REPORTING

Report Date:	JUN-06-2024
Receipt Date:	JUN-01-2024
Collection Date:	MAY-31-2024
Specimen:	Blood
Status:	FINAL

PHYSICIAN

Chih-Hsueh Chen
Account: Genconn Biotech Co., LTD
Address: F15., No 207-5 Sec 3, Beixin Rd, Xindian Dist, New Taipei City, 23143, Taiwan
Ph: +886 963 820 633 | Fax: N/A
Additional Recipient: N/A

Complete Tumor Response Map on page 3

Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

KEY ✓ Approved in indication ~ Approved in other indication ⊗ Lack of response

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 4)	% cfDNA or Amplification
KRAS Q61H	⊗ Cetuximab, Panitumumab	Yes	13.3%
NRAS Q61R	⊗ Cetuximab, Panitumumab	Yes	9.1%
KRAS G12C	~ Sotorasib ⊗ Cetuximab, Panitumumab	Yes	2.9%
MAP2K1 K57T	⊗ Adagrasib, Cetuximab, Encorafenib+cetuximab, Panitumumab, Vemurafenib	Yes	1.5%
KRAS G12D	⊗ Cetuximab, Panitumumab	Yes	0.9%
MAP2K1 K57E	⊗ Cobimetinib, Dabrafenib, Vemurafenib	Yes	0.6%
KRAS Q61H	⊗ Cetuximab, Panitumumab	Yes	0.4%
KRAS G12V	⊗ Cetuximab, Panitumumab	Yes	0.2%
KRAS G12A	⊗ Cetuximab, Panitumumab	Yes	0.06%

Synonymous Alterations
BRCA1 G1770G (19.2%)
This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Comments

Two KRAS Q61H variants, c.183A>C at 13.3% and c.183A>T at 0.4%, were detected in this patient's sample. While these variants are genetically unique with distinct allele frequencies, they both result in the same protein change.
Reported by: JV4,NT3

Additional Biomarkers

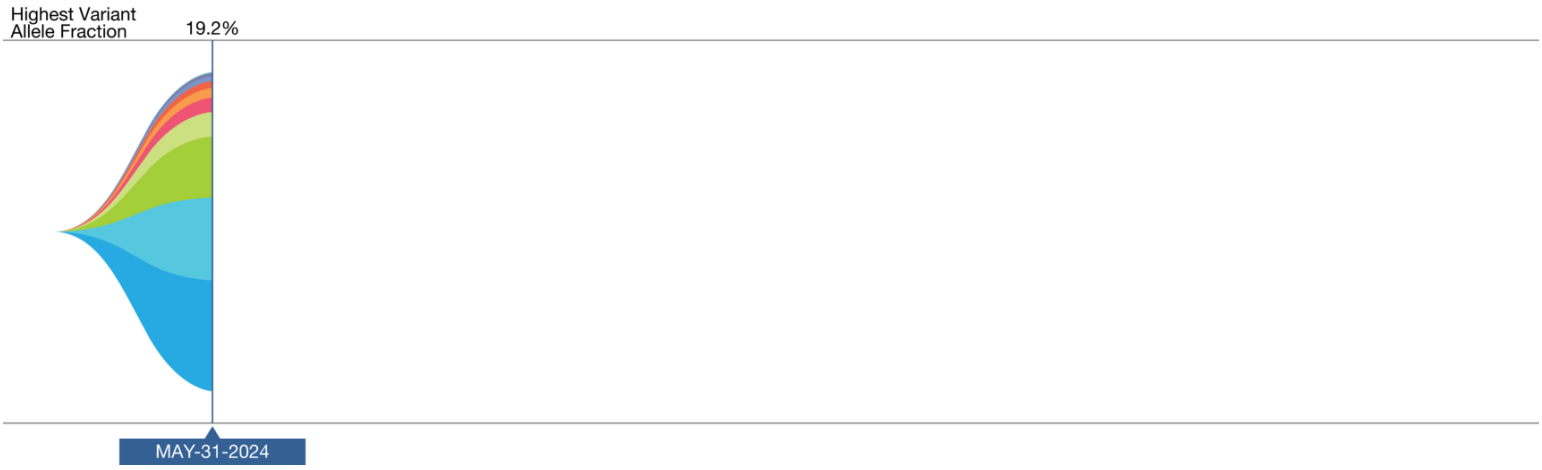
Biomarker	Additional Details
MSI-High	NOT DETECTED

We evaluated this sample for 74 genes, including the following guideline-recommended genes for CRC

MSI-High | *KRAS* | *NRAS* | *BRAF* | *ERBB2*(HER2) | *NTRK*

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the variant allele fraction (% cfDNA) of observed somatic variants at each sample submission. Amplifications are not plotted, and only the first and last five test dates are plotted. Please see the Physician Portal (portal.guardanthealth.com) for the Tumor Response Map with all test dates.



Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	
BRCA1 G1770G	19.2%	Synonymous Alteration §
KRAS Q61H	13.3%	
NRAS Q61R	9.1%	
KRAS G12C	2.9%	
MAP2K1 K57T	1.5%	
KRAS G12D	0.9%	
MAP2K1 K57E	0.6%	
KRAS Q61H	0.4%	
KRAS G12V	0.2%	
KRAS G12A	0.06%	

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.
§ See definitions section for more detail

Available Clinical Trials (within the same state as the ordering physician)

There may be additional trials not listed here. Visit: **portal.guardanthealth.com** or email **clientservices@guardanthealth.com** with A1059095 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
KRAS Q61H	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
NRAS Q61R	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
KRAS G12C	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
MAP2K1 K57T	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
KRAS G12D	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
MAP2K1 K57E	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
KRAS Q61H	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
KRAS G12V	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
KRAS G12A	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			

More clinical trial options available at **portal.guardanthealth.com**

Definitions

Synonymous Alteration: This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Interpretation

Somatic alterations were detected in the circulating cell-free DNA isolated from this patient's blood specimen. These genomic alterations are cancer-associated somatic variants, some of which have been associated with either increased or reduced clinical response to specific treatments. The percentage of altered cell-free DNA circulating (% cfDNA) in blood is related to the unique tumor biology of each patient. Factors that may affect the % cfDNA of detected somatic alterations include tumor growth, turn over, size, heterogeneity, vascularization, disease progression, and treatment.

Method and Limitations

Guardant360 sequences 74 cancer-associated genes to identify somatic alterations. Cell-free DNA (cfDNA) is extracted from plasma, enriched for targeted regions, and sequenced using the Illumina platform and hg19 as the reference genome. All exons are sequenced in some genes; only clinically significant exons are sequenced in other genes. The types of genomic alterations detected by Guardant360 include single nucleotide variants, gene amplifications, fusions, short insertions/deletions (longest detected, 70 base pairs), and splice site disrupting events (see Table 1). Microsatellite Instability (MSI) is assessed for all cancer types by evaluating somatic changes in the length of repetitive sequences on the Guardant360 panel. A "Not Detected" result in samples where the highest % cfDNA is < 0.2% is an inconclusive result because it does not preclude MSI-High status in tissue. MSI status is currently not reported for earlier panel versions. This version of the Guardant360 test is not validated for the detection of other types of genomic alterations, such as complex rearrangements or gene deletions. Certain sample or variant characteristics, such as low cfDNA concentration, may result in reduced analytic sensitivity. Guardant360 cannot discern the source of circulating cfDNA, and for some variants in the range of ~40 to 60% cfDNA, the test cannot easily distinguish germline variants from somatic alterations. Guardant360 is not validated for the detection of germline or de novo variants that are associated with hereditary cancer risk. Tissue genotyping should be considered when plasma genotyping is negative, if clinically appropriate.

