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

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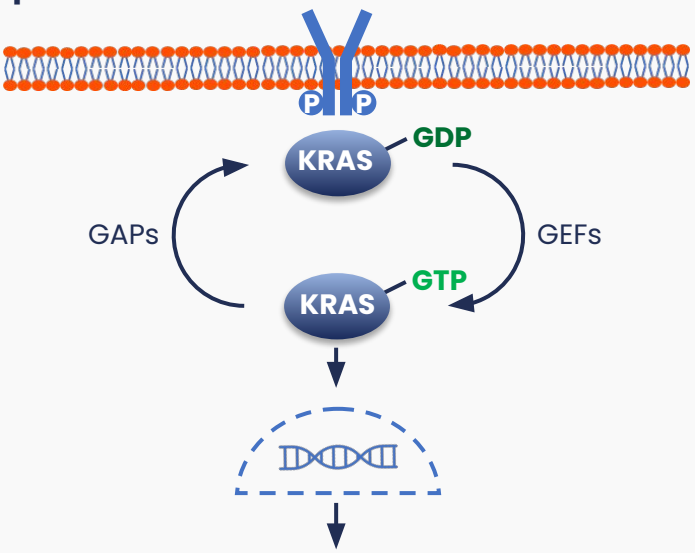
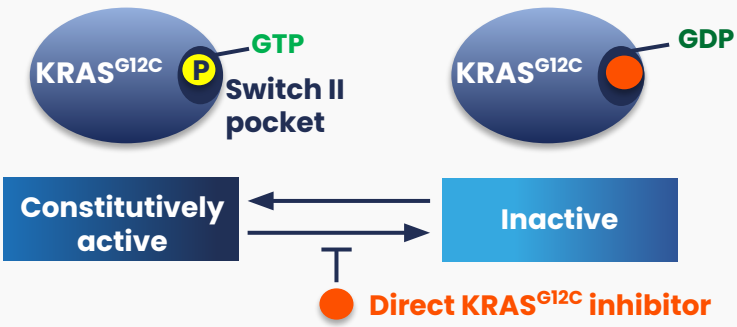
Why target KRAS in solid tumours?

KRAS signalling controls cell survival and proliferation[1,2]



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

The KRAS switch II pocket forms the binding interface for GAPs and GEFs and represents an actionable target[6]



KRAS mutations in NSCLC and CRC

- Mutation incidence: **>30%**[3]
- ***KRAS*^{G12C}** mutations represent 41% of *KRAS* alterations in NSCLC and 7% in CRC[2]
- Associated with significantly **worse OS** relative to *KRAS*^{wt}[4,5]

Molecular subtyping guidelines[7–12]

- Molecular subtyping is recommended for NSCLC and CRC and informs treatment decisions
- Only the NCCN currently recommend testing for *KRAS* mutations in advanced NSCLC and metastatic CRC
- According to JSMO-ESMO guidelines, *RAS* testing to confirm *RAS*^{wt} status in CRC is mandatory before treatment with cetuximab or panitumumab
- Recommendations are likely to evolve as novel KRAS-targeted treatments become available
- *KRAS* mutations can be detected by PCR and NGS

Key KRAS^{G12C} inhibitors[6]	Ongoing clinical trials	Approval status
Sotorasib	CodeBreaK 100, 101, 105, 200, 201, Lung-MAP	Approved in the EU[13] and Japan[14] 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, GDC-6036, LY3537982, BI 1823911 and JAB-21822		Investigational, phase I/II

Clinical trials with direct KRAS^{G12C} inhibitors

Sotorasib monotherapy efficacy and safety data (CodeBreaK 100)[15–17]

Advanced NSCLC: 2-year data (N=174)[15]
- ORR, 40.7%
- mPFS, 6.3 months
- mOS, 12.5 months

Advanced CRC: phase II data (N=62)[16]
- ORR, 9.7%
- mPFS, 4.0 months
- mOS, 10.6 months

NSCLC safety data[17]

TRAEs

Grade 3/4 AEs

Most common AEs: Diarrhoea, nausea, increase in ALT and AST

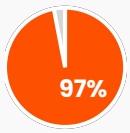
Adagrasib monotherapy efficacy and safety data (KRYSTAL-1)[18,19]

Advanced NSCLC: phase I/II data (N=116)[18]
- ORR, 43%
- mPFS, 6.5 months
- mOS, 12.6 months

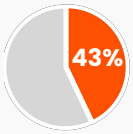
Advanced CRC: phase I/II data (N=45)[19]
- Response rate, 22%
- mPFS, 5.6 months

NSCLC safety data[18]

TRAEs



Grade 3/4 AEs



Most common AEs: Diarrhoea, nausea, vomiting, fatigue

JDQ443 monotherapy efficacy and safety data (KontRASt-01)[20]

Dose escalation study in **advanced NSCLC** (n=20) and **advanced CRC** (n=16)
- RP2D: 200 mg twice daily
- ORR for NSCLC, 57% at RP2D

Most common AEs: Fatigue, nausea, oedema, diarrhoea, vomiting

Resistance to KRAS^{G12C} inhibitors

~50% of patients in clinical trials with sotorasib/adagrasib do not experience significant tumour shrinkage[21]

All patients who initially experience an objective response or stable disease with a KRAS^{G12C} inhibitor will eventually progress[21]

Resistance to direct KRAS^{G12C} inhibitors may be caused by **co-mutations**, **acquired *KRAS* mutations** and **bypass mechanisms**[22]

Direct KRAS^{G12C} inhibitor combinations with upstream, downstream, cell cycle and immune checkpoint inhibitors are being investigated to overcome resistance[6,23–25]

Abbreviations and references

2L	Second line
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CRC	Colorectal cancer
ESMO	European Society of Medical Oncology
GAP	GTPase activating proteins
GDP	Guanosine diphosphate
GEF	Guanine nucleotide exchange factor
GTP	Guanosine triphosphate
JSMO	Japanese Society of Medical Oncology
m	median
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
RP2D	Recommended phase II dose
TRAE	Treatment-related AE
wt	wildtype

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