

**Supplementary Table S1. Active clinical trials of ERK1/2 cascade inhibitors with approval for clinical use.** This list was compiled in March 2024 from clinicaltrials.gov, selecting those which are active (recruiting or not-recruiting) or for which recruiting is due to start. It may not be fully comprehensive, but is designed to highlight the most significant ongoing studies of inhibitors that have already been approved for treatment of one or more cancer.

Inhibitor	Target	Trial no. (dates, trial name, drug combinations)	Comments
Sotorasib (AMG-510)	KRAS(G12C)	<p><b>Phase 1:</b>  NCT05480865 (2022-2025; Argonaut; with BBP-398 SHP2 inhibitor)  NCT05054725 (2021-2024)  NCT06249282 (2024-2026; with carfilzomib)</p> <p><b>Phase 1/2:</b>  NCT03600883 (2018-2027; CodeBreak 100; alone or with other drugs)  NCT04185883 (2019-2027; CodeBreak 101; alone or with other drugs)  NCT05074810 (2022-2027; with sotorasib, with or without defactinib)  NCT05815173 (2023-2026; with ladarixin)</p> <p><b>Phase 2:</b>  NCT04625647 (2021-2026; Lung-MAP trial)  NCT04933695 (2022-2024; CodeBreak 201)  NCT05311709 (2022-2025; SOLUCOM)  NCT05118854 (2022-2025; with other drugs)  NCT05398094 (2022-2028)  NCT05564377 (2023-2030; ComboMATCH; alone or with panitumumab)  NCT05638295 (2024-2025; ComboMATCH; alone or with panitumumab)  NCT06333678 (2024-2027; vs durvalumab)  NCT6068153 (2024-2026; AMBER; with Lenvatinib)</p> <p><b>Phase 3:</b>  NCT04303780 (2020-2026)  NCT05198934 (2022-2025; CodeBreak 300; with panitumumab)  NCT05920356 (2023-2026; CodeBreak 202)  NCT06252649 (2024-2030; CodeBreak 301; with other drugs)</p>	<p>Covalent inhibitor [1]</p> <p>FDA accelerated approval 2021 for emergency use with advanced NSCLC [2]</p> <p>In trials for various cancers (e.g. breast cancer, colorectal cancer, NSCLC, solid tumours, thoracic tumours)</p>
Adagrasib (MRTX-849)	KRAS(G12C)	<p><b>Phase 1:</b>  NCT06039384 (2023-2025; with INCB099280)  NCT05634525 (2023-2027)</p> <p><b>Phase 1/2:</b>  NCT03785249 (2019-2024; KRYSTAL-1; alone or with other drugs)  NCT05375994 (2022-2025; with adagrasib)  NCT05840510 (2023-2025; KRYSTAL-19; with Nab-sirolimus)  NCT05375994 (2022-2025; RAMP204; with avutometinib)</p> <p><b>Phase 2:</b></p>	<p>Covalent inhibitor [3]</p> <p>FDA accelerated approval 2022 for emergency use with advanced NSCLC [4]</p> <p>QT prolongation</p> <p>In trials for various cancers (e.g. colorectal cancer, NSCLC, pancreatic cancer, solid tumours)</p>