Table 1: Genes on the Guardant360 Panel

Guardant360 reports single nucleotide variants, splice site mutations, and insertion and deletion variants (indels) in all clinically relevant exons in 74 genes and reports other variant types in select genes as indicated below.

AKT1	*ALK* #	*APC*	*AR* †	*ARAF*	*ARID1A*	*ATM*	*BRAF* †	*BRCA1*
BRCA2	*CCND1* †	*CCND2* †	*CCNE1* †	*CDH1*	*CDK12*	*CDK4* †	*CDK6* †	*CDKN2A*
CTNNB1	*DDR2*	*EGFR* †	*ERBB2* †	*ESR1*	*EZH2*	*FBXW7*	*FGFR1* †	*FGFR2* † #
FGFR3 #	*GATA3*	*GNA11*	*GNAQ*	*GNAS*	*HNF1A*	*HRAS*	*IDH1*	*IDH2*
JAK2	*JAK3*	*KIT* †	*KRAS* †	*MAP2K1*	*MAP2K2*	*MAPK1*	*MAPK3*	*MET* †
MLH1	*MPL*	*MTOR*	*MYC* †	*NF1*	*NFE2L2*	*NOTCH1*	*NPM1*	*NRAS*
NTRK1 #	*NTRK3*	*PDGFRA* †	*PIK3CA* †	*PTEN*	*PTPN11*	*RAF1* †	*RB1*	*RET* #
RHEB	*RHOA*	*RIT1*	*ROS1* #	*SMAD4*	*SMO*	*STK11*	*TERT* ‡	*TP53*
TSC1	*VHL*							

‡ Guardant360 reports alterations in the promoter region of this gene.

† Guardant360 reports amplifications of this gene.

Guardant360 reports fusion events involving this gene.

About the Test

The Guardant360 assay was developed and its performance characteristics were determined by Guardant Health, Inc. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test may be used for clinical purposes and should not be regarded as investigational or for research only. Guardant Health's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing. The laboratory report should be interpreted in the context of other clinical information and laboratory, pathology, and imaging studies by a qualified medical professional prior to initiating or changing a patient's treatment plan. The selection of any, all, or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) is entirely at the discretion of the treating medical professional. Drug and trial information are based on the diagnosis written on the submitted test request form; this information is not based on any supplemental information provided by the requesting medical professional, including pathology reports or other molecular studies. Some drugs listed in this report may not be approved or cleared by the FDA for the indicated use. Guardant Health makes no endorsement, express or implied, of any product, physician, or procedure contained in this report. This report makes no promises or guarantees that a particular medication will affect (or not affect) the clinical outcome of any patient.

Testing Performed at: Guardant Health

Laboratory Director: Martina Lefterova, MD PhD | CLIA ID: 05D2070300 | CAP #: 8765297 | 505 Penobscot Drive, Redwood City, CA, 94063, USA

Additional information is available

Any therapeutic annotations are based on publicly available information. This information is described in the "Detailed Therapy Results" and "Relevance of Detected Alterations" sections.

Visit **portal.guardanthealth.com** or email **clientservices@guardanthealth.com** with A1059095 in the subject line of the email for:

- Additional clinical trials
- Detailed Therapy Results
- Relevance of Detected Alterations
- References

If you would like to receive this additional information with every Guardant360 report, please call client services at **855.698.8887** to opt-in.

Additional information begins on the next page.

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
KRAS Q61H	NCT03905148 BeiGene,clinicaltrials@beigene.com,1 (877) 828-5568	Study of the Safety and Pharmacokinetics of BGB-283 (Lifirafenib) and PD-0325901 (Mirdametinib) in Participants With Advanced or Refractory Solid Tumors	Phase 1	Houston, TX; Santa Monica, CA; Australia (4)
	NCT04985604 Day One Biopharmaceuticals, clinicaltrials@dayonebio.com,650-484-0899	Tovorafenib (DAY101) Monotherapy or in Combination With Other Therapies for Patients With Melanoma and Other Solid Tumors	Phase 1 /Phase 2	Los Angeles, CA; Newport Beach, CA; Indianapolis, IN; Pittsburgh, PA; Portland, OR; Jacksonville, FL; Nashville, TN; Canada (2)
	NCT05111561 See https://clinicaltrials.gov/ct2/show /NCT05111561	Testing the Combination of the Anticancer Drugs ZEN003694 and Binimetinib in Patients With Advanced/Metastatic or Unresectable Solid Tumors With RAS Alterations and Triple Negative Breast Cancer	Phase 1	Houston, TX; Boston, MA; Galveston, TX
	NCT05221320 Biomed Valley Discoveries, Inc., ERK@biomed-valley.com,816-960-6600	Trial of Ulixertinib in Combination With Hydroxychloroquine in Patients With Advanced Gastrointestinal (GI) Malignancies	Phase 2	Tucson, AZ; Saint Louis, MO; Cleveland, OH; Richmond, VA; New York, NY; New Brunswick, NJ; Fairway, KS; San Francisco, CA
	NCT05379985 Revolution Medicines, Inc.,rmc-6236_ct-inquiry@revmed.com,(650) 779-2300	Study of RMC-6236 in Patients With Advanced Solid Tumors Harboring Specific Mutations in RAS	Phase 1	Houston, TX; Boston, MA; Cincinnati, OH; Austin, TX; Dallas, TX; Orange, CA; Baltimore, MD; San Antonio, TX; Salt Lake City, UT; Nashville, TN; Santa Monica, CA; Fairfax, VA; New York, NY (3)
	NCT05907304 Erasca Clinical Team,clinicaltrials@erasca.com,1-858-465-6511	A Study to Assess Naporafenib (ERAS-254) Administered With Trametinib in Patients With RAS Q61X Mutations	Phase 1	Las Vegas, NV; Houston, TX; Detroit, MI; Saint Louis, MO; Madison, WI; Atlanta, GA; Saint Petersburg, FL; Portland, OR; Sarasota, FL; San Francisco, CA; Nashville, TN; Fairfax, VA (2); Canada (4); Korea, Republic of (6); United Kingdom (3); Australia (3)
NRAS Q61R	NCT03905148 BeiGene,clinicaltrials@beigene.com,1 (877) 828-5568	Study of the Safety and Pharmacokinetics of BGB-283 (Lifirafenib) and PD-0325901 (Mirdametinib) in Participants With Advanced or Refractory Solid Tumors	Phase 1	Houston, TX; Santa Monica, CA; Australia (4)
	NCT04985604 Day One Biopharmaceuticals, clinicaltrials@dayonebio.com,650-484-0899	Tovorafenib (DAY101) Monotherapy or in Combination With Other Therapies for Patients With Melanoma and Other Solid Tumors	Phase 1 /Phase 2	Los Angeles, CA; Newport Beach, CA; Indianapolis, IN; Pittsburgh, PA; Portland, OR; Jacksonville, FL; Nashville, TN; Canada (2)
	NCT05111561 See https://clinicaltrials.gov/ct2/show /NCT05111561	Testing the Combination of the Anticancer Drugs ZEN003694 and Binimetinib in Patients With Advanced/Metastatic or Unresectable Solid Tumors With RAS Alterations and Triple Negative Breast Cancer	Phase 1	Houston, TX; Boston, MA; Galveston, TX
	NCT05221320 Biomed Valley Discoveries, Inc., ERK@biomed-valley.com,816-960-6600	Trial of Ulixertinib in Combination With Hydroxychloroquine in Patients With Advanced Gastrointestinal (GI) Malignancies	Phase 2	Tucson, AZ; Saint Louis, MO; Cleveland, OH; Richmond, VA; New York, NY; New Brunswick, NJ; Fairway, KS; San Francisco, CA
	NCT05585320 IMM1104-101 Study Team, clinicaltrials@immuneering.com,(860) 321-1302	A Phase 1/2a Study of IMM-1-104 in Participants With Previously Treated, RAS-Mutant, Advanced or Metastatic Solid Tumors	Phase 1 /Phase 2	Denver, CO; Houston, TX; Duarte, CA; Boston, MA; San Diego, CA; Lake Mary, FL; New York, NY; Chicago, IL; East Syracuse, NY; Nashville, TN; Santa Monica, CA; Fairfax, VA; Durham, NC

