RAS mutations and personalized cancer care: Targeting the future

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Beyond G12C: The potential of *RAS* mutations in cancer therapy

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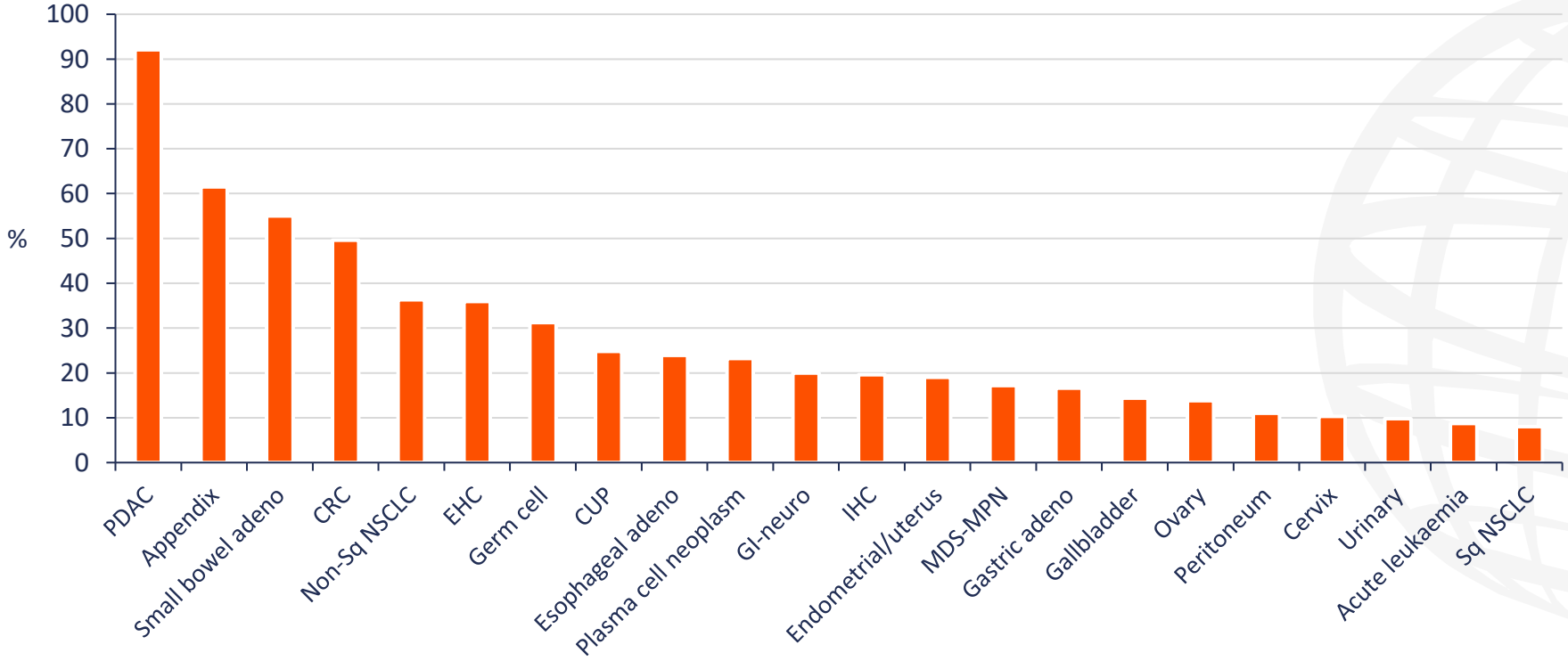
What is the epidemiology of *RAS* mutations beyond G12C and prevalence across different cancer types and patient demographics?

Prevalence of *RAS*-altered cancers



Adeno, adenocarcinoma; CRC, colorectal cancer; CUP, cancer of unknown primary; EHC, extra-hepatic cholangiocarcinoma; GI-neuro, gastrointestinal neuroendocrine; IHC, intra-hepatic cholangiocarcinoma; MDS-MPN, myelodysplastic-myeloproliferative neoplasm; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; Sq, squamous.