	<p>NCT05609578 (2022-2026; alone or with other drugs)  NCT05472623 (2023-2025; Neo-Kan; with or without nivolumab)  NCT05673187 (2023-2025; ADEPPT)  NCT05853575 (2023-2025; KRYSTAL-21; dose comparison)</p> <p><b>Phase 2/3:</b>  NCT04613596 (2020-2029; KRYSTAL-7; alone or with pembrolizumab)</p> <p><b>Phase 3:</b>  NCT04685135 (2021-2024; KRYSTAL-12)  NCT04793958 (2021-2025; KRYSTAL-10; with other drugs)</p>	
Vemurafenib (with/without cobimetinib)	<p><b>Phase 1:</b>  NCT01787500 (2013-2026; with irinotecan and cetuximab)  NCT02721459 (2016-2024; with XL888 and cobimetinib)  NCT03781219 (2018-2023; with tunlametinib)</p> <p><b>Phase 1/2:</b>  NCT03101254 (2017-2023; with cobimetinib and LY3022855)  NCT01638676 (2021-2027; with metformin)</p> <p><b>Phase 2 (with cobimetinib):</b>  NCT02036086 (2015-2024)  NCT02693535 (2016-2025; TAPUR)  NCT02902029 (2016-2024; followed by immunotherapy)  NCT02925234 (2016-2027; DRUP)  NCT03181100 (2017-2025)  NCT03224767 (2017-2026)  NCT03297606 (2018-2027; CAPTUR)  NCT03498521 (2018-2024; CUPISCO)  NCT03554083 (2018-2024; with antibody therapies)  NCT04302025 (2020-2029; NAUTIKA1)  NCT04341181 (2020-2025; ProTarget)  NCT04722575 (2020-2027; NEO-TIM; with atezolizumab)  NCT04551521 (2021-2025; CRAFT; with tezolizumab)  NCT04817956 (2021-2045; IMPRESS-N)</p> <p><b>Phase 2 (without cobimetinib):</b>  NCT01709292 (2012-2026)  NCT01711632 (2012-2025)  NCT02304809 (2014-2024)  NCT02314481 (2017-2026; DARWIN II)  NCT03155620 (2017-2027; MATCH)  NCT03220035 (2017-2024; MATCH)  NCT03297606 (2018-2027; CAPTUR; with combimetinib)  NCT03410875 (2018-2025; with obinutuzumab)</p>	<p>ATP competitive inhibitor (Type 1) [5]</p> <p>FDA approval for metastatic melanoma, 2011 [6]</p> <p>FDA approval for use in combination with cobimetinib for advanced melanoma, 2015 [7]</p> <p>FDA approval for Erdheim-Chester disease, 2017 [8]</p> <p>In trials for various cancers (e.g. cancers with BRAF V600 mutations, colorectal cancer, craniopharyngioma, hairy cell leukemia, histiocytosis, Langerhans cell histiocytosis, melanoma, non-Hodgkin lymphomas, NSCLC, pancreatic cancer, rare cancers, thyroid cancer)</p>

		<p>NCT03585686 (2018-2023; with cytarabine and 2-chlorodeoxyadenosine)  NCT04591431 (2020-2025; ROME)  NCT04943198 (2021-2026)  NCT05068752 (2021-2024, with sorafenib)  NCT05159245 (2021-2026; FINPROVE)  NCT05233332 (2021-2024; with tunlametinib)  NCT05263453 (2021-2024; with tunlametinib)  NCT05388123 (2022-2025; with rituximab)  NCT05900219 (2023-2025; with tunlametinib)</p> <p><b>Phase 3 (with cobimetinib):</b>  NCT02908672 (2017-2024; with combimetinib with/without atezolizumab)  NCT03178552 (2017-2024; B-FAST; with cobimetinib and atezolizumab)  NCT06008119 (2023-2026; with tunlametinib)</p> <p><b>Phase 3 (without cobimetinib):</b>  NCT01909453 (2013-2024; COLUMBUS; with LGX818)  NCT05540951 (2018-2022; with irinotecan and cetuximab)  NCT03768063 (2019-2028; IMbrella B; previous treatment with atezolizumab)  NCT05768178 (2023-2029; DETERMINE; with cobimetinib)</p>	
Dabrafenib (with/without Trametinib)		<p><b>Phase 1 (with trametinib):</b>  NCT03026517 (2017-2025; with phenformin)  NCT03455764 (2018-2025; with MCS110)  NCT03975231 (2020-2025)  NCT04903119 (2022-2027; with nilotinib)</p> <p><b>Phase 1/2 (with trametinib):</b>  NCT01989585 (2014-2024; with navitoclax)  NCT02872259 (2017-2024; with BGN324)  NCT04201457 (2020-2029; with hydroxychloroquine)  NCT04557956 (2021-2024; with tazemetostat)</p> <p><b>Phase 1/2 (dabrafenib alone):</b>  NCT05388877 (2022-2025)</p> <p><b>Phase 2 (with trametinib):</b>  NCT04439292 (2015-2025; MATCH)  NCT04238624 (2020-2024; with cemiplimab)  NCT03919071 (2020-2027)  NCT04452877 (2020-2024)  NCT04544111 (2020-2025; with PDR001)  NCT04527549 (2021-2025)  NCT04675710 (2021-2024; with pembrolizumab)  NCT05182931 (2022-2025; I FIRST)</p>	<p>ATP competitive inhibitor (Type 1) [9]</p> <p>FDA approval for metastatic melanoma 2013 [9]</p> <p>FDA approval in combination with trametinib for metastatic melanoma, 2014 [9]</p> <p>FDA approval in combination with trametinib for NSCLC, 2017 [10]</p> <p>FDA approval in combination with trametinib for thyroid cancer, 2018 [11]</p> <p>FDA accelerated approval with trametinib for BRAF(V600E) solid tumours (except colorectal cancer) 2022 [12]</p> <p>FDA approval in combination with trametinib for paediatric low grade glioma, 2023 [13]</p> <p>In trials for various cancers (e.g. cancers with BRAF(V600E/K) mutations, colorectal cancer,</p>

