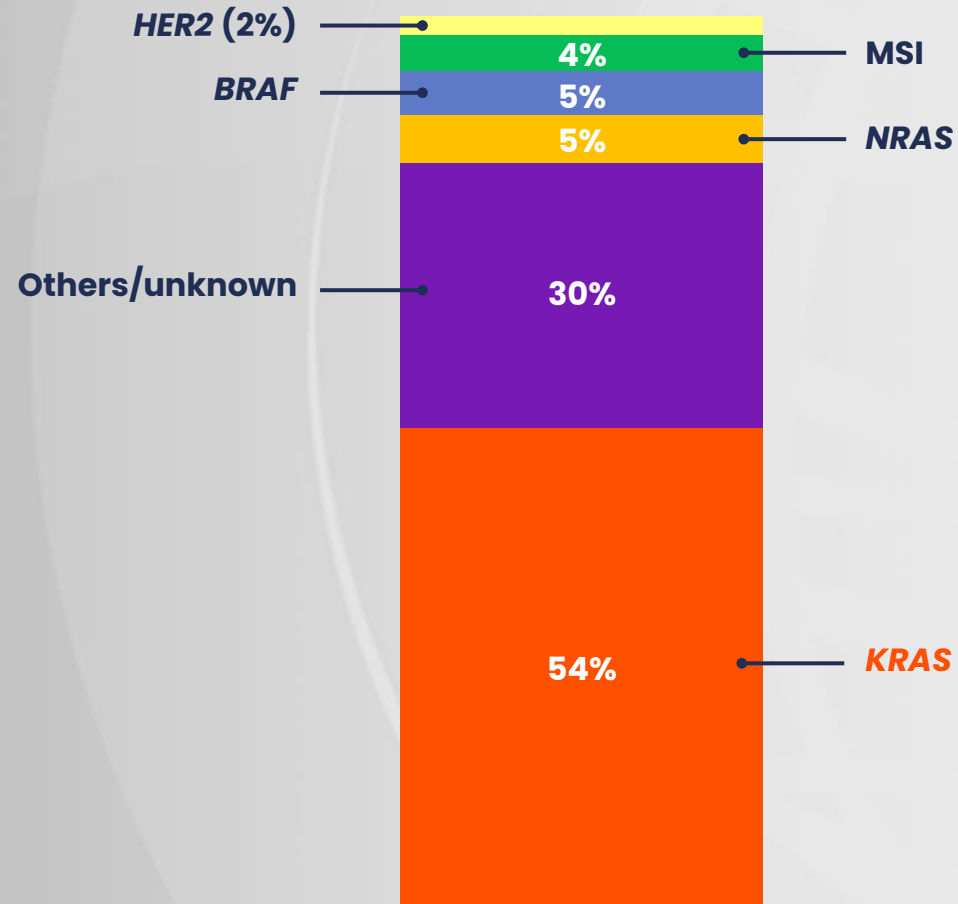
Potential targetable mutations in lung adenocarcinoma