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	NCT06104488 Sameer Farouk Sait, MD, faroukss@mskcc.org,212-639-3449	A Study of Avutometinib for People With Solid Tumor Cancers	Phase 1	Atlanta, GA; New York, NY
KRAS G12C	NCT04117087 Colleen Apostol, RN,GIClinicalTrials@jhmi.edu,410-614-3644	Pooled Mutant KRAS-Targeted Long Peptide Vaccine Combined With Nivolumab and Ipilimumab for Patients With Resected Mismatch Repair Protein (MMR-p) Colorectal and Pancreatic Cancer	Phase 1	Baltimore, MD
	NCT04449874 Reference Study ID Number: GO42144 whttps://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study to Evaluate the Safety, Pharmacokinetics, and Activity of GDC-6036 Alone or in Combination in Participants With Advanced or Metastatic Solid Tumors With a KRAS G12C Mutation	Phase 1	Duarte, CA; Oklahoma City, OK; Philadelphia, PA; Boston, MA; Pittsburgh, PA; La Jolla, CA; New York, NY; New Haven, CT; Orange, CA; Sarasota, FL; Hungary; Kenya; United Kingdom (4); Switzerland (2); Spain (7); New Zealand (3); Canada (3); Netherlands (3); Belgium (2); Norway (2); Poland (3); Korea, Republic of (4); Brazil (9); Italy (4); Israel (3); Australia (5)
	NCT04985604 Day One Biopharmaceuticals, clinicaltrials@dayonebio.com,650-484-0899	Tovorafenib (DAY101) Monotherapy or in Combination With Other Therapies for Patients With Melanoma and Other Solid Tumors	Phase 1 /Phase 2	Los Angeles, CA; Newport Beach, CA; Indianapolis, IN; Pittsburgh, PA; Portland, OR; Jacksonville, FL; Nashville, TN; Canada (2)
	NCT05221320 Biomed Valley Discoveries, Inc., ERK@biomed-valley.com,816-960-6600	Trial of Ulixertinib in Combination With Hydroxychloroquine in Patients With Advanced Gastrointestinal (GI) Malignancies	Phase 2	Tucson, AZ; Saint Louis, MO; Cleveland, OH; Richmond, VA; New York, NY; New Brunswick, NJ; Fairway, KS; San Francisco, CA
	NCT05379985 Revolution Medicines, Inc.,rmc-6236_ct-inquiry@revmed.com,(650) 779-2300	Study of RMC-6236 in Patients With Advanced Solid Tumors Harboring Specific Mutations in RAS	Phase 1	Houston, TX; Boston, MA; Cincinnati, OH; Austin, TX; Dallas, TX; Orange, CA; Baltimore, MD; San Antonio, TX; Salt Lake City, UT; Nashville, TN; Santa Monica, CA; Fairfax, VA; New York, NY (3)
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MAP2K1 K57T	NCT03905148 BeiGene,clinicaltrials@beigene.com,1 (877) 828-5568	Study of the Safety and Pharmacokinetics of BGB-283 (Lifirafenib) and PD-0325901 (Mirdametinib) in Participants With Advanced or Refractory Solid Tumors	Phase 1	Houston, TX; Santa Monica, CA; Australia (4)
	NCT04985604 Day One Biopharmaceuticals, clinicaltrials@dayonebio.com,650-484-0899	Tovorafenib (DAY101) Monotherapy or in Combination With Other Therapies for Patients With Melanoma and Other Solid Tumors	Phase 1 /Phase 2	Los Angeles, CA; Newport Beach, CA; Indianapolis, IN; Pittsburgh, PA; Portland, OR; Jacksonville, FL; Nashville, TN; Canada (2)
	NCT05111561	Testing the Combination of the Anticancer	Phase 1	Houston, TX; Boston, MA; Galveston,