	<p>NCT05370807 (2022-2025; RegoMel; with regorafenib)  NCT05525273 (2023-2028; Swecranio)  NCT05876806 (2023-2026)  NCT06079333 (2023-2028; NEO-ATACT)  NCT060541491 (2024-2027)</p> <p><b>Phase 2 (dabrafenib alone):</b>  NCT02925234 (2016-2027; DRUP)</p> <p><b>Phase 3 (with trametinib):</b>  NCT02224781 (2015-2024; after nivolumab or ipilimumab)  NCT02967692 (2017-2024; with PDR001/spartalizumab)  NCT04940052 (2021-2024)</p>	<p>craniopharyngioma, glioma, melanoma, NSCLC, papillary thyroid cancer)</p>
Encorafenib with/without binimetinib	<p><b>Phase 1 (with binimetinib):</b>  NCT06102902 (2024-2025)</p> <p><b>Phase 1 (without binimetinib):</b>  NCT04800822 (2021-2025; with PF-07284892)  NCT05538130 (2022-2027; with PF-07799933 and/or PF-07799544)  NCT05985954 (2024-2028; with cetuximab and ulixertinib)  NCT06102902 (2024-2025; with ZEN003694 and cetuximab)</p> <p><b>Phase 1/2 (with binimetinib):</b>  NCT04017650 (2019-2025; with cetuximab and nivolumab)  NCT04585815 (2020-2024; Landscape 1011; with sasanlimab)  NCT04720768 (2020-2024; CELEBRATE; with palbociclib)  NCT05039177 (2021-2024; HERKULES-3; with ERAS-007 and cetuximab)  NCT05743036 (2023-2026; with cetuximab and ZN-c3)  NCT06194929 (2024-2030; DETERMINE; without/with defactinib and avumetiniib)</p> <p><b>Phase 2 (with binimetinib):</b>  NCT02631447 (2016-2024; SECOMBIT; with immunotherapy)  NCT02910700 (2016-2024; with nivolumab)  NCT03563729 (2018-2028; MEMBRAINS; with ipilumab/nivolumab)  NCT03839342 (2019-2024; BEAVER)  NCT03915951 (2019-2024)  NCT04061980 (2020-2026; with or without nivolumab)  NCT04324112 (2020-2024)  NCT04511013 (2021-2027; with immunotherapy)  NCT04221438 (2021-2025)  NCT04526782 (2021-2026; ENCO-BRAF)  NCT05026983 (2021-2025)  NCT05097599 (2021-2029; Strata PATH)  NCT04074096 (2022-2029; BEPCOME-MB; with pembrolizumab)</p>	<p>ATP competitive inhibitor (Type 1) [14]</p> <p>FDA approval in combination with binimetinib for metastatic melanoma, 2018 [15]</p> <p>FDA approval in combination with cetuximab for metastatic colorectal carcinoma, 2020 [16]</p> <p>FDA approval in combination with binimetinib for NSCLC, 2023 [17]</p> <p>In trials for various cancers (e.g. cancers with BRAF(V600E/K) mutations, biliary cancer, colon cancer, colorectal cancer, gastrointestinal cancers, hairy cell leukemia, melanoma, NSCLC, thyroid cancer)</p>

