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RAS mutations and personalized cancer care: Targeting the future

Practice aid for the treatment of *RAS*-mutant cancer

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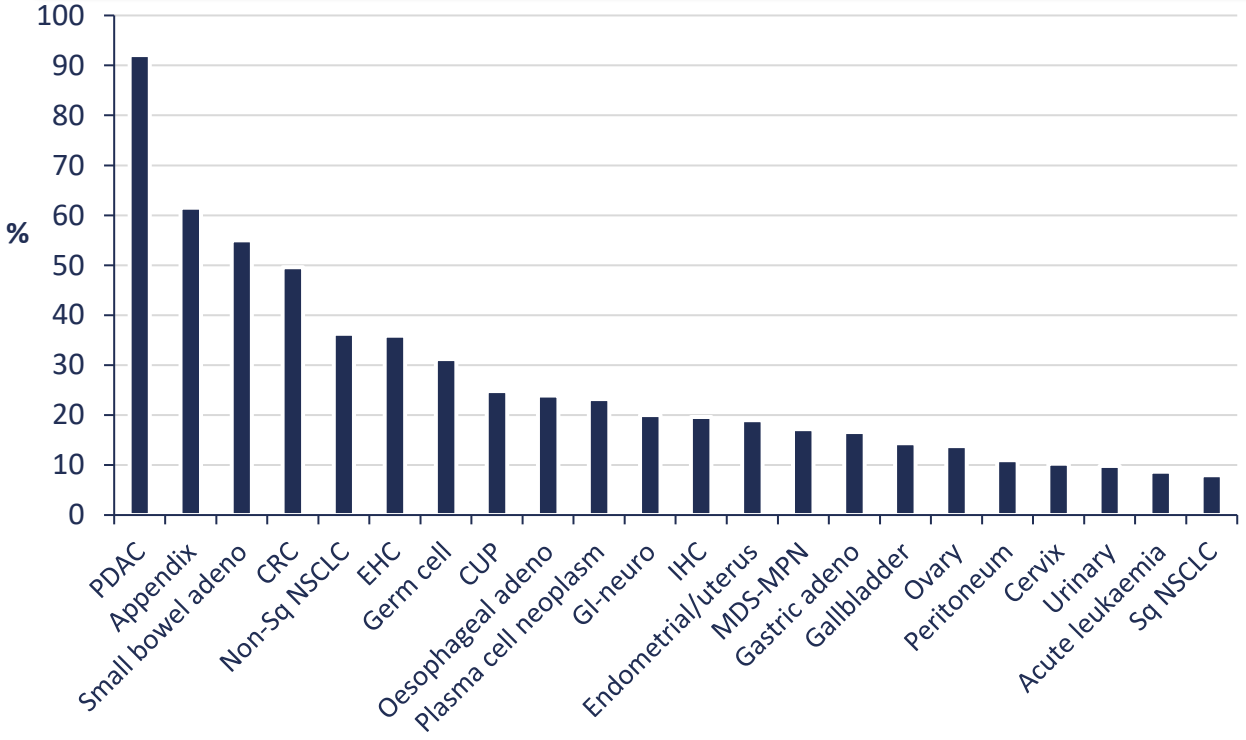
Prevalence of *RAS*-altered cancers[1]

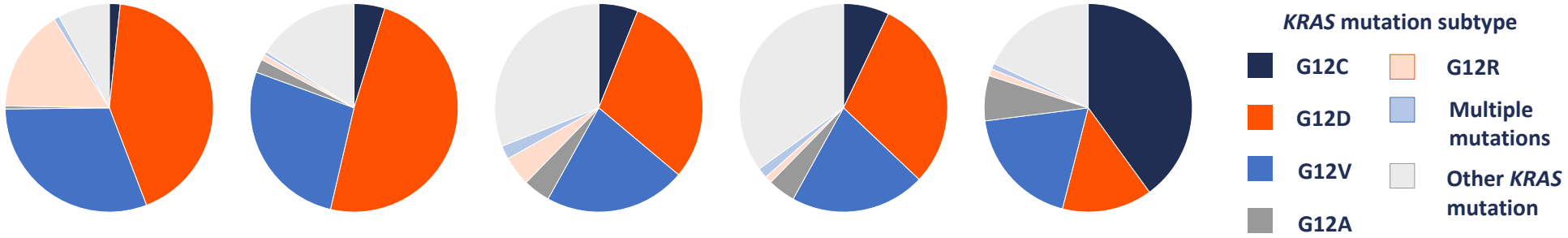


Future *RAS*-directed approaches[2]

Therapeutic strategies for targeting oncogenic *RAS* are currently in clinical development:

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

RAS mutation subtypes among common solid tumours[1]



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Pancreatic cancer

Latest NCCN guidelines for molecular profiling in pancreatic cancer[3]

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 immunohistochemistry

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

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

Trial info	Treatment	Efficacy	Safety
RMC-6236-001[4] **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[5] **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

*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.

NSCLC

Latest NCCN guidelines for molecular profiling in NSCLC[6]

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[6]

KRAS G12C should be part of routine biomarker testing and reporting prior to first-line therapy[7]

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

Multi-RAS inhibition

Agent	Phase	N (NSCLC)	MOA	ORR (%)	Safety
RMC-6236[8]	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[9]
- HRS-4642
- RMC-9805
- MRTX1133

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Abbreviations and references

Abbreviations

Adeno, adenocarcinoma; AE, adverse event; CRC, colorectal cancer; CUP, cancer of unknown primary; DCR, disease control rate; dMMR, mismatch repair deficiency; EGFR, epidermal growth factor receptor; EHC, extra-hepatic cholangiocarcinoma; FDA, Food and Drug Administration; GI-neuro, gastrointestinal neuroendocrine; HER2, human epidermal growth factor receptor 2; IHC, intra-hepatic cholangiocarcinoma; m, median; MDS-MPN, myelodysplastic-myeloproliferative neoplasm; MOA, mode of action; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; PDAC, pancreatic ductal adenocarcinoma; PD-L1, programmed death-ligand 1; SOC, standard of care; Sq, squamous; TMB, tumour mutational burden; TRAE, treatment-related AE; TTR, time to response.

References

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4. Arbour KC, et al. *Ann Oncol.* 2023;34(Suppl. 2):S458.
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6. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 2.2025. Available at: www.nccn.org/guidelines/ (accessed 8 January 2025).
7. Lim TKH, et al. *Lung Cancer.* 2023;184:107293.
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