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	See https://clinicaltrials.gov/ct2/show/NCT05111561	Drugs ZEN003694 and Binimetinib in Patients With Advanced/Metastatic or Unresectable Solid Tumors With RAS Alterations and Triple Negative Breast Cancer		TX
	NCT05221320 Biomed Valley Discoveries, Inc., ERK@biomed-valley.com,816-960-6600	Trial of Ulixertinib in Combination With Hydroxychloroquine in Patients With Advanced Gastrointestinal (GI) Malignancies	Phase 2	Tucson, AZ; Saint Louis, MO; Cleveland, OH; Richmond, VA; New York, NY; New Brunswick, NJ; Fairway, KS; San Francisco, CA
	NCT05585320 IMM1104-101 Study Team, clinicaltrials@immuneering.com,(860) 321-1302	A Phase 1/2a Study of IMM-1-104 in Participants With Previously Treated, RAS-Mutant, Advanced or Metastatic Solid Tumors	Phase 1 /Phase 2	Denver, CO; Houston, TX; Duarte, CA; Boston, MA; San Diego, CA; Lake Mary, FL; New York, NY; Chicago, IL; East Syracuse, NY; Nashville, TN; Santa Monica, CA; Fairfax, VA; Durham, NC
	NCT05907304 Erasca Clinical Team,clinicaltrials@erasca.com,1-858-465-6511	A Study to Assess Naporafenib (ERAS-254) Administered With Trametinib in Patients With RAS Q61X Mutations	Phase 1	Las Vegas, NV; Houston, TX; Detroit, MI; Saint Louis, MO; Madison, WI; Atlanta, GA; Saint Petersburg, FL; Portland, OR; Sarasota, FL; San Francisco, CA; Nashville, TN; Fairfax, VA (2); Canada (4); Korea, Republic of (6); United Kingdom (3); Australia (3)
KRAS G12D	NCT04117087 Colleen Apostol, RN,GIClinicalTrials@jhmi.edu,410-614-3644	Pooled Mutant KRAS-Targeted Long Peptide Vaccine Combined With Nivolumab and Ipilimumab for Patients With Resected Mismatch Repair Protein (MMR-p) Colorectal and Pancreatic Cancer	Phase 1	Baltimore, MD
	NCT04985604 Day One Biopharmaceuticals, clinicaltrials@dayonebio.com,650-484-0899	Tovorafenib (DAY101) Monotherapy or in Combination With Other Therapies for Patients With Melanoma and Other Solid Tumors	Phase 1 /Phase 2	Los Angeles, CA; Newport Beach, CA; Indianapolis, IN; Pittsburgh, PA; Portland, OR; Jacksonville, FL; Nashville, TN; Canada (2)
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	NCT05726864 Clinical Trial Inquiries, clinicaltrialinquiries@elicio.com,617-714-9884	A Study of ELI-002 7P in Subjects With KRAS /NRAS Mutated Solid Tumors	Phase 1 /Phase 2	Milwaukee, WI; Philadelphia, PA; Phoenix, AZ; Iowa City, IA; Orange, CA; Jacksonville, FL; Los Angeles, CA; Houston, TX; Duarte, CA; Rochester, MN; Boston, MA; Dallas, TX; Lake Success, NY; Aurora, CO; Gainesville, FL; Tampa, FL; Coral Gables, FL; New York, NY (2); Nashville, TN (2)
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	NCT05111561 See https://clinicaltrials.gov/ct2/show /NCT05111561	Testing the Combination of the Anticancer Drugs ZEN003694 and Binimetinib in Patients With Advanced/Metastatic or Unresectable Solid Tumors With RAS Alterations and Triple Negative Breast Cancer	Phase 1	Houston, TX; Boston, MA; Galveston, TX
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KRAS Q61H	NCT03905148 BeiGene,clinicaltrials@beigene.com,1 (877) 828-5568	Study of the Safety and Pharmacokinetics of BGB-283 (Lifirafenib) and PD-0325901 (Mirdametinib) in Participants With Advanced or Refractory Solid Tumors	Phase 1	Houston, TX; Santa Monica, CA; Australia (4)
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List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
				Portland, OR; Sarasota, FL; San Francisco, CA; Nashville, TN; Fairfax, VA (2); Canada (4); Korea, Republic of (6); United Kingdom (3); Australia (3)
KRAS G12V	NCT03905148 BeiGene,clinicaltrials@beigene.com,1 (877) 828-5568	Study of the Safety and Pharmacokinetics of BGB-283 (Lifirafenib) and PD-0325901 (Mirdametinib) in Participants With Advanced or Refractory Solid Tumors	Phase 1	Houston, TX; Santa Monica, CA; Australia (4)
	NCT04117087 Colleen Apostol, RN,GIClinicalTrials@jhmi.edu,410-614-3644	Pooled Mutant KRAS-Targeted Long Peptide Vaccine Combined With Nivolumab and Ipilimumab for Patients With Resected Mismatch Repair Protein (MMR-p) Colorectal and Pancreatic Cancer	Phase 1	Baltimore, MD
	NCT04985604 Day One Biopharmaceuticals, clinicaltrials@dayonebio.com,650-484-0899	Tovorafenib (DAY101) Monotherapy or in Combination With Other Therapies for Patients With Melanoma and Other Solid Tumors	Phase 1 /Phase 2	Los Angeles, CA; Newport Beach, CA; Indianapolis, IN; Pittsburgh, PA; Portland, OR; Jacksonville, FL; Nashville, TN; Canada (2)
	NCT05221320 Biomed Valley Discoveries, Inc., ERK@biomed-valley.com,816-960-6600	Trial of Ulixertinib in Combination With Hydroxychloroquine in Patients With Advanced Gastrointestinal (GI) Malignancies	Phase 2	Tucson, AZ; Saint Louis, MO; Cleveland, OH; Richmond, VA; New York, NY; New Brunswick, NJ; Fairway, KS; San Francisco, CA
	NCT05379985 Revolution Medicines, Inc.,rmc-6236_ct-inquiry@revmed.com,(650) 779-2300	Study of RMC-6236 in Patients With Advanced Solid Tumors Harboring Specific Mutations in RAS	Phase 1	Houston, TX; Boston, MA; Cincinnati, OH; Austin, TX; Dallas, TX; Orange, CA; Baltimore, MD; San Antonio, TX; Salt Lake City, UT; Nashville, TN; Santa Monica, CA; Fairfax, VA; New York, NY (3)
	NCT05907304 Erasca Clinical Team,clinicaltrials@erasca.com,1-858-465-6511	A Study to Assess Naporafenib (ERAS-254) Administered With Trametinib in Patients With RAS Q61X Mutations	Phase 1	Las Vegas, NV; Houston, TX; Detroit, MI; Saint Louis, MO; Madison, WI; Atlanta, GA; Saint Petersburg, FL; Portland, OR; Sarasota, FL; San Francisco, CA; Nashville, TN; Fairfax, VA (2); Canada (4); Korea, Republic of (6); United Kingdom (3); Australia (3)
KRAS G12A	NCT03905148 BeiGene,clinicaltrials@beigene.com,1 (877) 828-5568	Study of the Safety and Pharmacokinetics of BGB-283 (Lifirafenib) and PD-0325901 (Mirdametinib) in Participants With Advanced or Refractory Solid Tumors	Phase 1	Houston, TX; Santa Monica, CA; Australia (4)
	NCT04117087 Colleen Apostol, RN,GIClinicalTrials@jhmi.edu,410-614-3644	Pooled Mutant KRAS-Targeted Long Peptide Vaccine Combined With Nivolumab and Ipilimumab for Patients With Resected Mismatch Repair Protein (MMR-p) Colorectal and Pancreatic Cancer	Phase 1	Baltimore, MD
	NCT04985604 Day One Biopharmaceuticals, clinicaltrials@dayonebio.com,650-484-0899	Tovorafenib (DAY101) Monotherapy or in Combination With Other Therapies for Patients With Melanoma and Other Solid Tumors	Phase 1 /Phase 2	Los Angeles, CA; Newport Beach, CA; Indianapolis, IN; Pittsburgh, PA; Portland, OR; Jacksonville, FL; Nashville, TN; Canada (2)
	NCT05221320 Biomed Valley Discoveries, Inc., ERK@biomed-valley.com,816-960-6600	Trial of Ulixertinib in Combination With Hydroxychloroquine in Patients With Advanced Gastrointestinal (GI) Malignancies	Phase 2	Tucson, AZ; Saint Louis, MO; Cleveland, OH; Richmond, VA; New York, NY; New Brunswick, NJ; Fairway, KS; San Francisco, CA
	NCT05379985 Revolution Medicines, Inc.,rmc-6236_ct-inquiry@revmed.com,(650) 779-2300	Study of RMC-6236 in Patients With Advanced Solid Tumors Harboring Specific Mutations in RAS	Phase 1	Houston, TX; Boston, MA; Cincinnati, OH; Austin, TX; Dallas, TX; Orange, CA; Baltimore, MD; San Antonio, TX; Salt Lake City, UT; Nashville, TN;

