Patient Name:	Dummy	**Booking ID:**	XXX
Age:	81 Years	**Sample Type:**	FFPE Tissue Block
Gender:	Female	**Sample collection date:**	XXX
Referring doctor:	NA	**Sample receiving date:**	XXX
Test Requested:	Solid Tumor Advanced Panel by NGS (DNA+RNA)	**Reporting date:**	XXX

SOLID TUMOR ADVANCED PANEL REPORT BY NGS

CLINICAL INDICATION

Diagnosis: Known case of invasive ductal carcinoma, metastatic to liver, post chemo, post radiation recurrent occurrence. (Tumor content was 70%, test performed on FFPE Block H2403501).

TEST RESULT SUMMARY

(Clinically relevant actionable mutation were detected in *IDH1* & *KRAS* gene)

SUMMARY OF VARIANTS

SNVs/InDels

Genes & transcript	Variants	Exon & Locus	Overall coverage & Allele frequency	Function of gene in cancer	*Tier Classification
IDH1 (-) NM_005896.4	p.Arg132Cys c.394C>T	Exon 4 chr2:209113113	1998x & AF-22.22	Gain-of-Function (variant class-Hotspot)	Tier: IIC
KRAS (-) NM_033360.4	p.Gln61His p.(Q61H) c.183A>C	Exon 3 chr12:25380275	1989x & AF- 85.67 %	Gain-of-Function (variant class-Hotspot)	Tier: IIC

*Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

Fusions genes status:

Genes & transcript IDs	Breakpoints	Chromosome & Exon	Tier Classification
Not Detected			

Variant description & clinical interpretation:

1. Potential relevance of IDH1 p.(R132C) c.394C>T: IDH1 inhibitor, olutasidenib10 is approved (2022) for the treatment of IDH1 R132C/G/H/L/S variants in AML. Ivosidenib11 is also FDA approved (2018) for the treatment of AML or cholangiocarcinoma patients with IDH1 R132C/G/H/L/S variants12. Ivosidenib was granted breakthrough therapy designation (2020) for the treatment of IDH1 mutated relapsed or refractory myelodysplastic syndrome (MDS)13. The FDA also granted fast track designation (2023) to the small-molecule IDH1 and IDH2 selective inhibitor, vorasidenib, for IDH-mutant (Grade 2) gliomas14. IDH1 mutations are associated with inferior leukemia-free survival in primary myelofibrosis (PMF) and inferior overall survival in polycythemia vera (PV) but have been shown to confer improved prognosis in lower grade gliomas15,16,17. Mutations in IDH1 are diagnostic of astrocytoma IDH-mutant and oligodendroglioma IDH-mutant and 1p/19q codeleted subtypes of central nervous system (CNS) tumors18.

2. Potential relevance of KRAS p.(Q61H) c.183A>C: FDA has approved the small molecule inhibitors, sotorasib25 (2021) and adagrasib26 (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Sotorasib and adagrasib are also useful in certain circumstances for KRAS G12C-mutated pancreatic adenocarcinoma27. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-603628, for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-39829 was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutometinib30 was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor. The PLK1 inhibitor, onvansertib31, was granted fast track designation (2020) in combination with bevacizumab and FOLFIRI for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab32 and panitumumab33, are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)24. Additionally, KRAS mutations are associated with poor prognosis in NSCLC34.

COMMENT

- ✓ Please correlate clinically.
- ✓ Genetic counseling for accurate interpretation of test results is recommended.
- ✓ Correlation of the genetic findings with the clinical condition of the patient is required to arrive at an accurate diagnosis, prognosis or therapeutic decisions.
- ✓ We recommend the confirming of above variants by an alternate method i.e. Sanger sequencing technique.
- ✓ For questions about this report, or for assistance in locating nearby genetic counseling services, please contact the Laboratory: geneticcounselors@redcliffelabs.com, ccsupport@redcliffelabs.com.

