
Supplementary information

The current state of the art and future trends in RAS-targeted cancer therapies

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Supplementary Table 1 | Selected ongoing clinical trials targeting KRAS in advanced-stage cancers

Trial	Phase	Indication	Agent	Combination or comparator therapies	Current status and results
KRAS^{G12C} inhibitors					
CodeBreak 100 (NCT03600883)	Phase I/II	KRAS ^{G12C} -mutant solid tumours	Sotorasib (AMG 510)	With or without an anti-PD-(L)1 antibody	Phase I: ORR 32.2%; mDoR 10.9 months; mPFS 6.3 months. Phase II, NSCLC cohort: ORR 37.1%; mDoR 11.1 months; mPFS 6.8 months; mOS 12.5 months; Grade ≥3 TRAE rate: 20.6%. PDAC cohort: ORR 21.1%. CRC cohort: ORR 9.7%
CodeBreak 101 (NCT04185883)	Phase I	KRAS ^{G12C} -mutant solid tumours	Sotorasib	With or without various drugs (trametinib and/or panitumumab, AMG 404, RMC-4630 (SAR442720), afatinib, pembrolizumab, panitumumab ± FOLFIRI, atezolizumab, carboplatin/pemetrexed /docetaxel/ pembrolizumab, palbociclib, everolimus, bevacizumab-awwb + FOLFIRI or FOLFOX, or TNO155)	Recruiting
CodeBreak 200 (NCT04303780)	Phase III	Previously treated KRAS ^{G12C} -mutant NSCLC	Sotorasib	Versus docetaxel	Active, not recruiting
CodeBreak 201 (NCT04933695)	Phase II	Previously untreated KRAS ^{G12C} -mutant stage IV NSCLC	Sotorasib	NA	Recruiting
Lung-MAP cohort (NCT04625647)	Phase II	Previously treated KRAS ^{G12C} -mutant nonsquamous NSCLC	Sotorasib	NA	Recruiting
MERIT-lung (NCT05398094)	Phase II	Unresectable stage III KRAS ^{G12C} -mutant NSCLC in patients ineligible for chemoradiotherapy	Sotorasib	NA	Recruiting
RAMP203 (NCT05074810)	Phase I/II	Previously treated and untreated KRAS ^{G12C} -mutant NSCLC	Sotorasib	With VS-6766	Recruiting
CodeBreak 105 (NCT04380753)	Phase I	KRAS ^{G12C} -mutant solid tumours in patients of Chinese descent	Sotorasib	NA	Active, not recruiting
SOLUCOM (NCT05311709)	Phase II	KRAS ^{G12C} -mutant NSCLC in patients with comorbidities	Sotorasib	NA	Recruiting
NCT05054725	Phase II	KRAS ^{G12C} -mutant NSCLC	Sotorasib	With RMC-4630	Recruiting
NCT05400577	Phase II	Stage IB–IIIA KRAS ^{G12C} -mutant NSCLC	Sotorasib (neoadjuvant)	NA	Not yet recruiting
NCT05180422	Phase I/II	KRAS ^{G12C} -mutant NSCLC with asymptomatic brain metastasis	Sotorasib	With MVASI	Recruiting

CodeBreak 300 (NCT05198934)	Phase III	Previously treated <i>KRAS</i> ^{G12C} -mutant CRC	Sotorasib	With panitumumab, compared to investigator choice of regorafenib, or trifluridine and tipiracil	Recruiting
NCT05374538	Phase I	<i>KRAS</i> ^{G12C} -mutant NSCLC	Sotorasib	With VIC-1911	Not yet recruiting
NCT05313009	Phase I/II	<i>KRAS</i> ^{G12C} -mutant NSCLC previously treated with <i>KRAS</i> inhibitors	Sotorasib	With tarloxotinib	Recruiting
NCT05118854	Phase II	Stage IIA–IIIB <i>KRAS</i> ^{G12C} -mutant NSCLC	Sotorasib (neoadjuvant)	With platinum and pemetrexed chemotherapy	Recruiting
NCT05251038	Phase I/II	<i>KRAS</i> ^{G12C} -mutant PDAC	Sotorasib	With liposomal irinotecan and 5-FU and leucovorin, or gemcitabine and nab- paclitaxel	Not yet recruiting
NCT04892017	Phase I/II	<i>KRAS</i> ^{G12C} -mutant NSCLC	Sotorasib	With DCC-3116	Recruiting
HERKULES-2 (NCT04959981)	Phase I/II	<i>KRAS</i> ^{G12C} -mutant NSCLC	Sotorasib	With ERAS-601	Recruiting
NCT04720976	Phase I/II	Advanced-stage solid tumours	Sotorasib	With JAB-3312	Recruiting
KRYSTAL-1 (NCT03785249)	Phase I/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	Adagrasib (MRTX849)	With or without cetuximab, afatinib or pembrolizumab	Phase II NSCLC cohort: ORR 42.9%; mDoR 8.5 months; mPFS: 6.5 months; mOS 12.6 months; grade ≥3 TRAE rate: 3%. NSCLC brain metastases cohort: intracranial ORR 33.3%. Pancreatic and non- CRC GI cancer cohort: ORR 41%; DCR 100%. CRC cohort: ORR 22% with monotherapy, 43% in combination with cetuximab.
KRYSTAL-2 (NCT04330664)	Phase I/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	Adagrasib	With or without TNO155	Active, not recruiting
KRYSTAL-7 (NCT04613596)	Phase II	Previously untreated <i>KRAS</i> ^{G12C} -mutant NSCLC	Adagrasib	With or without pembrolizumab	Recruiting
KRYSTAL-10 (NCT04793958)	Phase III	Second-line treatment of <i>KRAS</i> ^{G12C} -mutant CRC	Adagrasib	With cetuximab versus either FOLFOX or FOLFIRI alone	Recruiting
KRYSTAL-12 (NCT04685135)	Phase III	Previously treated <i>KRAS</i> ^{G12C} -mutant NSCLC	Adagrasib	Versus docetaxel	Recruiting
KRYSTAL-14 (NCT04975256)	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	Adagrasib	With BI 1701963	Active, not recruiting
KRYSTAL-16 (NCT05178888)	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	Adagrasib	With palbociclib	Recruiting
RAMP204 (NCT05375994)	Phase I/II	<i>KRAS</i> ^{G12C} -mutant NSCLC previously treated with <i>KRAS</i> inhibitors	Adagrasib	With VS-6766	Not yet recruiting
NCT05263986	Phase I	Chinese patients with <i>KRAS</i> ^{G12C} -mutant solid tumours	Adagrasib	NA	Recruiting