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
				Santa Monica, CA; Fairfax, VA; New York, NY (3)
	NCT05907304 Erasca Clinical Team,clinicaltrials@erasca.com,1-858-465-6511	A Study to Assess Naporafenib (ERAS-254) Administered With Trametinib in Patients With RAS Q61X Mutations	Phase 1	Las Vegas, NV; Houston, TX; Detroit, MI; Saint Louis, MO; Madison, WI; Atlanta, GA; Saint Petersburg, FL; Portland, OR; Sarasota, FL; San Francisco, CA; Nashville, TN; Fairfax, VA (2); Canada (4); Korea, Republic of (6); United Kingdom (3); Australia (3)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
KRAS G12A Q61H G12C G12D G12V	ASN007		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	ASTX029		ERK1/2 kinase inhibitor.	Phase 2 (Solid Tumor)
	Avutometinib		Dual Raf/MEK kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 2 (Non-small cell lung carcinoma (NSCLC), Uveal melanoma, Ovarian carcinoma)
	BBP-398		Shp-2 inhibitor.	Phase 1 (Solid Tumor)
	BDTX-4933		Braf class 1, 2, and 3 inhibitor.	Phase 1 (Solid Tumor)
	BI 1701963		Pan-K-Ras inhibitor targeting the interaction of K-Ras and SOS-1.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	BI 3011441		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Binimetinib	Mektovi	MEK1,2 inhibitor.	Phase 3 (Colorectal carcinoma (CRC)) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation)
	BMF-219		Covalent menin inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 2 (Diabetes)
	Brimarafenib		Braf class 1, 2, and 3 inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 2 (Solid Tumor)
	Defactinib		Focal adhesion kinase (FAK) inhibitor, upstream of MAPK pathway.	Phase 2 (Solid Tumor) Phase 2 (Lymphoma, Multiple myeloma (MM))
	E6201		MEK1,2, Mekk1, and Flt3 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	ERAS-601		Shp-2 inhibitor.	Phase 2 (Solid Tumor)
	ET0038		Shp-2 inhibitor.	Phase 1 (Solid Tumor)
	HBI-2376		Shp-2 inhibitor.	Phase 1 (Solid Tumor)
	HMPL-295		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	IMM-1-104		MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Non-small cell lung carcinoma (NSCLC), Pancreatic ductal adenocarcinoma)
	JAB-3068		Shp-2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Non-small cell lung carcinoma (NSCLC), Head and neck squamous cell carcinoma (HNSCC), Esophageal carcinoma)
	JAB-3312		Shp-2 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	LTT462		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	LUNA18		Ras peptide inhibitor.	Phase 1 (Solid Tumor)
	Mirdametinib		MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 2 (Glioma, Non-small cell lung carcinoma (NSCLC), Neurofibroma, Breast carcinoma, Glioneuronal tumor, Neurofibromatosis type 1, Lung cancer)
	MK-8353		ERK1/2 kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Solid Tumor)
	MRTX0902		Pan-K-Ras inhibitor targeting the	Phase 1 (Solid Tumor)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
			interaction of K-Ras and SOS-1.	
	PF-07284892		Shp-2 inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)
	PF-07799544		MEK Brain Penetrant Inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Glioma, Melanoma, Non-small cell lung carcinoma (NSCLC), Thyroid carcinoma)
	Pimasertib		MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 2 (Melanoma, Pancreatic ductal adenocarcinoma, Ovarian carcinoma, Hematologic malignancies)
	RMC-6236		Multispecific K-Ras inhibitor.	Phase 1 (Solid Tumor)
	RSC-1255		Ras inhibitor.	Phase 1 (Solid Tumor)
	Selumetinib	Koselugo	MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) FDA Approved in other indications (NF1-related plexiform neurofibroma)
	SHR7390		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Temuterkib		ERK1/2 kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Pancreatic ductal adenocarcinoma, Solid Tumor)
	Tizaterkib		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Hematologic malignancies)
	TNO155		Shp-2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 2 (Non-small cell lung carcinoma (NSCLC))
	Trametinib	Mekinist	MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) FDA Approved in other indications (Melanoma with BRAF V600 mutation)
	Ulixertinib		ERK1/2 kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 2 (Gastric carcinoma, Melanoma, Histiocytic and dendritic cell neoplasms, Langerhans cell histiocytosis (LCH), Uveal melanoma, Acute myeloid leukemia (AML), Gastrointestinal carcinoma, Non-Hodgkin lymphoma (NHL), Myelodysplastic Syndrome (MDS))
	Vociprotafib		Shp-2 inhibitor.	Phase 2 (Solid Tumor)
NRAS Q61R	ASN007		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	ASTX029		ERK1/2 kinase inhibitor.	Phase 2 (Solid Tumor)
	Avutometinib		Dual Raf/MEK kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 2 (Non-small cell lung carcinoma (NSCLC), Uveal melanoma, Ovarian carcinoma)
	BDTX-4933		Braf class 1, 2, and 3 inhibitor.	Phase 1 (Solid Tumor)
	BI 3011441		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Binimetinib	Mektovi	MEK1,2 inhibitor.	Phase 3 (Colorectal carcinoma (CRC)) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation)
	Brimarafenib		Braf class 1, 2, and 3 inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 2 (Solid Tumor)
	Defactinib		Focal adhesion kinase (FAK) inhibitor, upstream of MAPK	Phase 2 (Solid Tumor) Phase 2 (Lymphoma, Multiple myeloma (MM))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
			pathway.	
	E6201		MEK1,2, Mekk1, and Flt3 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	HBI-2376		Shp-2 inhibitor.	Phase 1 (Solid Tumor)
	HMPL-295		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	IMM-1-104		MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Non-small cell lung carcinoma (NSCLC), Pancreatic ductal adenocarcinoma)
	LTT462		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	LUNA18		Ras peptide inhibitor.	Phase 1 (Solid Tumor)
	Mirdametinib		MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 2 (Glioma, Non-small cell lung carcinoma (NSCLC), Neurofibroma, Breast carcinoma, Glioneuronal tumor, Neurofibromatosis type 1, Lung cancer)
	MK-8353		ERK1/2 kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Solid Tumor)
	PF-07284892		Shp-2 inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)
	PF-07799544		MEK Brain Penetrant Inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Glioma, Melanoma, Non-small cell lung carcinoma (NSCLC), Thyroid carcinoma)
	Pimasertib		MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 2 (Melanoma, Pancreatic ductal adenocarcinoma, Ovarian carcinoma, Hematologic malignancies)
	RSC-1255		Ras inhibitor.	Phase 1 (Solid Tumor)
	Selumetinib	Koselugo	MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) FDA Approved in other indications (NF1-related plexiform neurofibroma)
	SHR7390		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Temuterkib		ERK1/2 kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Pancreatic ductal adenocarcinoma, Solid Tumor)
	Tizaterkib		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Hematologic malignancies)
	Trametinib	Mekinist	MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) FDA Approved in other indications (Melanoma with BRAF V600 mutation)
	Ulixertinib		ERK1/2 kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 2 (Gastric carcinoma, Melanoma, Histiocytic and dendritic cell neoplasms, Langerhans cell histiocytosis (LCH), Uveal melanoma, Acute myeloid leukemia (AML), Gastrointestinal carcinoma, Non-Hodgkin lymphoma (NHL), Myelodysplastic Syndrome (MDS))
KRAS G12C	BBO-8520		KRAS G12C inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
	BI 1823911		KRAS G12C inhibitor.	Phase 1 (Solid Tumor)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	BPI-421286		KRAS G12C inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	D3S-001		KRAS G12C inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	Divarasib		KRAS G12C inhibitor.	Phase 1 (Solid Tumor)
	Garsorasib		KRAS G12C inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	GH35		KRAS G12C inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	HBI-2438		KRAS G12C inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	HS-10370		KRAS G12C inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Non-small cell lung carcinoma (NSCLC))
	IBI351		KRAS G12C inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	JAB-21822		KRAS G12C inhibitor.	Phase 1 (Solid Tumor)
	JDQ443		KRAS G12C inhibitor.	Phase 2 (Solid Tumor)
	LY3537982		KRAS G12C inhibitor.	Phase 1 (Solid Tumor)
	MK-1084		KRAS G12C inhibitor.	Phase 1 (Solid Tumor)
	RMC-6291		KRAS G12C inhibitor.	Phase 1 (Solid Tumor)
	Sotorasib	Lumakras	KRAS G12C inhibitor.	Phase 3 (Colorectal carcinoma (CRC)) FDA Approved in other indications (NSCLC with KRAS G12C)
	Sotorasib+cetuximab	Lumakras+Erbitux	KRAS G12C inhibitor + anti-Egfr monoclonal antibody combination.	
	Sotorasib+panitumumab	Lumakras+Vectibix	KRAS G12C inhibitor + anti-Egfr monoclonal antibody combination.	Phase 3 (Colorectal carcinoma (CRC))
	YL-15293		KRAS G12C inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Non-small cell lung carcinoma (NSCLC))
MAP2K1 K57T K57E	ASN007		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	ASTX029		ERK1/2 kinase inhibitor.	Phase 2 (Solid Tumor)
	BI 3011441		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Binimetinib	Mektovi	MEK1,2 inhibitor.	Phase 3 (Colorectal carcinoma (CRC)) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation)
	E6201		MEK1,2, Mekk1, and Flt3 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	HMPL-295		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	IMM-1-104		MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Non-small cell lung carcinoma (NSCLC), Pancreatic ductal adenocarcinoma)
	LTT462		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	Mirdametinib		MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 2 (Glioma, Non-small cell lung carcinoma (NSCLC), Neurofibroma, Breast carcinoma, Glioneuronal tumor, Neurofibromatosis type 1, Lung cancer)
	MK-8353		ERK1/2 kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Solid Tumor)
	PF-07799544		MEK Brain Penetrant Inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Glioma, Melanoma, Non-small cell lung carcinoma (NSCLC), Thyroid carcinoma)
	Pimasertib		MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 2 (Melanoma, Pancreatic ductal adenocarcinoma, Ovarian carcinoma, Hematologic malignancies)
	Selumetinib	Koselugo	MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) FDA Approved in other indications (NF1-related plexiform neurofibroma)
	SHR7390		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Temuterkib		ERK1/2 kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Pancreatic ductal adenocarcinoma, Solid Tumor)
	Tizaterkib		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Hematologic malignancies)
	Trametinib	Mekinist	MEK1,2 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) FDA Approved in other indications (Melanoma with BRAF V600 mutation)
	Ulixertinib		ERK1/2 kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 2 (Gastric carcinoma, Melanoma, Histiocytic and dendritic cell neoplasms, Langerhans cell histiocytosis (LCH), Uveal melanoma, Acute myeloid leukemia (AML), Gastrointestinal carcinoma, Non-Hodgkin lymphoma (NHL), Myelodysplastic Syndrome (MDS))
KRAS G12D	Anti-KRAS G12D mTCR cells		Peripheral blood lymphocytes transduced with a murine T-Cell receptor recognizing K-Ras G12D.	Phase 2 (Solid Tumor)
	ASP3082		KRAS G12D degrader.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	ELI-002		Amph-modified KRAS G12D and G12R peptide immunotherapy.	Phase 1 (Solid Tumor)
	HRS-4642		KRAS G12D inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	Mesenchymal stromal cells-derived exosomes with KRAS G12D siRNA		Mesenchymal stromal cells-derived exosomes with KRAS G12D siRNA.	Phase 1 (Pancreatic carcinoma)
	MRTX1133		KRAS G12D inhibitor.	Phase 1 (Solid Tumor)
	QTX3034		KRAS G12D inhibitor.	Phase 1 (Solid Tumor)
	siG12D-LODER		Antisense oligonucleotide targeting G12D mutant K-Ras.	Phase 2 (Pancreatic carcinoma)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
KRAS G12V	Anti-KRAS G12V mTCR cells		Peripheral blood lymphocytes transduced with a murine T-Cell receptor recognizing K-Ras G12V.	Phase 2 (Cancer)
	KRAS G12V-specific T-cells		Mutant KRAS G12V-specific TCR transduced autologous T-cells.	Phase 2 (Pancreatic carcinoma)
KRAS G12C G12D G12V	GI-4000		Mutant K-Ras vaccine.	Phase 2 (Colorectal carcinoma (CRC)) Phase 2 (Pancreatic carcinoma, Non-small cell lung carcinoma (NSCLC))
	V941		Mutant K-Ras vaccine.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Pancreatic carcinoma, Non-small cell lung carcinoma (NSCLC))
KRAS G12A G12C G12D G12V	Pooled mutant KRAS-targeted long peptide vaccine		KRAS G12-mutant targeted vaccine.	Phase 1 (Non-small cell lung carcinoma (NSCLC))