Spectrum of actionable mutations in East Asia and Western populations



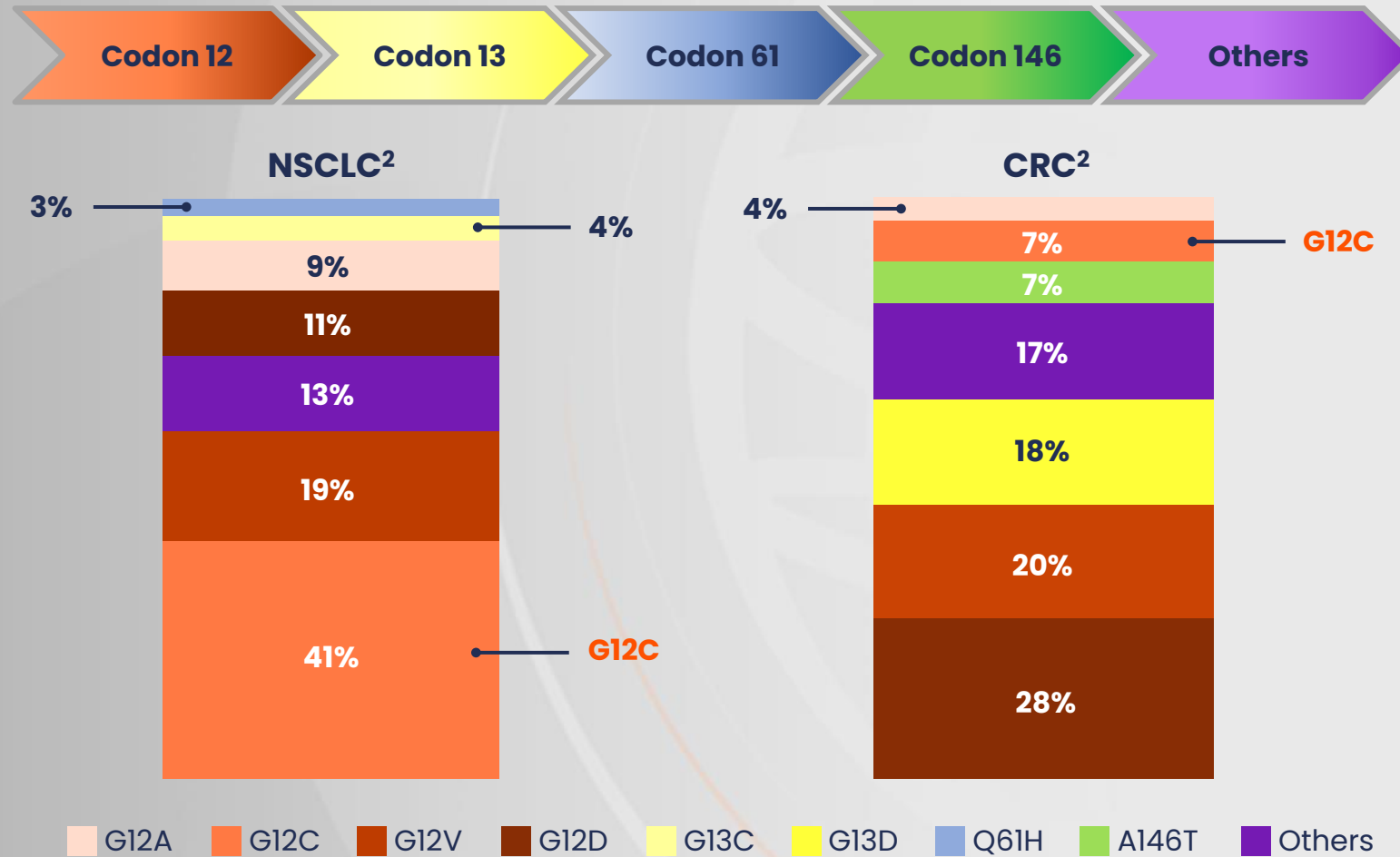
Potential targetable mutations in CRC

Spectrum of actionable mutations in CRC globally



Activating *KRAS* mutations

KRAS 'hotspot' codons¹



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

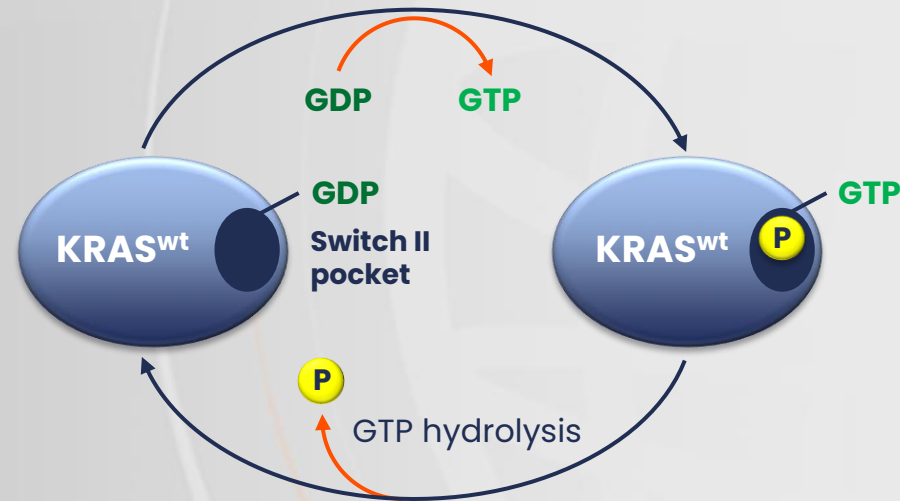
1. Cook JH, et al. *Nat Commun.* 2021;12:1808; 2. Huang L, et al. *Signal Transduct Target Ther.* 2021;6:386.

KRAS GTPase activity

GEFs and GAPs control KRAS activation and inactivation

GEFs (guanine nucleotide exchange factors)

SOS1, SOS2, GRB2, SHC1-4, RASGRP1-4,
RAPGEF1-2, RADGRF1-2



GAPs (GTPase activation protein)

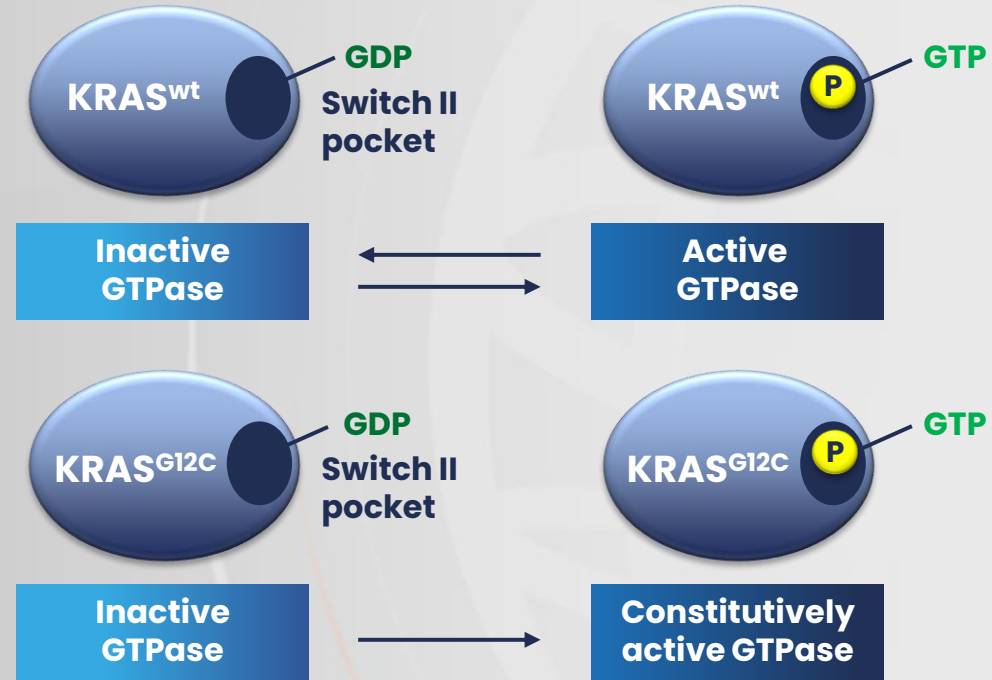
RASA1-3, RASAL1-3, DAB2IP, NFI,
SPRED1-3, SYNGAP1

Inactive state

Active state

The $KRAS^{G12C}$ mutation

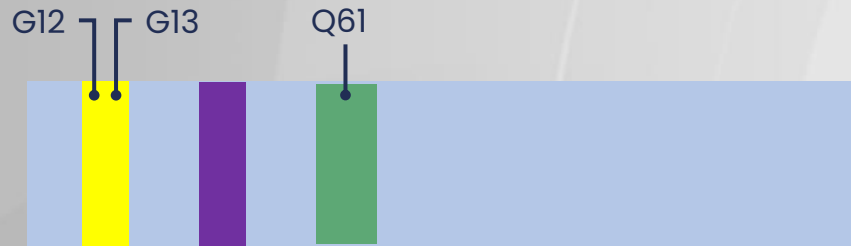
Signal transduction through the $KRAS^{G12C}$ protein