METHODOLOGY & VARIANT ANALYSIS

Methodology: Next Generation Sequencing: The clinically relevant genes have been selected on the basis of their known impact as actionable targets of existing and emerging anti-cancer therapies, and prognostic features in various tumor types. The sensitivity of the assays depends on the quality of the FFPE tissue block/slide, and its tumor percentage (>10-15%). In the multiple validation studies, the limit of detection (LOD) were observed at 5% with depth >500x. In process quality controls were determined for prepared library. The libraries were sequenced at range mean depth: >500-1500x on Ion Torrent next generation sequencing platform. Reference sequence to the GRCh37 (hg19) assembly of the human genome were used. Genomic DNA and RNA were isolated from FFPE tissue block sample using commercial kit according to manufacturer's instructions and the target regions of interest were amplified using the targeted gene panel. Library preparation was performed and sequenced on the Ion Torrent Gene Studio S5 plus sequencer. The FASTQ/BAM file reads were aligned against the hg19 in the Torrent suite software (v5.18.1). Variant calling and annotations were done using Variant Annotator v3.3. AMP-ASCO-CAP guidelines were followed for variant classification. Clinically relevant mutations were identified and annotated using published variants in literature and a set of databases. The effect of non-synonymous variant is calculated using multiple prediction algorithms such as PolyPhen, SIFT, Mutation Taster2.

Tools and Databases employed for analysis: Clinvar, OMIM, HGMD, UCSC genome browser, Uniprot, Ensembl, dbSNP, gnomAD, ExAC, Pubmed, Dgap, icgc, Kaviar, various bioinformatics analysis, predictive tools and disease specific databases used as available and appropriate. Such tools/databases would be mentioned wherever used.

TEST LIMITATIONS

- ✓ It should be noted that this test is limited to a limited number of genes and does not include all intronic and non-coding regions.
- ✓ This report only includes variants that meets a level of evidence threshold for cause or contribute to disease. Test results are interpreted in the context of clinical & pathological findings and laboratory data.
- ✓ The accuracy and completeness may vary due to variable information available in different databases. Synonymous mutations were not considered while preparing this report.
- ✓ Variant with minimum 250x coverage or more as 500x are considered for clinical correlation with the disease. Only mutations having VAF >5% will be reported. PCR primer binding site polymorphisms or mutations might lead to allele dropout & cause false negative results.

- ✓ Mutations in under-performing amplicon (<100x coverage) may be missed. Fusions having deep intronic breakpoints might be missed. Indel exceeding 50 bp size may not be detected.
- ✓ The variants have not been confirmed using Sanger sequencing and/or alternate technologies. To rule out germ line mutations i.e. variant with variant allele frequency at nearly 50% or 100%, whole blood sample is recommended to process along with tissue sample.
- ✓ The sensitivity of this assay to detect small deletions/duplication is upto certain number of bases only. CNVs if detected with this assay have to be confirmed by alternate method such as MLPA & Micro-array.
- ✓ Variations with high minor allele frequencies which are benign/likely benign will be given upon request if required. Certain genes may not be covered completely, and few mutations could be missed.
- ✓ Due to inherent technology limitations, coverage is not uniform across all regions. Hence, pathogenic variants present in areas of insufficient coverage as well as those variants which currently do not correlate with the provided phenotype may not be analyzed/ reported. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity.
- ✓ This assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements. Incidental or secondary findings (if any) that meet the ACMG/AMP-ASCO-CAP guidelines can be given upon request.
- ✓ Genes with pseudo-genes, para-log genes and genes with low complexity may have decreased sensitivity and specificity of variant detection and interpretation due to inability of the data and analysis tools to unambiguously determine the origin of the sequence data in such regions. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS).
- ✓ All laboratory tests are associated with an error rate of ~1%. These could be due to sample mismatch, inappropriate labeling, processing or technological limitations. Please correlate with clinical features and other investigations for final conclusion and send a repeat sample for analysis if necessary.
- ✓ The transcript used for clinical reporting generally represents the canonical transcript, which is usually the longest coding transcript with strong/multiple supporting evidence. However, clinically relevant variants annotated in alternate complete coding transcripts could also be reported.