	<p>NCT05195632 (2022-2025)  NCT05370807 (2022-2025; RegoMel; with regorafenib)  NCT05510895 (2022-2025; NeoBRAF; with cetuximab)  NCT05767879 (2022-2026; NASAM)  NCT05304546 (2023-2027; followed by immunotherapy)  NCT05926960 (2023-2027; PORTSIDE; with pembrolizumab)  NCT06207656 (2024-2029; CEBBRA; with cetuximab)</p> <p><b>Phase 2 (without binimetinib):</b>  NCT05004350 (2021-2024; NAUTICALCRC; with cetuximab)  NCT05217446 (2022-2027; SEAMARK; with cetuximab/pembrolizumab)  NCT05308446 (2022-2024; with cetuximab with/wihout nivolumab)  NCT05576896 (2022-2025; with hydroxychloroquine and immunotherapy)  NCT05725200 (2022-2038; EVIDENT)  NCT05706779 (2023-2027; NEORAF; with cetuximab)  NCT05957367 (2023-2027; with cetuximab and DCC-3116)  NCT06194929 (2024-2030; DETERMINE; with defactinib/avutometinib)</p> <p><b>Phase 2/3 (without binimetinib):</b>  NCT05710406 (2023-2034; with cetuximab)</p> <p><b>Phase 3 (with binimetinib):</b>  NCT03803553 (2020-2027; with cetuximab)  NCT04657991 (2021-2026; with pembrolizumab)  NCT05270044 (2022-2035; COLUMBUS-AD)  NCT05615818 (2024-2028)</p> <p><b>Phase 3 (without binimetinib):</b>  NCT04607421 (2020-2026; with cetuximab)</p>	
Trametinib (trials without dabrafenib)	<p><b>Phase 1:</b>  NCT03299088 (2018-2024; with pembrolizumab)  NCT04303403 (2018-2024; with ruxolitinib)  NCT03825289 (2019-2026; THREAD; with hydroxychloroquine)  NCT04111458 (2019-2024; in combination with BI1701963 SOS inhibitor)  NCT04485559 (2020-2027; with everolimus)  NCT04965220 (2022-2025; with HLX208 BRAF(V600E inhibitor)  NCT05435846 (2022-2027; with capmatinib) 05510895  NCT05907304 (2023-2025; SEACRAFT-1; with naporafenib)  NCT05440942 (2023-2027; with ruxolitinib and retifanlimab)</p> <p><b>Phase 1/2:</b>  NCT03225664 (2018-2024; with pembrolizumab)  NCT03377361 (2018-2024; CheckMate 9N9; with nivolumab)  NCT04892017 (2021-2024; with DCC-3116)  NCT05358249 (2022-2027; KontRASt-03; with JDQ443)</p>	<p>Allosteric inhibitor [18]</p> <p>FDA approval for metastatic melanoma, 2013 [19]</p> <p>FDA approval in combination with dabrafenib for metastatic melanoma, 2014 [9]</p> <p>FDA approval in combination with dabrafenib for NSCLC, 2017 [10]</p> <p>FDA approval in combination with dabrafenib for thyroid cancer, 2018 [11]</p>

		<p>NCT05668585 (2022-2027; alone or with CFT1946)  NCT05874414 (2023-2026; with GNS561)  NCT05275374 (2024-2026; ENHANCE; with XP-102)  NCT05658640 (2023-2029; HEM-iSMART; with other drugs)</p> <p><b>Phase 2:</b>  NCT01990196 (2014-2024; with other drugs)  NCT02925234 (2016-2027; DRUP)  NCT02881242 (2018-2025)  NCT03363217 (2018-2027)  NCT03190915 (2018-2024)  NCT03563729 (2018-2028; MEMBRAINS; with other drugs)  NCT04258046 (2020-2024)  NCT04803318 (2021-2027; with everolimus and Lenvatinib)  NCT05180825 (2022-2031)  NCT05518110 (2022-2025; PaTch; with hydroxychloroquine)  NCT06229340 (2023-2026; NTO-RAS; with hydroxychloroquine and bevacizumab)</p>	<p>FDA accelerated approval with dabrafenib for tumour agnostic BRAF(V600E) solid tumours (except colorectal cancer) 2022 [12]</p> <p>FDA approval in combination with dabrafenib for paediatric low grade glioma, 2023 [13]</p> <p>In trials for various cancers and disorders (e.g. arteriovenous malformation, cholangiocarcinoma, colorectal cancer, gliomas, haematological malignancies, melanoma, NSCLC, myelomonocytic leukemia, pancreatic cancer, prostate cancer, RAS(Q61X) solid tumours, thyroid cancer)</p>
Cobimetinib (trials without vemurafenib)	MEK1	<p><b>Phase 1:</b>  NCT03284502 (2017-2024; with belvarafenib)  NCT04109456 (2020-2024; with IN10018)  NCT04190628 (2020-2025; alone or with ABM-1310)  NCT04835805 (2021-2025; with Bbelvarafenib with/without nivolumab)  NCT05441514 (2022-2025; with enasidenib)  NCT05691504 (2023-2026; with pelcitoclast)</p> <p><b>Phase 1/2:</b>  NCT01928394 (2013-2024; with ipilimumab/nivolumab)  NCT03193190 (2017-2026; with other drugs)  NCT03202940 (2017-2024; with alectinib)  NCT03281369 (2017-2025; with other drugs)  NCT04214418 (2020-2024; with hydroxychloroquine/atezolizumab)  NCT04216953 (2020-2027; COTESARC; with atezolizumab)</p> <p><b>Phase 2:</b>  NCT02060188 (2014-2024; CheckMate 142; with ipilimumab/nivolumab)  NCT03108131 (2017-2025; with atezolizumab)  NCT03175432 (2017-2024; with immunotherapy)  NCT03202316 (2017-2024; with atezolizumab/eribulin)  NCT03337698 (2018-2027; with atezolizumab)  NCT03363867 (2018-2025; BEACON; with immunotherapy)  NCT03600701 (2018-2024; with atezolizumab)  NCT04079179 (2021-2029; NACHO-COBI)  NCT04409639 (2021-2026; CONCERTO)  NCT04931342 (2021-2028; BOUQUET)</p>	<p>Allosteric inhibitor [20]</p> <p>100-fold greater selectivity for MEK1 over MEK2 [21]</p> <p>FDA approval for use in combination with vemurafenib for advanced melanoma, 2015 [7]</p> <p>FDA approval for histiocytic neoplasms, 2022 [22]</p> <p>In trials for various cancers and disorders (e.g. arteriovenous malformations, acute myeloid leukemia, biliary cancer, breast cancer, gastrointestinal cancers, histiocytic disorders, melanoma, NSCLC, ovarian cancer, pancreatic cancer, solid tumours, soft tissue sarcoma, thyroid cancer)</p>