Lee JK, et al. *NPJ Precis Oncol.* 2022;6:91.

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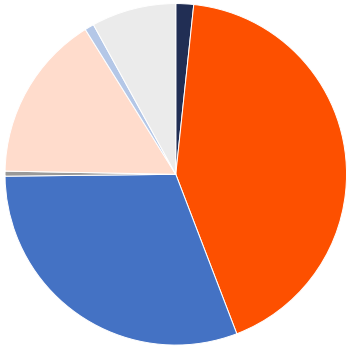
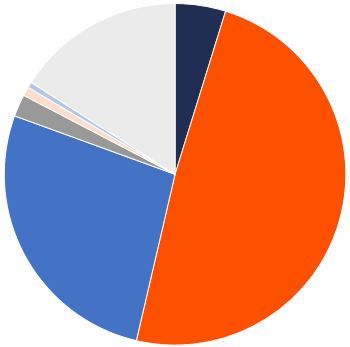
RAS mutation subtypes among common solid tumours

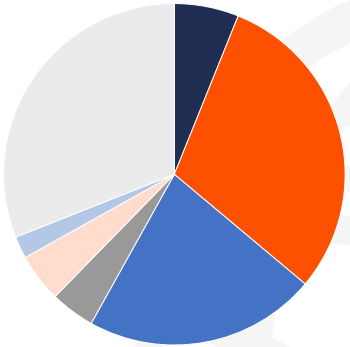
PDAC



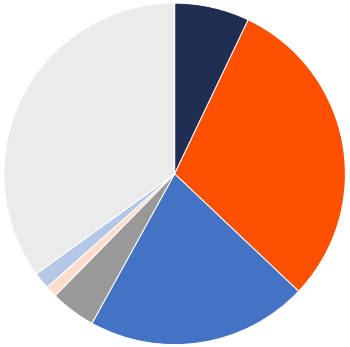
Appendiceal adenocarcinoma



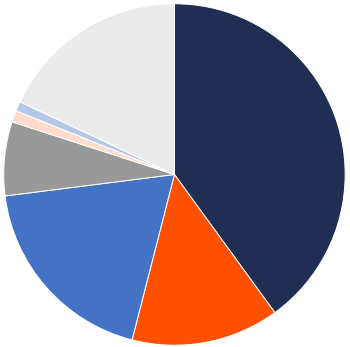
Small bowel adenocarcinoma



CRC



Non-Sq NSCLC



***KRAS* mutation subtype**

- G12C
- G12D
- G12V
- G12A
- G12R
- Multiple mutations
- Other *KRAS* mutation

CRC, colorectal cancer; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; Sq, squamous.
Lee JK, et al. *NPJ Precis Oncol.* 2022;6:91.

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What are best practices for establishing *RAS* mutation in solid tumours?

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Challenges associated with *RAS* testing

- *RAS* testing on tumour tissue samples presents several practical challenges, including poor tissue quality, lack of standardization of testing methodologies and delays in treatment
- A single-site tissue sample obtained at diagnosis may not fully represent disease heterogeneity and may not be informative of *RAS* mutation status
- Locating appropriate tissue specimens for mutational testing at the time of therapy selection can present challenges and delay administration of therapy
- The rapid turn-around time of ctDNA *RAS* mutational testing may overcome some of the limitations of tissue testing and enable timely initiation of first-line therapy

ctDNA, circulating tumour DNA.

Germetaki T, et al. *Future Oncol.* 2020;16:2177–89.

How does *RAS* mutation profiling enable treatment selection across multiple tumour types?

Selected *RAS*-directed therapy approaches

- A number of therapeutic strategies for targeting oncogenic RAS, are currently in clinical development:

Mutant-specific direct KRAS inhibitors	SHP2 inhibitors	Adoptive cell therapy
Pan-RAS inhibitors	RAS degraders	Cancer vaccines
SOS1 inhibitors	RAS toxins	*KRAS* siRNAs

siRNA, small interfering RNA.