DISCLAIMER

- ❖ Test has been performed assuming that the sample received belongs to the above-named individual(s) and that any stated relationships between individuals are accepted as true. It is also assumed that consent for the same was provided after pre- test counseling at the point of collection/referral.
- ❖ The results should be interpreted in the context of the patient's medical evaluation, family history and racial/ethnic background. Please note that variant classification and/or interpretation may change over time if more information available. Re-interpretation of multi gene next generation sequencing data is recommended on an annual basis and may be requested by a medical provider.
- ❖ More evidence for disease association of genes and causal pathogenic variants are discovered every year, and it is recommended that genetic variants are re-interpreted with updated software and annotations periodically.
- ❖ Rare polymorphisms may lead to false negative or positive results. False negative results may be due to sampling error/errors in sample handling as well as clonal density below the limit of detection. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. Identification of a mutation in one or more of these genes does not guarantee activity of the drug in a given indication due to the presence of contraindicated mutation in the gene not covered by the panel.
- ❖ The information provided should only be utilized as a guide or aid and the decision to select any therapy option based on the information reported here resides solely with the discretion of the treating physician.
- ❖ Patient care and treatment decisions should only be made by the physician after taking into account all relevant information available including but not limited to the patient's condition, family history, findings upon examination, results of other diagnostic tests, and the current standards of care.
- ❖ This report should only be used as an aid and the physician should employ sound clinical judgment in arriving at any decision for patient care or treatment.

- By providing drug information for the reported diagnosis, Redcliffe Lab Pvt. Ltd. is not guaranteeing that any drug or clinical trial is necessarily appropriate for this patient.
- Healthcare providers should evaluate and interpret the information provided in this report, along with all other available clinical information about this patient, to determine the best treatment decisions in their own independent medical judgment. Patient management decisions should not be based on a single test, including this one, nor solely on the information contained in this report.

LIST OF GENES ASSAYED

- **Genes Assayed for the Detection of DNA Sequence Variants**
  AKT1, ALK, AR, BRAF, CDK4, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FGFR2, FGFR3, GNA11, GNAQ, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, PDGFRA, PIK3CA, RAF1, RET, ROS1, SMO
- **Genes Assayed for the Detection of Copy Number Variations**
  ALK, AR, BRAF, CCND1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, FGFR4, KIT, KRAS, MET, MYC, MYCN, PDGFRA, PIK3CA
- **Genes Assayed for the Detection of Fusions**
  ALK, RET, ROS1, NTRK1, NTRK2, NTRK3, FGFR1, FGFR2, FGFR3, MET, BRAF, RAF1, ERG, ETV1, ETV4, ETV5, ABL1, AKT3, AXL, EGFR, ERBB2, PDGFRA, PPARG

VARIANT REPORTING CLASSIFICATION BASED ON AMP-ASCO-CAP RECOMMENDATIONS

Variants	**A change in a gene. This could be disease causing (pathogenic) or not disease causing(benign).**
Tier I	***Variants with Strong Clinical Significance (Level A and B Evidence)*** **Level A**, biomarkers that predict response or resistance to US FDA-approved therapies for a specific type of tumor or have been included in professional guidelines as therapeutic, diagnostic, and/or prognostic biomarkers for specific types of tumors; **Level B**, biomarkers that predict response or resistance to a therapy based on well- powered studies with consensus from experts in the field or have diagnostic and/or prognostic significance of certain diseases based on well-powered studies with expert consensus.
Tier II	***Variants with Potential Clinical Significance (Level C and D Evidence)*** **Level C**, biomarkers that predict response or resistance to therapies approved by FDA or professional societies for a different tumor type (i.e., off-label use of a drug), serve as inclusion criteria for clinical trials, or have diagnostic and/or prognostic significance based on the results of multiple small studies. **Level D**, biomarkers that show plausible therapeutic significance based on preclinical studies or may assist disease diagnosis and/or prognosis themselves or along with other biomarkers based on small studies or multiple case reports with no consensus.
Tier III	***Variants of Unknown Significance*** Not observed at a significant allele frequency in the general or specific sub population or pan cancer or tumor specific variant databases. No convincing published evidence of Cancer Association
Tier IV	***Benign or Likely Benign***