		<p>NCT04941287 (2021-2024; with atezolizumab and varlilumab)  NCT05125471 (2022-2026; COBI-AVM)  NCT06229340 (2023-2026; MTO-RAS; with hydroxychloroquine and bevacizumab)</p> <p><b>Phase 3:</b>  NCT03768063 (2019-2028; IMbrella B; previous treatment with atezolizumab)</p>	
Binimetinib without encorafenib		<p><b>Phase 1:</b>  NCT03170206 (2017-2025; with palbociclib)  NCT03991819 (2019-2026; with pembrolizumab)  NCT04132505 (2019-2023; with hydroxychloroquine)  NCT04543188 (2021-2023; with tinlorafenib)  NCT04800822 (2021-2025; with tinlorafenib)  NCT04913285 (2021-2024; with and without KIN-2787)  NCT05111561 (2022-2025; with ZEN003694)  NCT05355701 (2022-2028; with PF-07799933 with/without cetuximab)</p> <p><b>Phase 1/2:</b>  NCT01991379 (2013-2024; with imatinib)  NCT02285439 (2016-2023)  NCT03947385 (2019-2025; with IDE196NCT05340621 (2022-2026; NAUTILUS; WITH OKI-179)  NCT04720976 (2021-2024; with JAB-3312)  NCT04892017 (2021-2024; with DCC-3116)</p> <p><b>Phase 2:</b>  NCT02465060 (2015-2025)  NCT03475004 (2018-2024; followed by other drug combinations)  NCT03971409 (2019-2025; InCI Te; with doxorubicin)  NCT04375527 (2020-2025; with Nivolumab)  NCT04322383 (2021-2024)  NCT04598009 (2021-2026; with imatinib)  NCT05170334 (2021-2024; with belinostat)  NCT05286788 (2023-2027)  NCT05554367 (2023-2026; with palociclib)  NCT05564377 (2023-2030)  NCT06159478 (2023-2027; Perfume)  NCT05554354 (2024-2026; with fulvestrant)  NCT05564403 (2024-2025; with mFULFOX6)  NCT06229340 (2023-2026; NTO-RAS; with hydroxychloroquine and bevacizumab)</p>	<p>Allosteric inhibitor [23]</p> <p>FDA approval in combination with encorafenib for metastatic melanoma, 2018 [15]</p> <p>FDA approval in combination with encorafenib for NSCLC, 2023 [17]</p> <p>In trials for NSCLC, pancreatic cancer, glioma, breast cancer, melanoma, craniopharyngioma, lymphoma, NRAS cancers, hairy cell leukemia, colon cancer, colorectal cancer, uveal cancer, biliary tract cancers, lung cancer</p>
Selumetinib (AZD-6244)	MEK1	<p><b>Phase 1:</b>  NCT01034051 (2011-2025; with cediranib)</p>	Allosteric inhibitor [23]