- 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 escape²

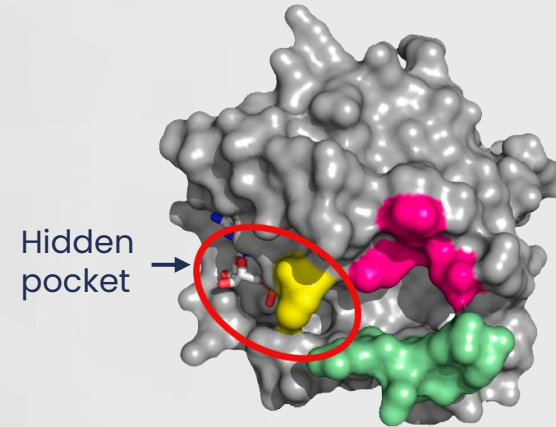
Not all *KRAS* mutations are the same

Key *KRAS* mutations at codons 12, 13 and 61 affect *KRAS* GTP binding¹



- Yellow: GTP binding
- Purple: Switch I: Effector/GAP interaction
- Green: 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 site²

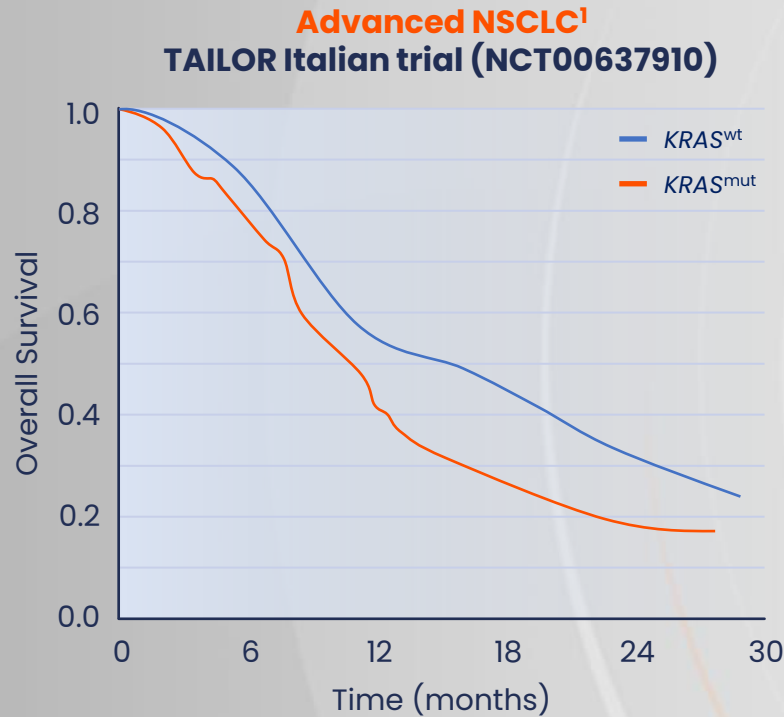


- Yellow: Phosphate binding loop
- Green: Switch II and helix 2
- Pink: Helix 3

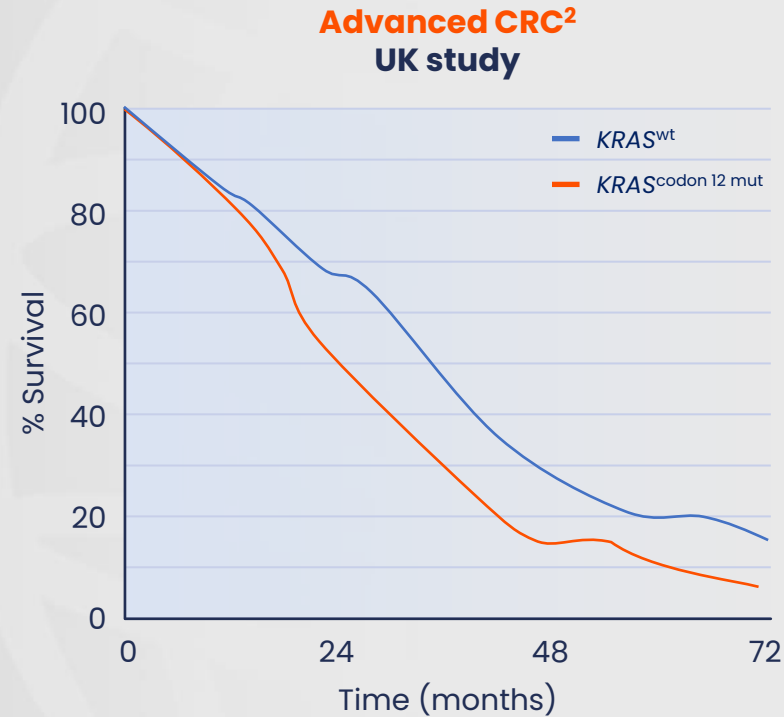
- Covalent binding of small molecules prevents the conversion of mutant *KRAS* to its active state³

KRAS mutations as a prognostic factor in NSCLC and CRC

Prognostic effect of KRAS mutations relative to wt



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



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

Predictive biomarker testing in advanced NSCLC

ESMO, JLCS and NCCN guideline recommendations



Molecular subtyping is necessary for therapeutic decision making¹⁻³



Systematic testing of *EGFR* and *BRAF* mutations; analysis of *ALK*, *ROS1* and *NTRK* rearrangements; and determination of PD-L1 expression¹⁻³



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

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

Testing for *KRAS* mutations

Recommended methodologies

 DNA or RNA is extracted from tissue specimens¹

 Plasma samples can be used when tumour tissue is insufficient or unobtainable¹

	PCR ^{1,2}	NGS ¹
	<ul style="list-style-type: none">• Turnaround time 1-2 days*• Low limits of detection ~1%• Less-costly equipment and infrastructure• Reduced hands-on time	<ul style="list-style-type: none">• Provides comprehensive molecular profiling<ul style="list-style-type: none">– Codons 12, 13, and 61 routinely detected• High accuracy of 98%
	<ul style="list-style-type: none">• May not identify specific mutations	<ul style="list-style-type: none">• Time-consuming and long reporting times• Not accessible to all³

*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

CRC³

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

Conclusions

KRAS mutations are common in NSCLC and CRC and occur in four hotspot codons: 12, 13, 61 or 146¹

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;