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---------- **End Of Report** ----------

Reviewed by Imran Haider
Senior Scientific Officer
Onco-Genomics

Approved by
Dr. Himani Pandey
Postdoc-SGPGIMS Lucknow
Lab Head-Clinical Genomics

Patient Name: Dummy **Booking ID: XXX** **XXX**

Additional report for reference

Relevant Biomarkers

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

Tier	Genomic Alteration	FDA	NCCN	EMA	ESMO	Clinical Trials
IIC	*IDH1 p.(R132C) c.394C>T* isocitrate dehydrogenase (NADP(+)) 1, cytosolic Allele Frequency: 22.22% Locus: chr2:209113113 Transcript: NM_005896.4	○ (1)	○ (1)	○ (1)	○ (1)	● (4)
IIC	*KRAS p.(Q61H) c.183A>C* KRAS proto-oncogene, GTPase Allele Frequency: 85.67% Locus: chr12:25380275 Transcript: NM_033360.4	⊘ (2)	⊘ (2)	⊘ (3)	⚠ (6)	● (35)

FDA: United States-Food and Drug Administration, **NCCN:** United States-National Comprehensive Cancer Network, **EMA:** European Medicine Agency, **ESMO:** European Society for Medical Oncology. Numbers in parentheses indicate the number of relevant therapies with evidence.
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Relevant Breast Cancer Findings

Gene	Finding	Gene	Finding
AKT1	None detected	NTRK2	None detected
BRAF	None detected	NTRK3	None detected
ERBB2	None detected	PIK3CA	None detected
ESR1	None detected	RET	None detected
NTRK1	None detected		

Other Findings
IDH1 p.(R132C) c.394C>T, KRAS p.(Q61H) c.183A>C

Biomarker Descriptions

IDH1 p.(R132C) c.394C>T

isocitrate dehydrogenase (NADP(+)) 1, cytosolic

Background: The IDH1 and IDH2 genes encode homologous isocitrate dehydrogenase enzymes that catalyze the conversion of isocitrate to α-ketoglutarate (α-KG)[1]. The IDH1 gene encodes the NADP+ dependent cytoplasmic isocitrate dehydrogenase enzyme; IDH2 encodes the mitochondrial isoform.

Alterations and prevalence: Recurrent somatic mutations in IDH1 and IDH2 are mutually exclusive and observed in several malignancies including glioma, chondrosarcoma, intrahepatic cholangiocarcinoma, acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS)[2]. Recurrent IDH1 variants include predominately R132H/C plus other substitutions at lower frequencies. These gain of function variants confer neomorphic enzyme activity[3]. Although wild-type enzymatic activity is ablated, recurrent IDH1 variants catalyze the conversion of α-KG to D-2-hydroxyglutarate, an oncometabolite with diverse effects on cellular metabolism, epigenetic regulation, redox states, and DNA repair[1,4]. Recurrent IDH1 mutations are present in 5-10% of patients with AML and 5% of patients with MDS[5,6,7]. Recurrent IDH1 mutations are present in nearly 80% of lower grade diffuse gliomas[8,9].

Potential relevance: The IDH1 inhibitor, olutasidenib[10] is approved (2022) for the treatment of IDH1 R132C/G/H/L/S variants in AML. Ivosidenib[11] is also FDA approved (2018) for the treatment of AML or cholangiocarcinoma patients with IDH1 R132C/G/H/L/S variants[12]. Ivosidenib was granted breakthrough therapy designation (2020) for the treatment of IDH1 mutated relapsed or refractory myelodysplastic syndrome (MDS)[13]. The FDA also granted fast track designation (2023) to the small-molecule IDH1 and IDH2 selective inhibitor, vorasidenib, for IDH-mutant (Grade 2) gliomas[14]. IDH1 mutations are associated with inferior leukemia-free survival in primary myelofibrosis (PMF) and inferior overall survival in polycythemia vera (PV) but have been shown to confer improved prognosis in lower grade gliomas[15,16,17]. Mutations in IDH1 are diagnostic of astrocytoma IDH-mutant and oligodendroglioma IDH-mutant and 1p/19q-codeleted subtypes of central nervous system (CNS) tumors[18].