Punekar SR, et al. *Nat Rev Clin Oncol.* 2022;19:637–55.

Call to action: Why is it important to test for *RAS* mutations?

Pancreatic cancer: Opportunities and challenges for *RAS*-targeted therapies

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What are the current challenges in treating pancreatic cancer?

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Challenges in treating pancreatic cancer

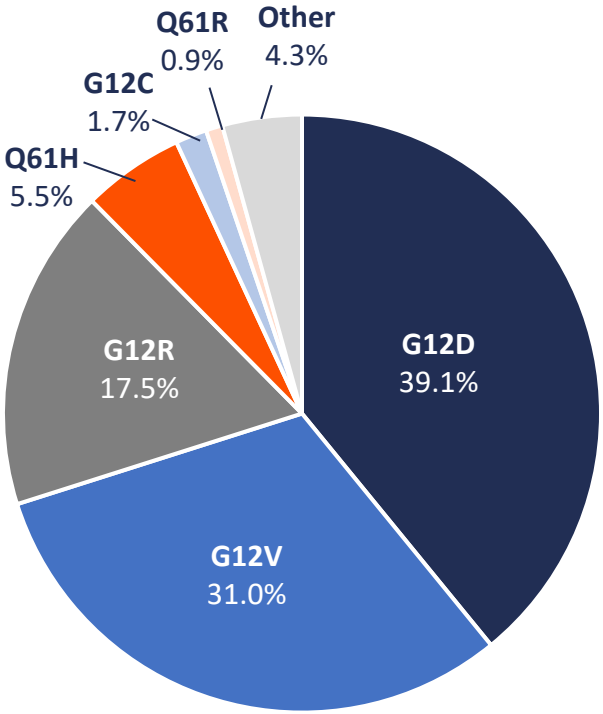
- At diagnosis 50–55% of patients have metastases[1]
- Only 15–20% of patients are eligible for potentially curative surgery at diagnosis[2]
- Recurrence rate is high after resection, suggesting the presence of micrometastases in patients with apparently localized tumours[2]
- Effective treatment options are limited, and tumours often develop resistance to therapy which is thought to be partly driven by a multifaceted tumour microenvironment[2–4]

1. Park W, et al. *JAMA*. 2021;326:851–62; 2. Grossberg AJ, et al. *CA Cancer J Clin.* 2020;70:375–403; 3. Long SA, et al. *Front Oncol.* 2024;14:1402128; 4. Zhen DB, et al. *Ther Adv Gastroenterol.* 2023;16:1–25.

What is the role of *RAS* mutation in pancreatic cancer?

KRAS variants in pancreatic cancer

Distribution of *KRAS* variants in clinical samples (n=348)



Approximately **85–95%** of PDAC cases have a ***KRAS* mutation**

G12D, G12V, G12R, Q61H and G13D account for **~ 95% of cases**

PDAC, pancreatic ductal adenocarcinoma.

Nusrat F, et al. *J Clin Med*. 2024;13:2103.

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Why is it important to test for *RAS* mutations in patients with pancreatic cancer?

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NCCN guidelines for molecular profiling in pancreatic cancer

Recommended:	Tumour/somatic molecular profiling for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations
Consider specific testing for:	Fusions: ALK, NRG1, NTRK, ROS1, FGFR2, and RET Mutations: *BRAF*, *BRCA1/2*, ***KRAS*** and *PALB2* Amplifications: HER2 MSI, dMMR or TMB via an FDA-approved and/or NGS-based assay HER2 overexpression via IHC

Testing on tumour tissue preferred;
however, cell-free DNA testing can be considered if tumour tissue testing not feasible

dMMR, mismatch repair deficiency; FDA, Food and Drug Administration; IHC, immunohistochemistry; MSI, microsatellite instability; NGS, next-generation sequencing; TMB, tumour mutational burden.

NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. Version 3.2024. Available at: www.nccn.org/guidelines/ (accessed 10 December 2024).

What are your thoughts on future directions for *RAS*-targeted therapies for pancreatic cancer?

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RAS G12C inhibitors in clinical trials in pancreatic cancer

Trial info	Treatment	Efficacy		Safety
KRYSTAL-1[1] **Phase I/II** **n=21**	**Adagrasib**	**ORR**: 33.3% **DCR**: 81.0% **mTTR**: 1.4 months*	**DOR**: 5.3%* **mPFS**: 5.4 months **mOS**: 8.0 months	TRAEs ≥20% patients: nausea (42.9%), diarrhoea (47.6%), fatigue (41.3%) and vomiting (39.7%)
CodeBreaK100[2] **Phase I/II** **N=38**	**Sotorasib**	**ORR**: 21.0% **DCR**: 84.0% **mTTR**: 1.5 months	**DOR**: 5.7% **mPFS**: 4.0 months **mOS**: 6.9 months	Most frequently occurring TRAEs (in 5% of patients): diarrhoea and fatigue
GO42144[3] **Phase I** **n=7**	**Divarasib (GDC-6036)**	**Partial response:** 42.9%	**Stable disease:** 57.1%	Mainly low-grade GI AEs that were reversible and manageable with supportive medications
LOXO-RAS-20001[4] **Phase I/II** **n=24**	**Olomorasib (LY3537982)**	**ORR**: 40%† **DCR**: 90%†	**mPFS**: 4–9 months*	TRAEs ≥10% patients: diarrhoea (24%), fatigue (10%) and nausea (10%)

*For the overall population of patients with solid tumours.
†In 88 patients with non-CRC tumours.
AE, adverse event; CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; GI, gastrointestinal; m, median; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related AE; TTR, time to response.
1. Bekaii-Saab TS, et al. *J Clin Oncol.* 2023;41:4097–106; 2. Strickler JH, et al. *N Engl J Med.* 2023;388:33–43; 3. Sacher A, et al. *N Engl J Med.* 2023;389:710–21;
4. Heist RS, et al. *J Clin Oncol.* 2024;42(Suppl. 16);3007.

Pan-RAS and RAS allele-specific inhibitors in clinical trials in pancreatic cancer

Trial info	Treatment	Efficacy	Safety
RMC-6236-001[1] **Phase I** **n=22** (G12D, n=13; G12V, n=7; G12R, n=2)	**RMC-6236** Pan-RAS(ON) inhibitor	**ORR:** 36%* **DCR:** 86%* **mTTR:** 6 weeks	TRAEs occurring in 10% of patients: rash (52%), diarrhoea (21%), nausea (21%) and vomiting (15%)
RMC-9805-001[2] **Phase I** **n=104** KRAS G12D mutations	**RMC-9805** RAS(ON) G12D-selective inhibitor	**ORR:** 30%† **DCR:** 80%†	Tolerability was favourable relative to SOC chemotherapy for PDAC and manageable across all dose levels and tumour types evaluated. Most common TRAEs (≥10% of patients): nausea (27%), diarrhoea (20%), vomiting (15%) and rash (10%); all grade 1/2 severity.

- **Ongoing phase III study: RASolute 302** (NCT06625320) evaluating safety and efficacy of RMC-6236 compared with SOC treatment[3]

*In 14 patients (10 PDAC, 4 NSCLC) dosed at least 8 weeks prior to the data cut-off date.
†In 40 patients with PDAC receiving RMC-9805 daily at 1,200 mg and enrolled at least 14 weeks prior to data cut-off.
DCR, disease control rate; mTTR, median time to response; ORR, objective response rate; PDAC, pancreatic ductal adenocarcinoma; SOC, standard of care; TRAE, treatment-related adverse event.
1. Arbour KC, et al. *Ann Oncol.* 2023;34(Suppl. 2):S458; 2. Hong DS, et al. *Eur J Cancer* 2024;211S1:114980; 3. ClinicalTrials.gov. NCT06625320. Available at: www.clinicaltrials.gov/study/NCT06625320 (accessed 7 January 2025).