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
KRAS Q61H	The KRAS gene is one of the most commonly mutated genes in human malignancies, with high incidences in pancreatic, colorectal, and lung cancers. [1-3]. Studies using xenograft models or cell lines of colorectal cancer have reported that activating KRAS mutations, often assessed in the context of other genetic alterations, can play a role in the development and progression of colorectal cancer. [4,5].	Many of the current attempts to target K-Ras are directed against its downstream signaling pathways, Raf /MEK/ERK and PI3K/Akt/mTOR. [6,7]. Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant. [8-17]. Other clinical approaches are being investigated preclinically and clinically in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors. [18-23]. In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically. [24-27]. Sotorasib and adagrasib have been FDA-approved in patients with locally advanced or metastatic non-small cell lung carcinoma harboring a KRAS G12C mutation, as determined by an FDA-approved test, following treatment with at least one prior systemic therapy. [28-32]. In addition, combinations of adagrasib or sotorasib with cetuximab or panitumumab have been reported to provide clinical benefit in CRC patients with KRAS G12C mutation and the combination of adagrasib with cetuximab has been granted “breakthrough” designation by the FDA for accelerated review. [33-36].	In some cancer types, such as colorectal cancer (CRC) and non-small cell lung cancer (NSCLC), activating KRAS mutations and KRAS amplification have been associated with resistance to Egfr-targeted therapies. [37-45]. For colorectal carcinoma patients with metastatic disease and tumors harboring a KRAS exon 2, 3, or 4 [amino acids 1-150] or NRAS exon 2, 3, or 4 [amino acids 1-150] mutation, numerous professional guidelines, including NCCN, ESMO, and Pan-Asian Guidelines, recommend against the use of single agent cetuximab and panitumumab. [46,47].
NRAS Q61R	Activation of N-Ras signaling causes cell growth, differentiation, and survival by activating the Raf/MEK/ERK, PI3K, and other pathways. [48]. NRAS mutations have been found to be mutually exclusive with KRAS and BRAF mutations in colorectal carcinoma. [49-55].	At present there are no approved therapies to directly target NRAS activating mutations. However, N-Ras activation may predict sensitivity to inhibitors of the Raf/MEK/ERK, PI3K /Akt, and other downstream pathways. [48,57]. Several MEK inhibitors are under clinical investigation and may be relevant for tumors harboring N-Ras activation. [7,58-60].	In some cancer types, such as colorectal cancer and non-small cell lung cancer, activating NRAS mutations have been associated with resistance to Egfr inhibitors and/or antibodies. [38-43]. For colorectal carcinoma patients with metastatic disease and tumors harboring a KRAS exon 2, 3, or 4 [amino acids 1-150] or NRAS exon 2, 3, or 4 [amino acids 1-150] mutation, numerous professional guidelines, including NCCN, ESMO, and Pan-Asian Guidelines, recommend against the use of single agent cetuximab and panitumumab. [46,47].
KRAS G12C	The KRAS gene is one of the most commonly mutated genes in human malignancies, with high incidences in pancreatic, colorectal, and lung cancers. [1-3]. Studies using xenograft models or cell lines of colorectal cancer have reported that activating	Many of the current attempts to target K-Ras are directed against its downstream signaling pathways, Raf /MEK/ERK and PI3K/Akt/mTOR. [6,7]. Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations	In some cancer types, such as colorectal cancer (CRC) and non-small cell lung cancer (NSCLC), activating KRAS mutations and KRAS amplification have been associated with resistance to Egfr-targeted therapies. [37-45]. For colorectal