	<p>NCT02143466 (2014-2024; with AZD9291)  NCT02188264 (2014-2025; with cyclosporin A)  NCT02546661 (2016-2024; with MEDI4736)  NCT03162627 (2017-2026; with olaparib)  NCT03326310 (2018-2025; with azacytidine)</p> <p><b>Phase 1/2:</b>  NCT01089101 (2011-2025)  NCT01362803 (2011-2025)  NCT02813135 (2016-2027)  NCT03326388 (2019-2023)  NCT03581487 (2019-2024; with immunotherapies)</p> <p><b>Phase 2:</b>  NCT02151084 (2014-2025; with cisplatin/gemcitabine)  NCT02664935 (2015-2023; with docetaxel)  NCT02407405 (2016-2025)  NCT03095248 (2017-2025)  NCT03213691 (2017-2024)  NCT03155620 (2017-2027; MATCH)  NCT03392246 (2018-2026; with Osimertinib)  NCT03801369 (2018-2027)  NCT03944772 (2019-2025; ORCHARD; with osimertinib)  NCT04348045 (2020-2024; MAZEPPA; with durvalumab)  NCT05554328 (2023-2024; alone or with Olaparib)  NCT05564377 (2023-2030)  NCT05253131 (2024-2030; with MEDI4736 and durvalumab)  NCT06188741 (2024-2031)</p> <p><b>Phase 3:</b>  NCT01933932 (2013-2023; with docetaxel)  NCT03871257 (2020-2027)  NCT04166409 (2020-2026)  NCT04576117 (2021-2026; alone or with vinblastine)  NCT04924608 (2021-2025; KOMET)</p>	<p>FDA approval for paediatric neurofibromatosis Type 1 plexiform neurofibromas, 2020 [24]</p> <p>In trials for various cancers (e.g. bladder cancer, breast cancer, endometrial cancer, glioma, leukemia, neurofibromatosis Type1 plexiform neurofibroma, NSCLC, optic nerve glioma, pancreatic cancer, solid tumours)</p>
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**Supplementary Table S2. Active clinical trials of RAS inhibitors.** This list was compiled in March 2024 from clinicaltrials.gov, selecting those which are active (recruiting or not-recruiting) or for which recruiting is due to start. It may not be fully comprehensive, but is designed to highlight the most significant ongoing studies. It excludes pharmacokinetic studies in healthy adults and trials that have completed or been withdrawn. All covalent inhibitors target the “off” form of KRAS(G12C). NSCLC, non-small cell lung cancer.

Inhibitor	Target	Trial no. (dates, trial name, drug combinations)	Comments
Divarasib (GDC-6036)	KRAS(G12C)	<p><b>Phase 1:</b> NCT04449874 (2020-2024; with other drugs) NCT04929223 (2021-2026; INTRINSIC; with other drugs)</p> <p><b>Phase 1/2:</b> NCT05789082 (2023-2025; with pembrolizumab)</p> <p><b>Phase 2:</b> NCT04302025 (NAUTIKA12020-2029; ; with other drugs)</p>	<p>Covalent inhibitor [25]</p> <p>In trial for solid tumours</p>
Garsorasib (D-1553)	KRAS(G12C)	<p><b>Phase 1:</b> NCT06105255 (2025-2025; with other drugs)</p> <p><b>Phase 1/2:</b> NCT04585035 (2020-2025 with other drugs) NCT05383898 (2021-2024; dose comparison) NCT05492045 (2022-2024; with other drugs) NCT06166836 (2022-2025; with IN10018)</p> <p><b>Phase 3:</b> NCT06300177 (2024-2027)</p>	<p>Covalent inhibitor [26]</p> <p>In trials for NSCLC</p>
Opnurasib (JDQ-443)	KRAS(G12C)	<p><b>Phase 1/2:</b> NCT05358249 (2022-2027; KontRASSt-03; with other drugs)</p> <p><b>Phase 2:</b> NCT05445843 (2022-2027) NCT05999357 (2024-2028)</p> <p><b>Phase 3:</b> NCT05132075 (2022-2025; KontRASSt-02; alone or with docetaxel)</p>	<p>Covalent inhibitor [27]</p> <p>In trials for NSCLC</p>
MRTX-1133	KRAS(G12D)	<p><b>Phase 1/2:</b> NCT05737706 (2023-2026)</p>	<p>Non-covalent inhibitor, binds to switch II pocket [28]</p> <p>In trial for solid tumours</p>
RMC-6236	RAS(G12X)	<p><b>Phase 1:</b> NCT05379985 (2022-2025)</p>	<p>Recruits cyclophilin A to the active “on” form of RAS forming a tricomplex to block interaction with RAF [29]</p>

			<p>Targets all RAS isoforms with mutation of Gly12 in the “on” state [30]</p> <p>In trial for solid tumours</p>
RMC-6291	RAS(G12X)	<p><b>Phase 1:</b> NCT06128551 (2023-2026; with RMC-6236) NCT05462717 (2022-2025; dose escalation and expansion)</p> <p><b>Phase 1/2:</b> NCT06162221 (2024-2028; with other drugs)</p>	<p>Recruits cyclophilin A to the active “on” form of RAS forming a tricomplex to block interaction with RAF [29]</p> <p>Targets all RAS isoforms with mutation of Gly12 in the “on” state</p> <p>In trial for solid tumours</p>

**Supplementary Table S3. Active clinical trials of inhibitors for RAF, MEK1/2 and ERK1/2.** This list was compiled in March 2024 from clinicaltrials.gov, selecting those which are active (recruiting or not-recruiting) or for which recruiting is due to start. It may not be fully comprehensive, but is designed to highlight the most significant ongoing studies of inhibitors that have already been approved for treatment of one or more cancer. It excludes pharmacokinetic studies in healthy adults and trials that have been completed or withdrawn. NSCLC, non-small cell lung cancer. N.B. The list does not include the multikinase inhibitors sorafenib [31] and regorafenib [32] that inhibit RAF.