NCT04418661	Phase I	<i>KRAS</i> ^{G12C} -mutant NSCLC	Adagrasib	With RMC-4630	Recruiting
NCT04449874	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	RG6330 (GDC-6036)	With or without atezolizumab, cetuximab, bevacizumab, erlotinib, GDC-1971 or inavolisib	Recruiting
D1553-101/ KEYNOTE-C15 (NCT04585035)	Phase Ib/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	D-1553	With other standard treatments (TBD) in phase II	Recruiting
D1553-102 (NCT05383898)	Phase I/II	<i>KRAS</i> ^{G12C} -mutant NSCLC	D-1553	NA	Recruiting
D1553-106 (NCT05379946)	Phase I/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	D-1553	With IN10018	Not yet recruiting
KontRASt-01 (NCT04699188)	Phase Ib/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	JDQ443	With or without TNO155 and/or tislelizumab	Recruiting
KontRASt-02 (NCT05132075)	Phase III	<i>KRAS</i> ^{G12C} -mutant NSCLC, after platinum-based chemotherapy and immune-checkpoint inhibitor therapy either in sequence or in combination	JDQ443	Versus docetaxel	Recruiting
KontRASt-03 (NCT05358249)	Phase I/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	JDQ443	With trametinib, ribociclib or cetuximab	Not yet recruiting
NCT04956640	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	LY3537982	With abemaciclib, pembrolizumab, erlotinib, temuterkib, LY3295668, cetuximab or TNO155	Recruiting
NCT04973163	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	BI 1823911	With BI 1701963	Recruiting
NCT05009329	Phase I/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	JAB-21822	NA	Recruiting
NCT05194995	Phase I/II	<i>KRAS</i> ^{G12C} -mutant CRC, small intestine cancer or appendiceal cancer	JAB-21822	With cetuximab	Recruiting
NCT05002270	Phase I/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	JAB-21822	Alone or with cetuximab	Recruiting
NCT05276726	Phase I/II	<i>KRAS</i> ^{G12C} -mutant NSCLC with <i>STK11</i> co-mutation and wild-type <i>KEAP1</i>	JAB-21822	NA	Not yet recruiting
NCT05288205	Phase I/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	JAB-21822	JAB-3312	Recruiting
NCT04006301	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	JNJ-74699157 (ARS-3248)	NA	Completed
NCT05067283	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	MK-1084	Alone or with pembrolizumab	Recruiting
Pan-RAS inhibitors					
NCT05379985	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	RMC-6236	NA	Recruiting
siRNAs					
2018-0126 (NCT03608631)	Phase I	<i>KRAS</i> ^{G12D} -mutant stage IV PDAC	iExosomes (exosomes delivering siRNA targeting <i>KRAS</i> ^{G12D} mRNA)	NA	Recruiting
SOS1-KRAS interaction inhibitors					
KRYSTAL-14 (NCT04975256)	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	BI 1701963	With adagrasib	Active, not recruiting
NCT04973163	Phase I	<i>KRAS</i> -mutant- solid tumours	BI 1701963	With BI 1823911	Recruiting
1432-0001 (NCT04111458)	Phase I	<i>KRAS</i> -mutant solid tumours	BI 1701963	With or without trametinib	Active, not recruiting