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	KRAS mutations, often assessed in the context of other genetic alterations, can play a role in the development and progression of colorectal cancer. [4,5].	of MEK inhibitors with other targeted therapies may still be relevant. [8-17]. Other clinical approaches are being investigated preclinically and clinically in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors. [18-23]. In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically. [24-27]. Sotorasib and adagrasib have been FDA-approved in patients with locally advanced or metastatic non-small cell lung carcinoma harboring a KRAS G12C mutation, as determined by an FDA-approved test, following treatment with at least one prior systemic therapy. [28-32]. In addition, combinations of adagrasib or sotorasib with cetuximab or panitumumab have been reported to provide clinical benefit in CRC patients with KRAS G12C mutation and the combination of adagrasib with cetuximab has been granted "breakthrough" designation by the FDA for accelerated review. [33-36]. One of the alterations in this report has been associated with resistance to the KRAS G12C inhibitor adagrasib. One or several of the alterations in this report have been described as acquired mutations associated with resistance or reduced sensitivity to the KRAS G12C inhibitor adagrasib. [61].	carcinoma patients with metastatic disease and tumors harboring a KRAS exon 2, 3, or 4 [amino acids 1-150] or NRAS exon 2, 3, or 4 [amino acids 1-150] mutation, numerous professional guidelines, including NCCN, ESMO, and Pan-Asian Guidelines, recommend against the use of single agent cetuximab and panitumumab. [46,47].
MAP2K1 K57T	Large-scale studies of human tumors and tumor cell lines have identified activating MAP2K1 mutations in a number of samples. [62,63]. Preclinical studies have reported that expression of activated forms of MEK1 is sufficient to transform intestinal epithelial cells, and is associated with the formation of high-grade adenocarcinoma tumors in mice. Furthermore, the inhibition of MAP2K1 expression was reported to weakly suppress proliferation in human colon adenocarcinoma cell lines. [64]. Also, a preclinical study reported that lung, colon, and gastric cell lines harboring suspected MAP2K1 activating alterations exhibited decreased viability after MEK1 depletion or trametinib treatment as compared with cancer cell lines that did not harbor such alterations. [65].	Some mutations in MAP2K1 may confer sensitivity to MEK inhibitors, several of which are in clinical development. [66]. Several MEK inhibitors are under clinical investigation, including several agency-approved therapies such as trametinib, cobimetinib, and binimetinib. [7,58-60,67-69].	Several MAP2K1 mutations have been associated with acquired resistance to treatment with Braf and/or MEK inhibitors. [70-74]. However, combination treatments with Braf and MEK inhibitors have been reported to overcome this resistance. [74]. MAP2K1 K57T has been reported in patients with acquired resistance to cetuximab, panitumumab, cetuximab with vemurafenib or encorafenib, vemurafenib, and adagrasib. [61,75-79]. A study of 129 colorectal cancer patient-derived tumor xenografts and 55 tumor samples reported that a mutation in MAP2K1 was associated with resistance to cetuximab therapy but sensitivity to combined treatment with ERK1/2 inhibitor SCH772984 and MEK1/2 inhibitor selumetinib. [80]. One study has reported MAP2K1 mutations in two CRC patients with primary resistance to panitumumab monotherapy. [81]. Additionally,

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
			acquired MAP2K1 mutations have been reported in ctDNA samples from BRAF V600E positive CRC patients after progression on treatment with vemurafenib and erlotinib. [82].
KRAS G12D	The KRAS gene is one of the most commonly mutated genes in human malignancies, with high incidences in pancreatic, colorectal, and lung cancers. [1-3]. Studies using xenograft models or cell lines of colorectal cancer have reported that activating KRAS mutations, often assessed in the context of other genetic alterations, can play a role in the development and progression of colorectal cancer. [4,5].	Many of the current attempts to target K-Ras are directed against its downstream signaling pathways, Raf /MEK/ERK and PI3K/Akt/mTOR. [6,7]. Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant. [8-17]. Other clinical approaches are being investigated preclinically and clinically in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors. [18-23]. In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically. [24-27]. Sotorasib and adagrasib have been FDA-approved in patients with locally advanced or metastatic non-small cell lung carcinoma harboring a KRAS G12C mutation, as determined by an FDA-approved test, following treatment with at least one prior systemic therapy. [28-32]. In addition, combinations of adagrasib or sotorasib with cetuximab or panitumumab have been reported to provide clinical benefit in CRC patients with KRAS G12C mutation and the combination of adagrasib with cetuximab has been granted “breakthrough” designation by the FDA for accelerated review. [33-36].	In some cancer types, such as colorectal cancer (CRC) and non-small cell lung cancer (NSCLC), activating KRAS mutations and KRAS amplification have been associated with resistance to Egfr-targeted therapies. [37-45]. For colorectal carcinoma patients with metastatic disease and tumors harboring a KRAS exon 2, 3, or 4 [amino acids 1-150] or NRAS exon 2, 3, or 4 [amino acids 1-150] mutation, numerous professional guidelines, including NCCN, ESMO, and Pan-Asian Guidelines, recommend against the use of single agent cetuximab and panitumumab. [46,47].
MAP2K1 K57E	Large-scale studies of human tumors and tumor cell lines have identified activating MAP2K1 mutations in a number of samples. [62,63]. Preclinical studies have reported that expression of activated forms of MEK1 is sufficient to transform intestinal epithelial cells, and is associated with the formation of high-grade adenocarcinoma tumors in mice. Furthermore, the inhibition of MAP2K1 expression was reported to weakly suppress proliferation in human colon adenocarcinoma cell lines. [64]. Also, a preclinical study reported that lung, colon, and gastric cell lines harboring suspected MAP2K1 activating alterations exhibited decreased viability after MEK1 depletion or trametinib treatment as	Some mutations in MAP2K1 may confer sensitivity to MEK inhibitors, several of which are in clinical development. [66]. Several MEK inhibitors are under clinical investigation, including several agency-approved therapies such as trametinib, cobimetinib, and binimetinib. [7,58-60,67-69]. However, MAP2K1 K57E has been reported to exhibit resistance to the MEK inhibitor, cobimetinib, and BRAF inhibitors, including vemurafenib, dabrafenib, and encorafenib as monotherapies, while a synergistic effect was observed following combination treatments with MEK and BRAF inhibitors in a BRAF V600E-mutated melanoma cell line. [83]. In	Several MAP2K1 mutations have been associated with acquired resistance to treatment with Braf and/or MEK inhibitors. [70-74]. However, combination treatments with Braf and MEK inhibitors have been reported to overcome this resistance. [74]. A study of 129 colorectal cancer patient-derived tumor xenografts and 55 tumor samples reported that a mutation in MAP2K1 was associated with resistance to cetuximab therapy but sensitivity to combined treatment with ERK1/2 inhibitor SCH772984 and MEK1/2 inhibitor selumetinib. [80]. One study has reported MAP2K1 mutations in two CRC patients with primary resistance to panitumumab