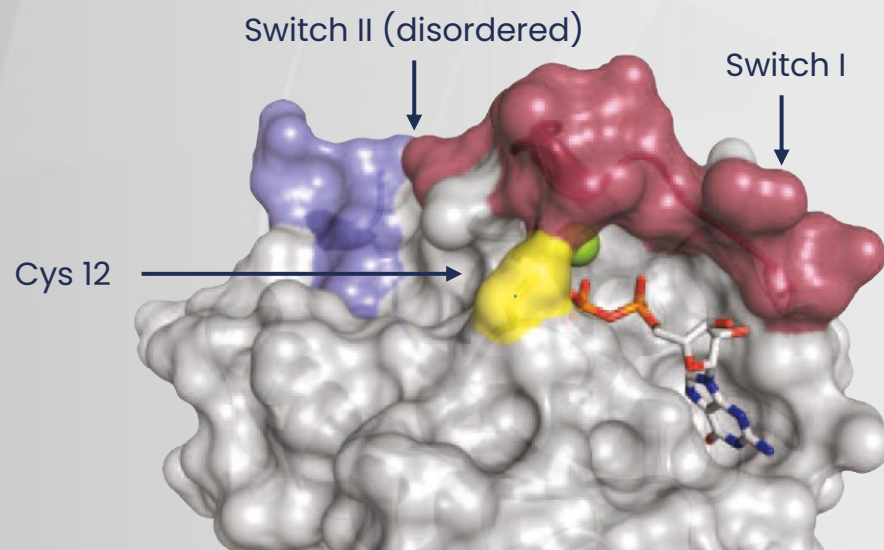
5. Akamatsu H, et al. *Int J Clin Oncol*. 2019;24:731-70; 6. NCCN. NCCN Guidelines: Colon cancer. Version 1.2022. Available at: https://www.nccn.org/guidelines/category_1

(accessed 10 May 2022); 7. Yoshino T, et al. *Ann Oncol*. 2018;29:44-70.

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

KRAS^{G12C} crystal structure

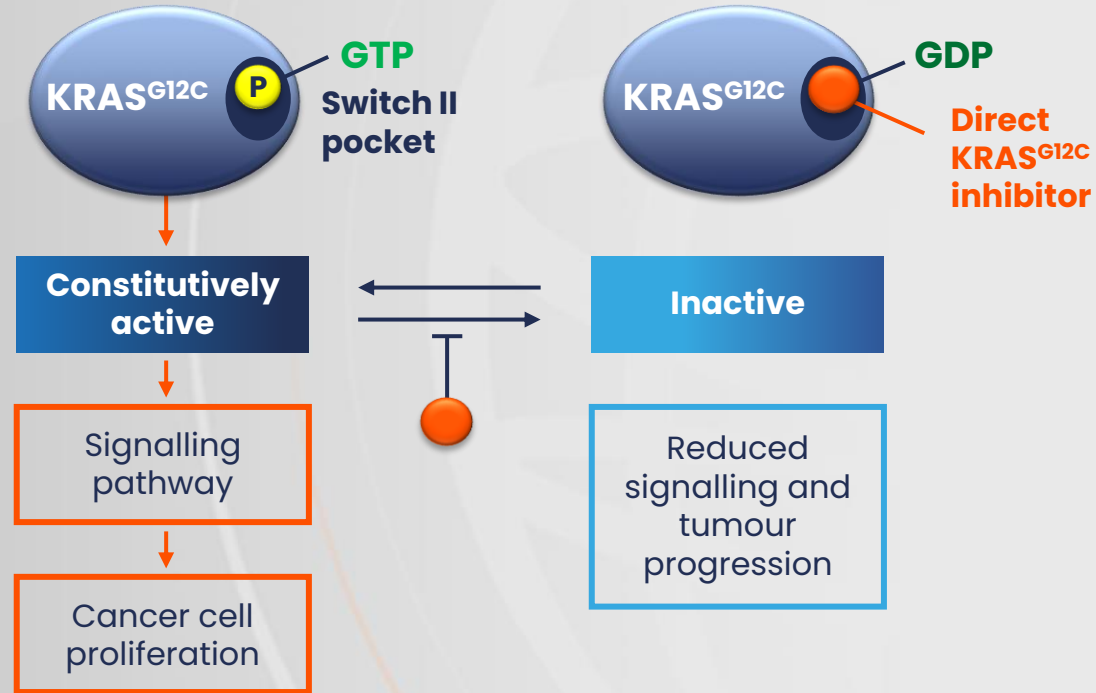
Switch II pocket¹



- 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 regions¹

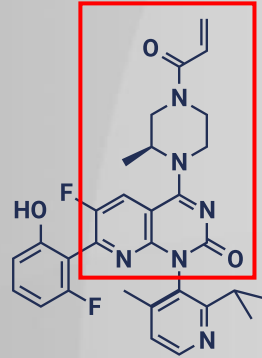
Direct KRAS^{G12C} inhibitors: Mechanism of action