NSCLC: Current and future perspectives on the use of *RAS*-targeted therapies

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Why is it important to test for *RAS* mutations in patients with NSCLC?

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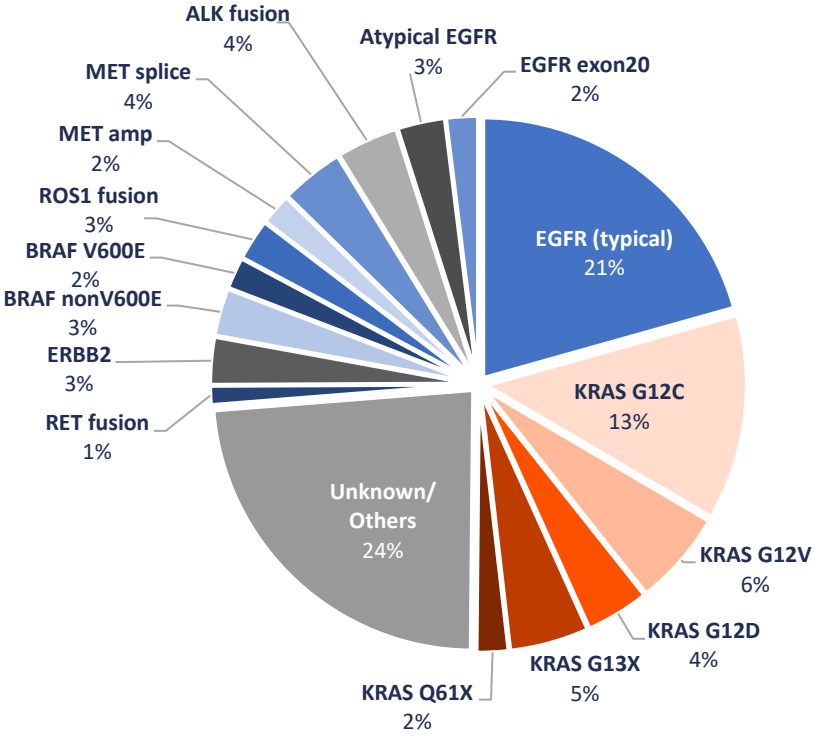
RAS mutations are common in NSCLC[1]



- ***KRAS* mutations occur in ~30% of NSCLC[2]**
- *KRAS* mutations are prognostic of poor survival[3]
- Until recently, these mutations were considered "undruggable"[2]
- With the approval of KRAS G12C-selective inhibitors sotorasib and adagrasib, ***KRAS* is now a druggable target[4]**

NSCLC, non-small cell lung cancer.

1. Friedlaender, et al. *Biomark Res.* 2024;12:24; 2. Sreter KB, et al. *Front Oncol*. 2024;14:357898; 3. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 2.2025. Available at: www.nccn.org/guidelines/ (accessed 8 January 2025); 4. Lim TKH, et al. *Lung Cancer*. 2023;184:107293.

What are the key challenges with respect to *RAS* mutation testing in NSCLC and potential solutions?