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	compared with cancer cell lines that did not harbor such alterations. (65).	addition, this alteration has been reported in a patient with resistance to the Braf inhibitor dabrafenib and has been shown to confer dabrafenib resistance when expressed in melanoma cells. (73,84).	monotherapy. (81). Additionally, acquired MAP2K1 mutations have been reported in ctDNA samples from BRAF V600E positive CRC patients after progression on treatment with vemurafenib and erlotinib. (82).
KRAS Q61H	The KRAS gene is one of the most commonly mutated genes in human malignancies, with high incidences in pancreatic, colorectal, and lung cancers. (1-3). Studies using xenograft models or cell lines of colorectal cancer have reported that activating KRAS mutations, often assessed in the context of other genetic alterations, can play a role in the development and progression of colorectal cancer. (4,5).	Many of the current attempts to target K-Ras are directed against its downstream signaling pathways, Raf /MEK/ERK and PI3K/Akt/mTOR. (6,7). Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant. (8-17). Other clinical approaches are being investigated preclinically and clinically in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors. (18-23). In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically. (24-27). Sotorasib and adagrasib have been FDA-approved in patients with locally advanced or metastatic non-small cell lung carcinoma harboring a KRAS G12C mutation, as determined by an FDA-approved test, following treatment with at least one prior systemic therapy. (28-32). In addition, combinations of adagrasib or sotorasib with cetuximab or panitumumab have been reported to provide clinical benefit in CRC patients with KRAS G12C mutation and the combination of adagrasib with cetuximab has been granted “breakthrough” designation by the FDA for accelerated review. (33-36).	In some cancer types, such as colorectal cancer (CRC) and non-small cell lung cancer (NSCLC), activating KRAS mutations and KRAS amplification have been associated with resistance to Egfr-targeted therapies. (37-45). For colorectal carcinoma patients with metastatic disease and tumors harboring a KRAS exon 2, 3, or 4 [amino acids 1-150] or NRAS exon 2, 3, or 4 [amino acids 1-150] mutation, numerous professional guidelines, including NCCN, ESMO, and Pan-Asian Guidelines, recommend against the use of single agent cetuximab and panitumumab. (46,47).
KRAS G12V	The KRAS gene is one of the most commonly mutated genes in human malignancies, with high incidences in pancreatic, colorectal, and lung cancers. (1-3). Studies using xenograft models or cell lines of colorectal cancer have reported that activating KRAS mutations, often assessed in the context of other genetic alterations, can play a role in the development and progression of colorectal cancer. (4,5).	Many of the current attempts to target K-Ras are directed against its downstream signaling pathways, Raf /MEK/ERK and PI3K/Akt/mTOR. (6,7). Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant. (8-17). Other clinical approaches are being investigated preclinically and clinically in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors. (18-23). In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically	In some cancer types, such as colorectal cancer (CRC) and non-small cell lung cancer (NSCLC), activating KRAS mutations and KRAS amplification have been associated with resistance to Egfr-targeted therapies. (37-45). For colorectal carcinoma patients with metastatic disease and tumors harboring a KRAS exon 2, 3, or 4 [amino acids 1-150] or NRAS exon 2, 3, or 4 [amino acids 1-150] mutation, numerous professional guidelines, including NCCN, ESMO, and Pan-Asian Guidelines, recommend against the use of single agent cetuximab and panitumumab. (46,47).

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
		and preclinically. [24-27]. Sotorasib and adagrasib have been FDA-approved in patients with locally advanced or metastatic non-small cell lung carcinoma harboring a KRAS G12C mutation, as determined by an FDA-approved test, following treatment with at least one prior systemic therapy. [28-32]. In addition, combinations of adagrasib or sotorasib with cetuximab or panitumumab have been reported to provide clinical benefit in CRC patients with KRAS G12C mutation and the combination of adagrasib with cetuximab has been granted "breakthrough" designation by the FDA for accelerated review. [33-36].	
KRAS G12A	The KRAS gene is one of the most commonly mutated genes in human malignancies, with high incidences in pancreatic, colorectal, and lung cancers. [1-3]. Studies using xenograft models or cell lines of colorectal cancer have reported that activating KRAS mutations, often assessed in the context of other genetic alterations, can play a role in the development and progression of colorectal cancer. [4,5].	Many of the current attempts to target K-Ras are directed against its downstream signaling pathways, Raf /MEK/ERK and PI3K/Akt/mTOR. [6,7]. Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant. [8-17]. Other clinical approaches are being investigated preclinically and clinically in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors. [18-23]. In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically. [24-27]. Sotorasib and adagrasib have been FDA-approved in patients with locally advanced or metastatic non-small cell lung carcinoma harboring a KRAS G12C mutation, as determined by an FDA-approved test, following treatment with at least one prior systemic therapy. [28-32]. In addition, combinations of adagrasib or sotorasib with cetuximab or panitumumab have been reported to provide clinical benefit in CRC patients with KRAS G12C mutation and the combination of adagrasib with cetuximab has been granted "breakthrough" designation by the FDA for accelerated review. [33-36].	In some cancer types, such as colorectal cancer (CRC) and non-small cell lung cancer (NSCLC), activating KRAS mutations and KRAS amplification have been associated with resistance to Egfr-targeted therapies. [37-45]. For colorectal carcinoma patients with metastatic disease and tumors harboring a KRAS exon 2, 3, or 4 [amino acids 1-150] or NRAS exon 2, 3, or 4 [amino acids 1-150] mutation, numerous professional guidelines, including NCCN, ESMO, and Pan-Asian Guidelines, recommend against the use of single agent cetuximab and panitumumab. [46,47].

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