KRAS p.(Q61H) c.183A>C

KRAS proto-oncogene, GTPase

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[19,20,21].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer[8]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[8,22,23]. Mutations at A59, K117, and A146 have also been observed but are less frequent[9,24].

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib[25] (2021) and adagrasib[26] (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Sotorasib and adagrasib are also useful in certain circumstances for KRAS G12C-mutated pancreatic adenocarcinoma[27]. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036[28], for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-398[29] was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutometinib[30] was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor. The PLK1 inhibitor, onvansertib[31], was granted fast track designation (2020) in combination with bevacizumab and FOLFIRI for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab[32] and panitumumab[33], are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[24]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[34].

Clinical Trials Summary

IDH1 p.(R132C) c.394C>T

NCT ID	Title	Phase
NCT04550494	A Pharmacodynamics-Driven Trial of Talazoparib, an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Aberrations in Genes Involved in DNA Damage Response	II
NCT04906473	A Phase I Clinical Study of Single-arm, Open, Single/Multiple Dose Escalation and Dose Extension to Assess the Safety, Tolerability, Pharmacokinetic, Pharmacodynamics and Efficacy of KY100001 in Patients With Advanced Solid Tumors	I
No NCT ID	Multicenter, dose escalation and cohort expansion single arm to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamic characteristics and preliminary anti-tumor efficacy of MT-001 capsules in patients with locally advanced/metastatic solid tumors , open-label phase I/IIa clinical study	I
NCT05814536	A Phase I, Multi-center, Open-label, Single-arm Study to Evaluate the Safety, Pharmacokinetics, and Preliminary Efficacy of AB-218 for Treating Adult Patients With Advanced IDH1 Mutant Cholangiocarcinoma and Other Solid Tumors	I

KRAS p.(Q61H) c.183A>C

NCT ID	Title	Phase
No NCT ID	A Dose Escalation Phase I Clinical Trial of ON 123300 in Patients With Advanced Relapsed/Refractory Cancer	I
NCT05379985	A Multicenter Open-Label Study of RMC-6236 in Patients With Advanced Solid Tumors Harboring Specific Mutations in RAS	I
NCT04116541	MegaMOST - A Multicenter, Open-label, Biology Driven, Phase II Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations /Characteristics in Advanced / Metastatic Tumors.	II
NCT05585320	A Phase I/II a, Open-Label, Multicenter, Nonrandomized, Safety and Anti-tumor Activity Study of IMM-1-104, a Novel Oral Dual MEK1/2 Inhibitor in Participants With Previously Treated RAS-Mutated Advanced or Metastatic Solid Tumors	I/II
NCT06208124	A Phase I/IIa Trial, to Evaluate Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, Dose Escalation Study of IMM-6-415 in Participants With Advanced or Metastatic Malignancies Harboring RAS or RAF Oncogenic Mutations	I/II
NCT05886374	A Multicenter, Open-Label Phase I Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of HMPL-415S1 in Patients With Advanced Malignant Solid Tumor	I
NCT06326411	A Phase I, Open Label Single-arm Two-part Study to Investigate Safety, Pharmacokinetics, and Preliminary Efficacy of Pan-RAF/MEK Glue NST-628 Oral Tablets in Subject With Solid Tumors Harboring Genetic Alterations in the MAPK Pathway and With Other Solid Tumors	I
NCT05111561	A Phase I Study of ZEN003694 in Combination With Binimetinib in Solid Tumors With RAS Pathway Alterations and Triple Negative Breast Cancer	I
NCT06229340	New Therapeutic Approaches for Tumors With RAS Gene Mutations	II
NCT05554367	A ComboMATCH Treatment Trial: Palbociclib and Binimetinib in RAS-Mutant Cancers	II
NCT05327010	Phase II Trial of the Combination of the BET Inhibitor, ZEN003694 (ZEN-3694), and the PARP Inhibitor Talazoparib, in Patients With Molecularly-Selected Solid Tumors (ComBET)	II
NCT06243354	An Open-label, Multi-center, Multi-cohort, Phase I/II Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of HYP-2090PTSA in Patients With Advanced Solidt Tumors Harboring KRAS Mutation	I/II