<i>SHP2 inhibitors</i>					
NCT05054725	Phase II	<i>KRAS</i> ^{G12C} -mutant NSCLC	RMC-4630	With sotorasib	Recruiting
CodeBreak 101 (NCT04185883)	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	RMC-4630	With sotorasib	Recruiting
NCT04418661	Phase I	<i>KRAS</i> ^{G12C} -mutant NSCLC	RMC-4630	With adagrasib	Recruiting
NCT04916236	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	RMC-4630	With LY3214996	Recruiting
NCT03989115	Phase I/II	<i>KRAS</i> -mutant or <i>KRAS</i> -amplified solid tumours	RMC-4630	With cobimetinib	Active, not recruiting
NCT03634982	Phase I	<i>KRAS</i> -amplified solid tumours or <i>KRAS</i> ^{G12C} -mutant NSCLC	RMC-4630	NA	Recruiting
CodeBreak 101 (NCT04185883)	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	TNO155	With sotorasib	Recruiting
KRYSTAL-2 (NCT04330664)	Phase I/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	TNO155	With adagrasib	Active, not recruiting
KontRASt-01 (NCT04699188)	Phase Ib/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	TNO155	With JDQ443 ± tislelizumab	Recruiting
NCT04956640	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	TNO155	With LY3537982	Recruiting
NCT04000529	Phase I	<i>KRAS</i> ^{G12C} -mutant NSCLC or CRC	TNO155	With spartalizumab (NSCLC) or ribociclib (CRC)	Recruiting
NCT03114319	Phase I	Advanced-stage solid tumours, including <i>KRAS</i> ^{G12C} -mutant NSCLC	TNO155	NA	Recruiting
NCT04720976	Phase I/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	JAB-3312	With sotorasib	Recruiting
NCT05288205	Phase I/II	<i>KRAS</i> ^{G12C} -mutant solid tumours	JAB-3312	With JAB-21822	Recruiting
GO42144 (NCT04449874)	Phase I	<i>KRAS</i> ^{G12C} -mutant solid tumours	GDC-1971	With RG6330	Recruiting
HERKULES-2 (NCT04959981)	Phase I/II	<i>KRAS</i> ^{G12C} -mutant NSCLC	ERAS-601	With sotorasib	Recruiting
<i>Aurora Kinase Inhibitors</i>					
NCT05374538	Phase I	<i>KRAS</i> ^{G12C} -mutant NSCLC	VIC-1911	With sotorasib	Not yet recruiting
<i>ULK Inhibitors</i>					
NCT04892017	Phase I/II	<i>KRAS</i> ^{G12C} -mutant NSCLC	DCC-3116	With sotorasib	Recruiting
<i>KRAS-targeted therapeutic vaccines</i>					
V941-001 (NCT03948763)	Phase I	<i>KRAS</i> ^{G12C/G12D/G12V/G13D} -mutant NSCLC, CRC, or PDAC (with HLA-A11:01 and/or HLA-C08:02 alleles)	mRNA-5671/V941 (targeting <i>KRAS</i> ^{G12C} , <i>KRAS</i> ^{G12D} , <i>KRAS</i> ^{G12V} and <i>KRAS</i> ^{G13D})	With or without pembrolizumab	Active, not recruiting
NCT04117087	Phase I	Previously treated <i>KRAS</i> -mutant pMMR/MSS CRC, or resected PDAC (after neoadjuvant/adjuvant therapy)	Mutant <i>KRAS</i> -targeted long-peptide vaccine	With nivolumab and ipilimumab	Recruiting

UPCC 04218 (NCT03592888)	Phase I	<i>KRAS</i> ^{G12C/G12D/G12R/G12V} -mutant PDAC (resectable)	mDC3/8-KRAS vaccine (autologous mature dendritic cells pulsed with mutant KRAS peptides specific to a patient's tumour mutation and HLA type)	NA	Recruiting
AMPLIFY-201 (NCT04853017)	Phase I	<i>KRAS</i> ^{G12D/G12R} -mutant solid tumours (adjuvant treatment of minimal residual disease)	ELI-002 P2 (a mixture of two lipid-conjugated peptide-based KRAS antigens, Amph-G12D and Amph-G12R, admixed with a lipid-conjugated immune-stimulatory oligonucleotide, Amph-CpG-7909)	NA	Recruiting
Adoptive cell therapy					
ChanghaiH-PP06 (NCT04146298)	Phase I/II	<i>KRAS</i> ^{G12V} -mutant PDAC (with HLA-A*11:01 allele)	Autologous T cells transduced with <i>KRAS</i> ^{G12V} -specific TCRs	NA	Recruiting

5-FU, 5-fluorouracil; CRC, colorectal cancer; DCR, disease control rate; FOLFIRI, folinic acid, 5-fluorouracil and irinotecan; FOLFOX, folinic acid, 5-fluorouracil and oxaliplatin; GI, gastrointestinal mDoR, median duration of response; mPFS, median progression-free survival; mOS, median overall survival; MSS/pMMR, microsatellite stable/mismatch repair proficient; MRD, minimal residual disease; NA, not applicable; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PDAC, pancreatic ductal adenocarcinoma; siRNA, small interfering RNA; TBD, to be disclosed; TCRs, T cell receptors; TRAE, treatment-related adverse event.