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Molecular profiling in NSCLC: NCCN Guidelines

NCCN 2025 recommendations for biomarker testing in advanced non-squamous NSCLC[1]

Immunotherapy

- PD-L1

Targeted therapy

- *EGFR*
- *ALK*
- *ROS1*
- ***KRAS G12C***
- *NTRK1/2/3*
- *BRAF*
- *MET exon 14*
- *EGFR exon 20*
- *ERBB2 (HER2)*
- *RET*

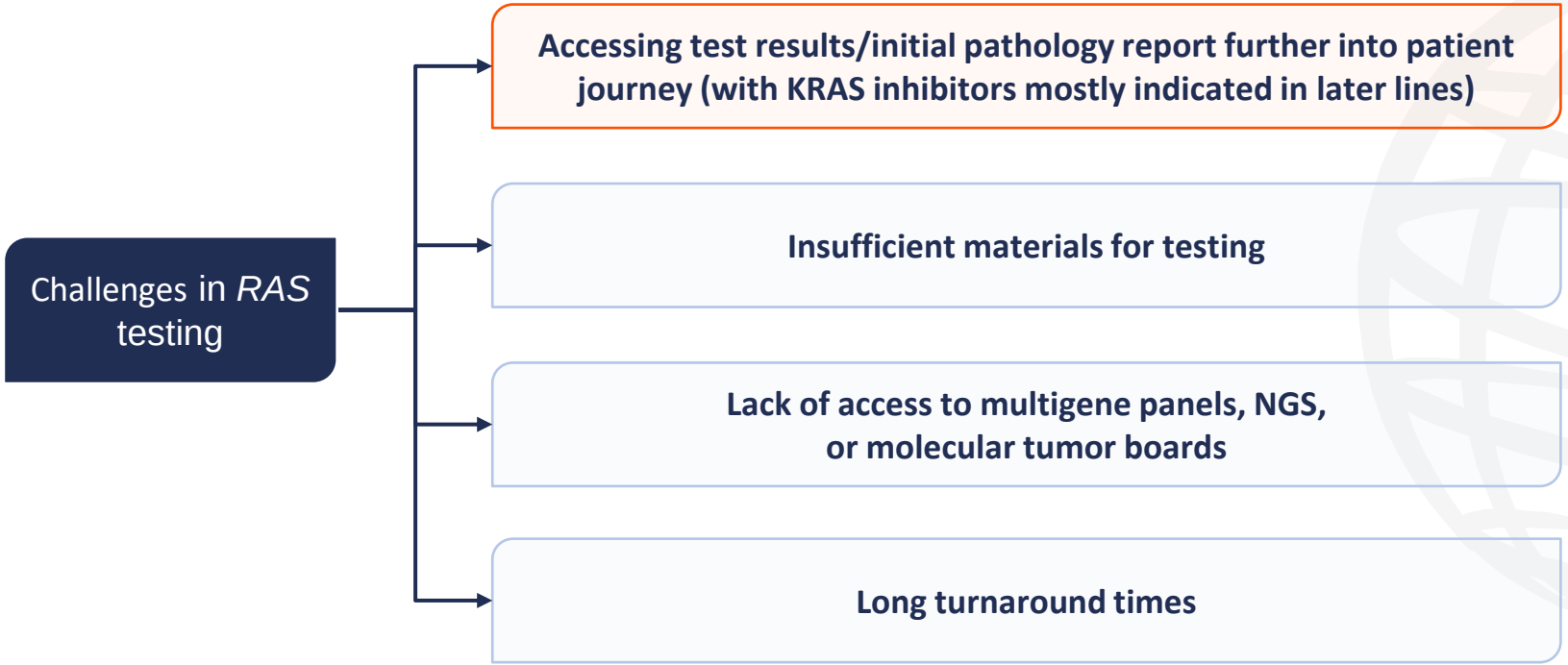
Broad molecular profiling is strongly recommended[1]

KRAS G12C should be part of routine biomarker testing and reporting prior to first-line therapy[2]

EGFR, epidermal growth factor receptor; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1.

1. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 2.2025. Available at: www.nccn.org/guidelines/ (accessed 8 January 2025);
2. Lim TKH, et al. *Lung Cancer*. 2023;184:107293.

Challenges to *RAS* testing in clinical practice



NGS, next-generation sequencing.
Lim TKH, et al. *Lung Cancer*. 2023;184:107293.

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What are the clinical benefits and limitations observed with current KRAS G12C inhibitors?