Inhibitor	Target	Trial no.	Comments
ABM-1310	BRAF(V600E)	<b>Phase 1:</b> NCT04190628 (2020-2025; alone or with cobimetinib)	No information on mechanism of action  FDA fast-track authorization for BRAF(V600E) glioblastoma (August 2023) <a href="http://www.abmtx.com/site/newsdetails/88">http://www.abmtx.com/site/newsdetails/88</a>  QT prolongation [33]
Exarafenib (KIN-2787)	Pan-RAF	<b>Phase 1:</b> NCT04913284 (2021-2024; alone and with binimetinib)	RAF dimer inhibitor [34]  In trial for melanoma, NSCLC, solid tumours
Naporafenib (LXH-254)	BRAF, RAF1 (ARAF)	<b>Phase 1:</b> NCT05907304 (2023-2025; SEACRAFT-1; with trametinib) NCT02974725 (2017-2024; with other drugs) NCT03333343 (2018-2024; with EGF816) NCT04294160 (2020-2024)  <b>Phase 2:</b> NCT04417621 (2020-2024; with LTT462)	Type II Raf dimer inhibitor [35]. Weak inhibitor of ARAF  In trial for colorectal cancer, melanoma, NSCLC, solid RAS Q61X tumours
Lifirafenib (BGB-283)	Pan-RAF, EGFR (and other kinases)	<b>Phase 1:</b> NCT03905148 (2019-2026; with mirdametinib)	ATP competitive (Type II) inhibitor [36]  In trial for solid tumours
Tovorafenib (TAK-580, MLN2480, DAY101)	BRAF, RAF1 (ARAF)	<b>Phase 1:</b> NCT03429803 (2018-2024)  <b>Phase 1/2:</b> NCT04984604 (2021-2025; alone or with pimasertib)  <b>Phase 2:</b> NCT05465174 (2022-2027; PNOC029; with nivolumab) NCT05280669 (2024-2025)	Type II Raf dimer inhibitor [35]. Weak inhibitor of ARAF  In trial for craniopharyngioma, gliomas, Langerhans cell histiocytosis, solid tumours

		<b>Phase 3:</b> NCT05566795 (2023-2030; LOGGIC/FIREFLY-2)	
Belvarafenib (HM-95573, GDC-5573, RG-6185)	Pan-RAF	<b>Phase 1:</b> NCT03284502 (2017-2024; with cobimetinib or cetuximab) NCT04835805 (2021-2025; alone or with cobimetinib/nivolumab)  <b>Phase 2:</b> NCT04589845 (2021-2032; TAPISTRY)	Type II Raf dimer inhibitor [37]. Weak inhibitor of ARAF  In trial for NRAS-mutant advanced melanoma, solid tumours
XP-102 (BI- 882370)	Pan-RAF	<b>Phase 1/2:</b> NCT05275374 (2024-2026; ENHANCE; alone or with trametinib)	ATP competitive inhibitor (Type II) [38]  In trial for melanoma, colorectal, non-small-cell lung, thyroid cancer
CFT1946	BRAF(V600)	<b>Phase 1/2:</b> NCT05668585 (2022-2027; alone or with trametinib)	BiDAC (protac degrader) [39, 40]
Tinlorafenib (PF- 07284890, ARRY-461)	BRAF	<b>Phase 1:</b> NCT04543188 (2021-2023; with binimetinib) NCT04800822 (2021-2025; with binimetinib)	ATP competitive inhibitor [41]  In trial for melanoma, NSCLC
PF- 07799933 (ARRY-460)	BRAF	<b>Phase 1:</b> NCT05355701 (2022-2028; with binimetinib with/without cetuximab) NCT05538130 (2022-2027; with encorafenib and/or PF-07799544)	ATP competitive inhibitor [42]  In trial for colorectal cancer, glioma, melanoma, NSCLC
Pimasertib (AS-703026)	MEK1/2	<b>Phase 1/2:</b> NCT04985604 (2021-2025; with tovorafenib) NCT06208657 (2024-2035; precision oncology trial; compared with other drugs)	Allosteric inhibitor [43]
Mirdametinib (PD0325901)	MEK1/2	<b>Phase 1:</b> NCT03905148 (2019-2026; with lifirafenib)  <b>Phase 1/2:</b> NCT04923126 (2022-2031) NCT05580770 (with BGB-3245) NCT06159166 NCT05937906 (with other drugs)  <b>Phase 2:</b> NCT03962542 NCT06153173 NCT05983159	Allosteric inhibitor [44]  In trials for low grade glioma, solid tumours, neurofibromatosis (NF1/cNF), histiocytic disorders, vascular malformations
E6201	MEK1/2	<b>Phase 1/2:</b> NCT05388877 (2022-2025; with dabrafenib)	ATP competitive inhibitor [45]  In trial for metastatic melanoma