Targeting the switch II pocket

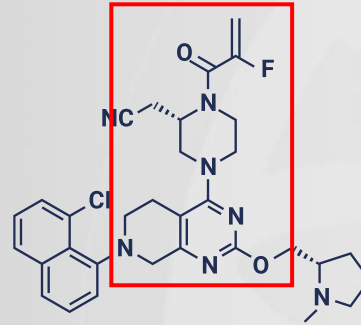


Direct KRAS^{G12C} inhibitors

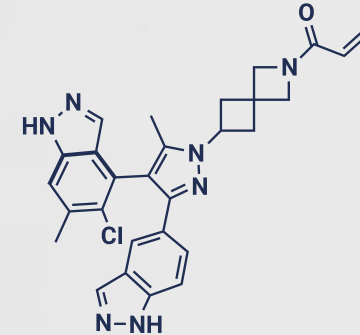
Chemical structures^{1,2}



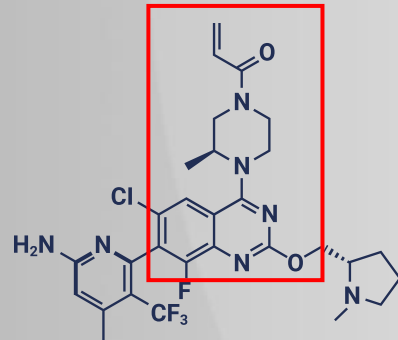
Sotorasib



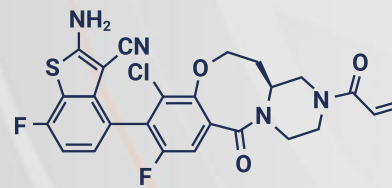
Adagrasib



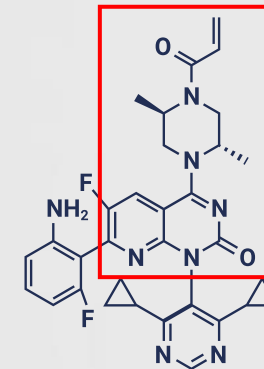
JDQ443



GDC-6036



LY3537982



D-1553

Direct KRAS^{G12C} inhibitors

Active clinical trials and approval status¹

KRAS ^{G12C} inhibitor	Ongoing clinical trials	Approval status
Sotorasib	CodeBreakK 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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Adagrasib	KRYSTAL-1 , -2, -7, -10, -12 , -14	Investigational, phase III
JDQ443	KontRASt-01 , -02 , -03	Investigational, phase III
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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 monotherapy¹
 - 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 monotherapy²
 - 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 monotherapy³
 - ORR, 9.7%
 - mDOR, 4.2 months
 - mPFS, 4.0 months
 - mOS, 10.6 months

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 monotherapy¹



- 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 monotherapy²

- 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%)

Sotorasib monotherapy: First-line in NSCLC

CodeBreak 201: Phase II open-label study



- **NCT04933695**
- **Study start:** January 2022
- **Estimated completion:** August 2023



Sotorasib 960 mg daily

Sotorasib 240 mg daily



N=170

Adults with untreated,*
stage IV NSCLC and
KRAS^{G12C} mutation,
PD-L1 <1% and/or *STK11*
co-mutation

**Primary
endpoint: ORR
up to 6 years**

*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).

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 monotherapy¹
 - 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 monotherapy²
 - 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 monotherapy³
 - 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/II** dose-finding study in 25 patients¹
 - 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 monotherapy²
 - 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 monotherapy³
 - 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.

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%)

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

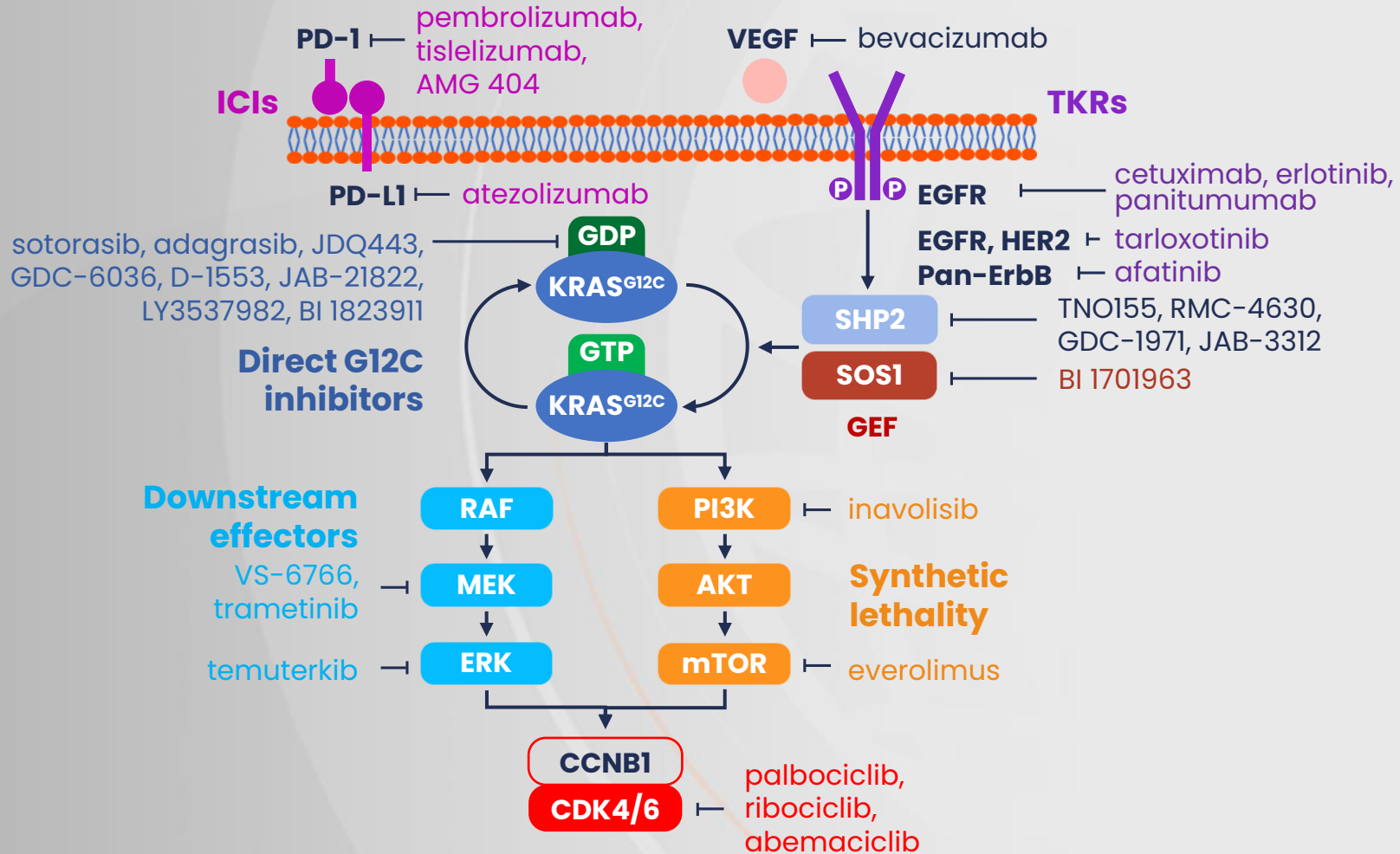
KRAS^{G12C} inhibitors vs docetaxel



	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

Potential combination strategies

Adding on to direct KRAS^{G12C} inhibitors to overcome resistance¹⁻³



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.