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Available KRAS G12C inhibitors in pre-treated NSCLC

Phase III Trial	Treatment Arms	Efficacy			Safety	
		ORR (%)	mPFS (months)	PFS HR (95% CI)	Grade ≥3 TRAEs (%)	Most common grade ≥3 TRAEs*
KRYSTAL-12 (N=453)[1,2]	**Adagrasib**	**32**	**5.5**	0.58 (0.45–0.76)	**47.0**	**Diarrhoea, vomiting, nausea, ALT/AST increases**
	Docetaxel	9	3.8		45.7	
CodeBreaK 200 (N=345)[3]	**Sotorasib**	**28.1**	**5.6**	0.66 (0.51–0.86)	**33**	**Diarrhoea, ALT/AST increases**
	Docetaxel	13.2	4.5		40	

Limited responses, 30–40% PFS benefit

*Occurring in >5% of patients in the treatment arm.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; m, median; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TRAE, treatment-related adverse event.

1. Mok TSK, et al. *J Clin Oncol.* 2024:42(Suppl. 17);LBA8509; 2. Luo FX, Arter ZL. *Lung Cancer (Auckl).* 2024;15:161-167; 3.de Langen AJ, et al. *Lancet.* 2023;401:733–46.

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What are the emerging options targeting *KRAS* G12C and beyond?

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Emerging KRAS G12C inhibitors in pre-treated NSCLC

Agent	Phase	N (NSCLC)	ORR (%)
RMC-6291[1]	I	KRAS-naïve = 10 KRAS-treated = 7	43 50
Divarasib[2]	I	60	53.4
Olomorasib[3]	I/II	39[a]	41[a]
MK-1084[4]	I	54[b]	22[b]
IBI351[5]	II	116	49.1
Glecirasib[6]	II	119	47.9
Garsorasib[7]	II	123	50

All listed agents had favourable/manageable safety profiles in early trials in pretreated patients[1-7], with some now initiating phase III trials[2,8]

[a]Forty-two patients were naïve to KRAS G12C inhibitors, and 41 had received a KRAS G12C inhibitor as their prior line of therapy. The ORR reported here is in patients who received KRAS G12C inhibitor. b Total population with solid tumours; 11/54 had NSCLC. ORR is for entire population; 5 of 11 patients with NSCLC had a PR.
NSCLC, non-small cell lung cancer; ORR, objective response rate, PR: partial response.

1. Sreter KB, et al. *Front Oncol.* 2024;14:1357898; 2. Brazel D, Nagasaka M. *Target Oncol.* 2024;19:297–301; 3. Heist R, et al. ASCO 2024. Abstract 3007; 4. Rojas CI, et al. ESMO Open. 2024;9:102273; 5. Zhou Q, et al. WCLC 2024. Abstract OA14.05; 6. Shi Y, et al. ASCO 2024. Abstract 468214; 7. Li Z, et al. *Lancet Respir Med.* 2024;12:589–98; 8. Clinicaltrials.gov NCT06345729. Available at: https://clinicaltrials.gov/study/NCT06345729 (Accessed 14 January 2025).

Emerging KRAS inhibitors with targets beyond G12C in pre-treated NSCLC

Multi-RAS Inhibition

Agent	Phase	N (NSCLC)	MOA	ORR (%)	Safety
RMC-6236[1]	I	46	On-state inhibitor	38	Most common TRAEs: Rash and GI-related toxicities (mostly grade 1/2)

KRAS G12D Inhibition

Agents in ongoing clinical trials[2]

- HRS-4642
- RMC-9805
- MRTX1133

GI, gastrointestinal; MOA, mechanism of action; NSCLC, non-small cell lung cancer; ORR, objective response rate; TRAEs, treatment-related adverse events.

1. Filis P et al. *Drug Discov Today*. 2025;30:104250; 2. Sreter KB, et al. *Front Oncol*. 2024;14:1357898.