Tunlametinib (HL-085)	MEK1/2	<p><b>Phase 1:</b> NCT03781219 (2018-2023; with vemurafenib)</p> <p><b>Phase 2:</b> NCT05331105 (2021-2028; with dabrafenib) NCT05233332 (2022-2024; alone and with vemurafenib) NCT05263453 (2021-2024; with tunlametinib) NCT05900219 (2023-2025; with tunlametinib)</p> <p><b>Phase 3:</b> NCT06008106 (2023-2027) NCT06008119 (2023-2026; with vemurafenib)</p>	<p>MEK inhibitor, mechanism undefined [46]</p> <p>In trials for neurofibromatosis (NF1/cNF), NSCLC, colorectal cancer, melanoma, solid tumours</p>
PF-07799544 (ARRY-134)	MEK1/2	<p><b>Phase 1:</b> NCT05538130 (2022-2027; with encorafenib and/or PF-07799933)</p>	<p>No additional information</p> <p>In trial for solid tumours</p>
Avutometinib (VS-6766, CH5126766 RO5126766)	Dual RAF/MEK inhibitor	<p><b>Phase 1:</b> NCT06104488 (2023-2029)</p> <p><b>Phase 1/2:</b> NCT05375994 (2022-2025; with adagrasib) NCT05074810 (2022-2027; with sortorasib, with or without defactinib) NCT05200442 (2022-2024; with cetuximab) NCT05669482 (2023-2025; with other drugs) NCT06194929 (2024-2030; DETERMINE; with defactinib, with or without encorafenib)</p> <p><b>Phase 2:</b> NCT04625270 (2020-2026; alone or with defactinib) NCT04720417 (2021-2025; with defactinib) NCT06007924 (2023-2027; alone or with defactinib) NCT05512208 (2023-2029; with defactinib) NCT05787561 (2023-2025; with defactinib)</p> <p><b>Phase 3:</b> NCT06072781 (2024-2031; RAMP 301; with defactinib)</p>	<p>Allosteric inhibitor. Inhibits catalytic activity of MEK and disrupts formation of RAF-MEK complexes [47]</p> <p>In trials for low grade ovarian cancer, thyroid cancer, solid tumours, thyroid cancer, NSCLC, metastatic melanoma, uveal cancer</p>
Ulixertinib (BVD-523)	ERK1/2	<p><b>Phase 1:</b> NCT03454035 (2018-2026; with palbociclib) NCT05804227 (2023-2025) NCT05985954 (2024-2028; with cetuximab, with or without encorafenib)</p> <p><b>Phase 2:</b> NCT03698994 (2018-2026) NCT03417739 (2018-2025)</p>	<p>ATP-competitive inhibitor [48]</p> <p>In trials for histiocytic disorders, low grade glioma, non-hodgkin's lymphoma, solid tumours, uveal melanoma,</p>

		NCT05221320 (2022-2025; with hydroxychloroquine) NCT05804227 (2023-2025)	
LY3214996	ERK1/2	<b>Phase 1:</b> NCT04081259 (2020-2024) NCT04916236 (2022-2024; with RMC-4630 SHP2 inhibitor)  <b>Phase 1/2:</b> NCT04391595 (2020-2025; with abemaciclib) NCT04616183 (2020-2024; with cetuximab, with or without abemaciclib)	ATP competitive inhibitor [49]  In trials for AML, metastatic colorectal cancer, recurrent glioblastoma
ERAS-007 (ASN007)	ERK1/2	<b>Phase 1/2:</b> NCT04866134 (2021-2024; HERKULES-1; with ERAS-601 SHP2 inhibitor) NCT05039177 (2021-2024; HERKULES-3; with encorafenib/cetuximab)	ATP competitive inhibitor [50]  In trial with SHP2 inhibitor for colorectal cancer, pancreatic ductal adenocarcinoma, solid tumours
ASTX029	ERK1/2	<b>Phase 1/2:</b> NCT03520075 (2018-2025)	Allosteric inhibitor. Inhibits phosphorylation and catalytic activity of ERK1/2 [51]  In trial for solid tumours

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