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 CRC¹⁻⁵

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 tumours⁹

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 progression¹



Response

- ~50% of patients in clinical trials with sotorasib/adagrasib do not experience significant tumour shrinkage¹



Disease progression

- ~10% of patients experience primary disease progression
- All patients who initially experience an objective response or stable disease will eventually progress¹

Intrinsic resistance

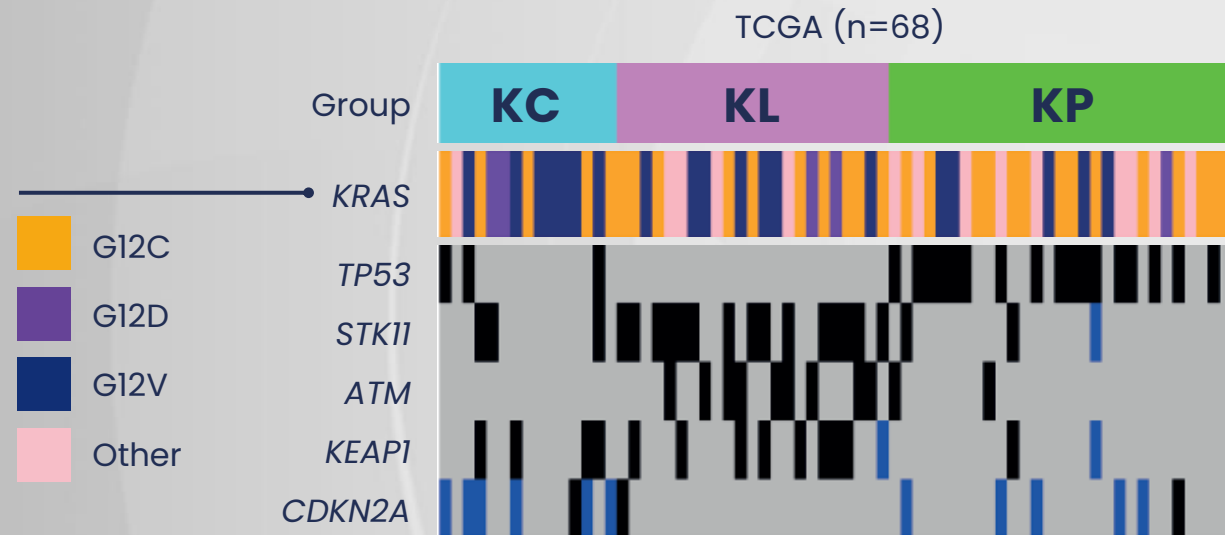
Secondary *KRAS* mutations mean another effector perpetuates the signalling²

Acquired resistance

Driven by the selective pressure of the therapy¹

KRAS and co-mutations

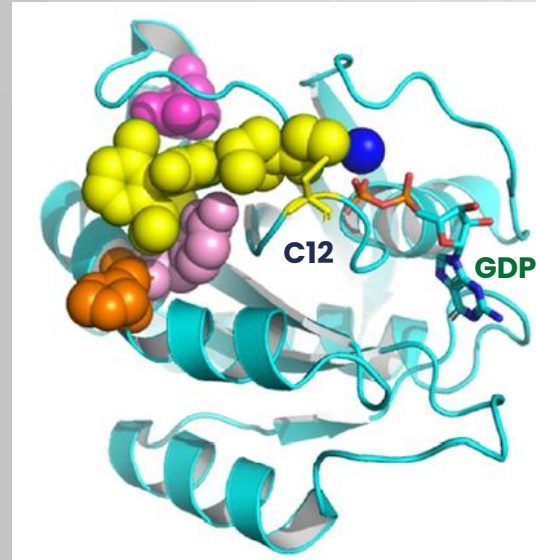
Identification of co-mutations in lung adenocarcinoma



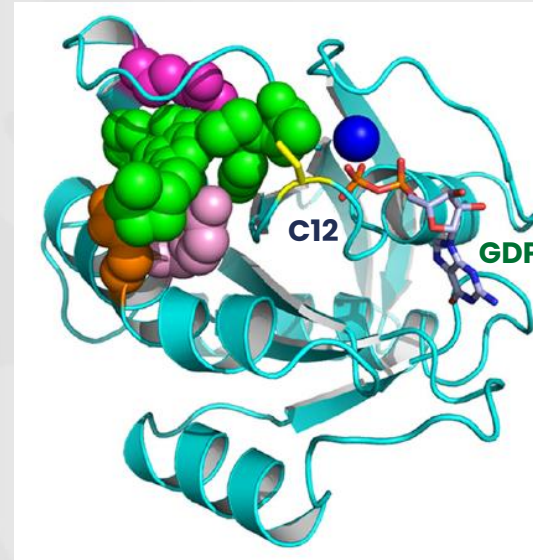
- **KC subgroup:** *CDKN2A/B* inactivation plus low *TTF1*
- **KL subgroup:** *STK11/LKB1* mutation
- **KP subgroup:** *TP53* mutation

Resistance to direct KRAS^{G12C} inhibitors

Acquired missense mutation in KRAS^{G12C} inhibitor binding sites¹⁻²



Sotorasib



Adagrasib

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

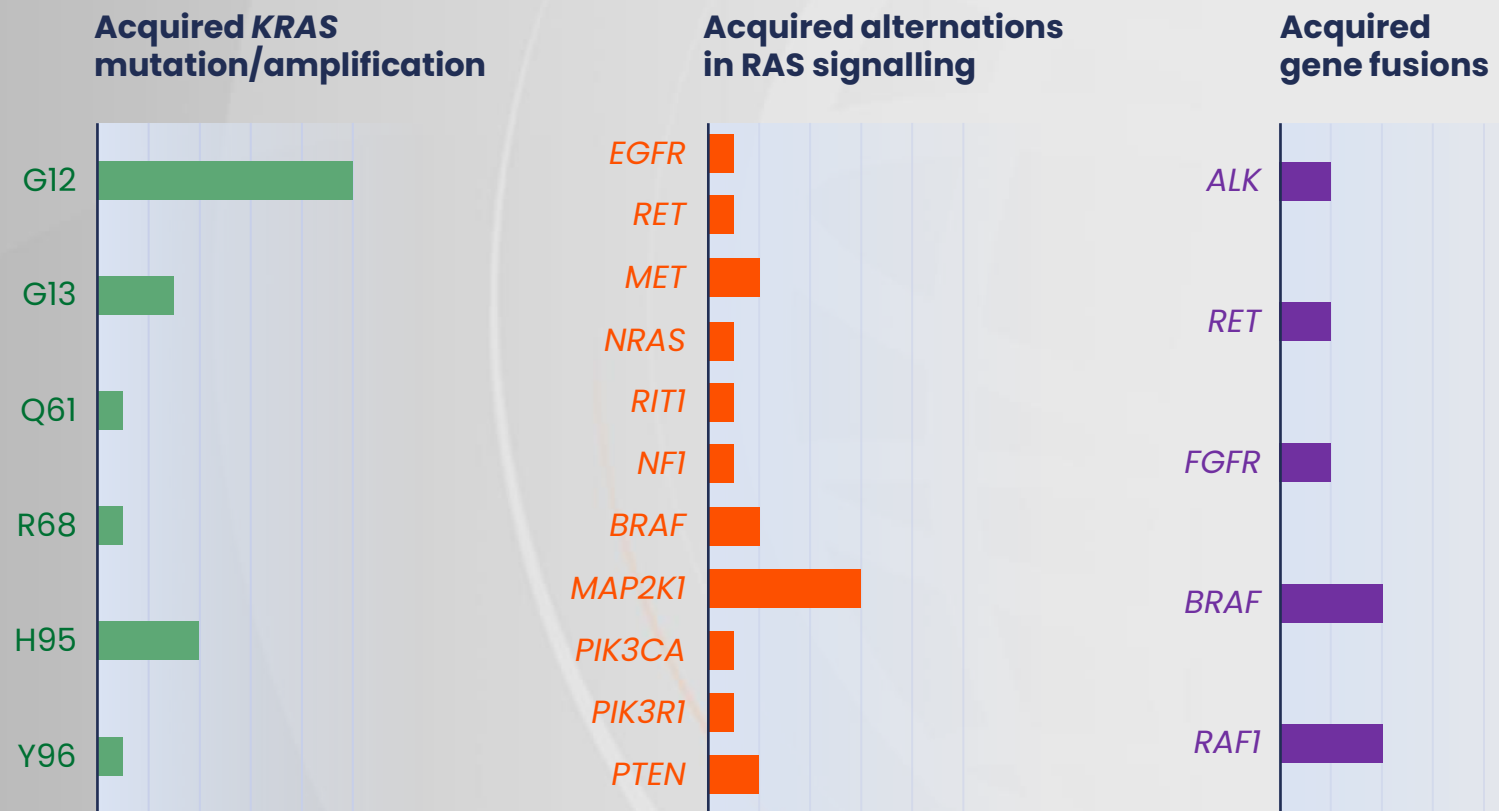
- Acquired mutations at R68, H95 and Y96 in the S1IP prevent adagrasib binding
- Activating mutations, e.g. G12D/V/R, G13D and Q61H
- High-level amplification of the *KRAS*^{G12} allele

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*

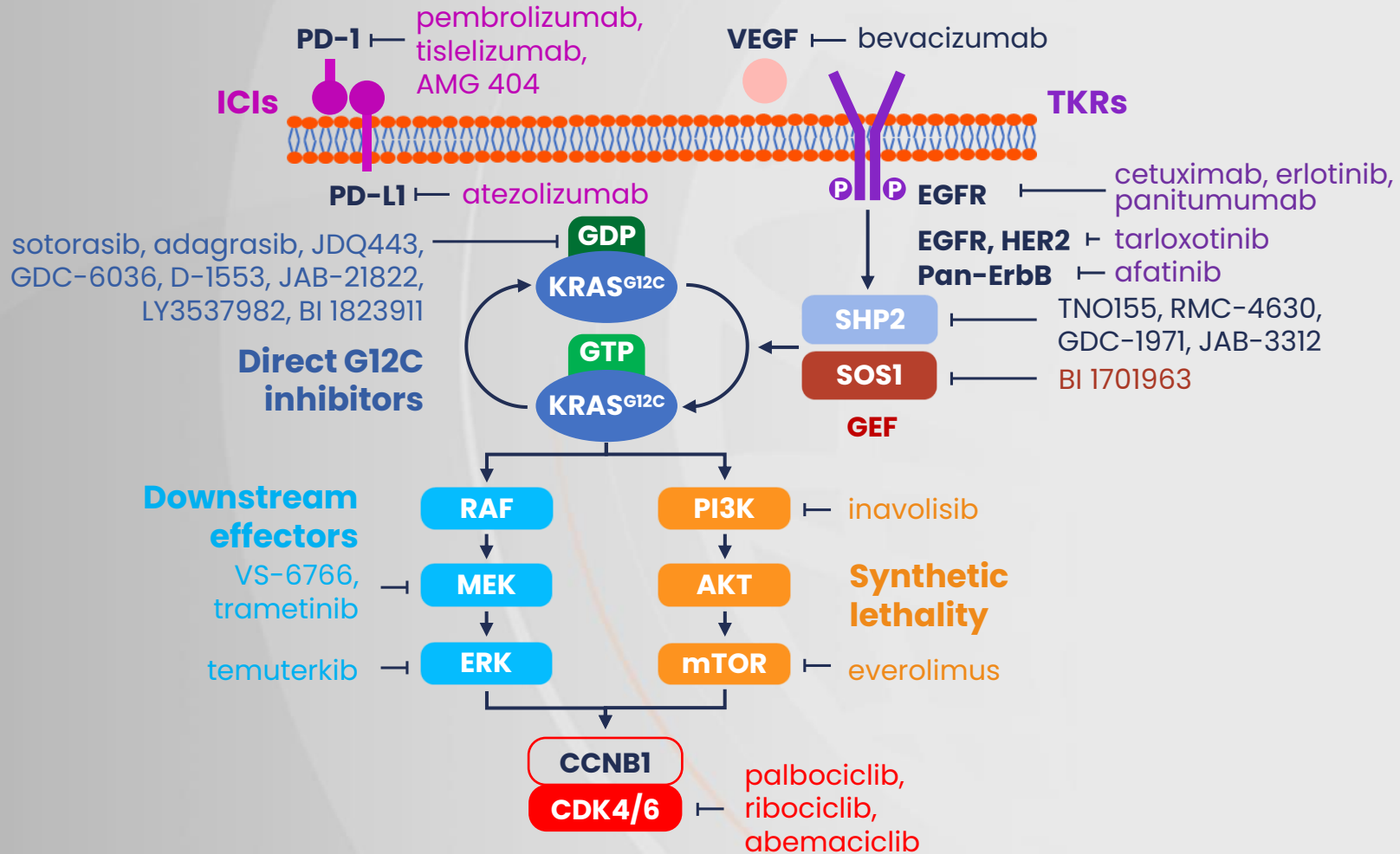
Resistance to direct KRAS^{G12C} inhibitors

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



Potential combination strategies

Adding on to direct KRAS^{G12C} inhibitors to overcome resistance¹⁻³



Direct KRAS^{G12C} inhibitor combinations

Sotorasib clinical trials

Trial details	Combination agent(s)	Results
<p>CodeBreak 101 NCT04185883</p> <ul style="list-style-type: none"> Phase Ib/II Solid tumours 	<ul style="list-style-type: none"> AMG 404 Trametinib RMC-4630 Afatinib Pembrolizumab Panitumumab Atezolizumab Everolimus Palbociclib Bevacizumab TNO155 FOLFIRI, FOLFOX Carboplatin-pemetrexed-docetaxel 	<p>Sotorasib + afatinib (NSCLC)</p> <ul style="list-style-type: none"> No new AEs observed ORR 20.0–34.8%¹ <p>Sotorasib + trametinib (solid tumours)</p> <ul style="list-style-type: none"> No new AEs observed mDOR, 84 days² <p>Sotorasib + panitumumab (CRC)</p> <ul style="list-style-type: none"> No new AEs observed mDOR, 4.4 months³ <p>Primary completion: Aug 2024</p>
<p>NCT05054725</p> <ul style="list-style-type: none"> Phase II NSCLC 	RMC-4630	Primary completion: Mar 2023
<p>RAMP203 NCT05074810</p> <ul style="list-style-type: none"> Phase I/II NSCLC 	VS-6766	Primary completion: Dec 2023
<p>NCT05313009</p> <ul style="list-style-type: none"> 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. Fakhri 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	<ul style="list-style-type: none"> • Pembrolizumab • Cetuximab • Afatinib 	Adagrasib + cetuximab (CRC) <ul style="list-style-type: none"> • 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

Direct KRAS^{G12C} inhibitor combinations

JDQ443 clinical trials

Trial details	Combination agents	Results
KontRASt-01 NCT04699188 <ul style="list-style-type: none">Phase I/IISolid tumours	<ul style="list-style-type: none">TNO155,Tislelizumab	Primary completion: Aug 2024
KontRASt-03 NCT05358249 <ul style="list-style-type: none">Phase I/IISolid tumours	<ul style="list-style-type: none">TrametinibRibociclibCetuximab	Study start: Jul 2022 Primary completion: Apr 2025

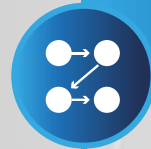
Direct KRAS^{G12C} inhibitor combinations

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	<ul style="list-style-type: none">• Atezolizumab• Erlotinib• Cetuximab• GDC-1971• Bevacizumab• Inavolisib	Primary completion: Aug 2023
LY3537982 NCT04956640 • Phase I	<ul style="list-style-type: none">• Abemaciclib• Erlotinib• Pembrolizumab• LY3295668• Cetuximab• TNO155• Temuterkib	Primary completion: Oct 2023
BI1823911 NCT04973163 • Phase I	BI 1701963	Primary completion: Jun 2024

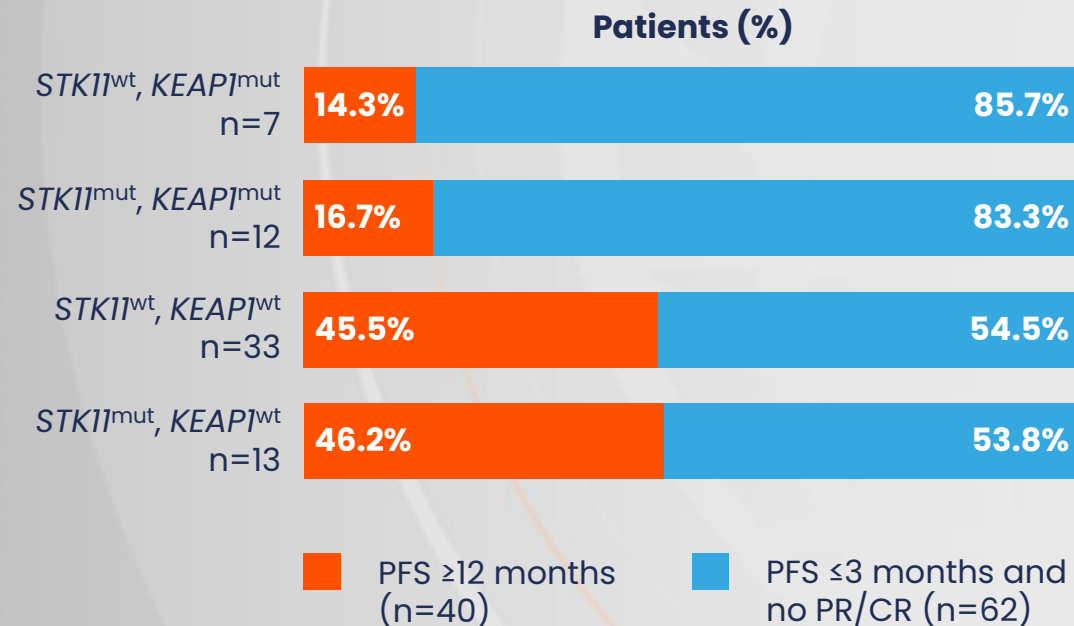
Biomarkers in patients with $KRAS^{G12C}$ mutations

Can biomarkers help to optimize treatment outcomes?



Biomarker selection

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



Novel approaches to targeting KRAS

Different target sites and mechanisms

GDP/GTP KRAS^{G12C} inhibitor¹

- 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 inhibitor⁴

- **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

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).