Clinical Trials Summary (continued)

KRAS p.(Q61H) c.183A>C (continued)

NCT ID	Title	Phase
NCT05578092	A Phase 1/2 Multiple Expansion Cohort Trial of the SOS1 Inhibitor MRTX0902 in Patients With Advanced Solid Tumors Harboring Mutations in the KRAS MAPK Pathway	I/II
NCT03919292	Phase 1/2 Study of Neratinib and Divalproex Sodium (Valproate) in Advanced Solid Tumors, With an Expansion Cohort in Ras-Mutated Cancers	I/II
NCT06237413	A Phase I/II Dose Escalation Study to Evaluating the Tolerability, Safety, Efficacy and Pharmacokinetics of ZG2001 Tosilate Tablets in Participants With KRAS Mutated Advanced Solid Tumours	I/II
NCT05173805	Phase I Clinical Study on the Safety, Tolerance, Pharmacokinetics and Efficacy of YL-15293 in Patients With Advanced Solid Tumor With KRAS Mutation	I/II
NCT04249843	A First-in-Human, Phase Ia/Ib, Open Label, Dose-Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, and Antitumor Activity of the RAF Dimer Inhibitor BGB-3245 in Patients With Advanced or Refractory Tumor	I
NCT05163028	A Phase I, Open-Label, Dose Escalation of HBI-2376 in Patients With Advanced Malignant Solid Tumors Harboring KRAS or EGFR Mutations	I
NCT06270082	A First-in-Human (FiH) Study of IK-595, an Oral Dual MEK/RAF Inhibitor, in Patients With RAS-or RAF-altered Advanced Solid Tumors	I
NCT05661201	Phase I Study of NEROFE and Doxorubicin in KRAS-mutated ST2-positive Solid Tumors	I
NCT06078800	Phase I Clinical Study on the Safety, Tolerance, Pharmacokinetics and Efficacy of Pan-KRAS Inhibitor YL-17231 in Patients With Advanced Solid Tumors With KRAS Mutation	I
NCT03905148	A Phase Ib, Open-Label, Dose-escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of a RAF Dimer Inhibitor BGB-283 in Combination With MEK Inhibitor PD-0325901 in Patients With Advanced or Refractory Solid Tumors	I/II
NCT05831995	A Phase I, First-In-Human, Multicenter, Open Label, Dose Escalation and Dose Expansion Study to Evaluate the Safety and Efficacy of ABM-168 Administered Orally in Adult Patients With Advanced Solid Tumors	I
NCT06104488	A Multi-Center Phase I Dose Escalation Study of Avutometinib, a RAF/MEK Clamp, in Pediatric Patients With Refractory or Recurrent Solid Tumors Harboring Activating MAPK Pathway Alterations	I
NCT05886920	A Phase I, Open-label, Dose-escalation Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Recommended Phase 2 Dose of D3S-002 Monotherapy in Adult Subjects With Advanced Solid Tumors With MAPK Pathway Mutations	I
NCT06299839	A Phase I, Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PAS-004, a MEK (1/2) Inhibitor, in Patients With MAPK Pathway-driven Advanced Solid Tumors With a Documented RAS, NF1, or RAF Mutation or Patients Who Have Failed BRAF/MEK Inhibition	I
NCT06310382	A Phase I/II Clinical Study to Evaluate The Safety, Tolerability, Pharmacokinetics, And Pharmcodynamics of Oral Administration of GH55 in Patients With MAPK Mutant Advanced Solid Tumors	I/II
NCT04985604	A Phase Ib/II, Open Label Study of DAY101 Monotherapy or Combination With Other Therapies for Patients With Recurrent, Progressive, or Refractory Solid Tumors Harboring MAPK Pathway Aberrations	I/II
NCT06239623	To Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of JSI-1187 Capsule in the Treatment of Advanced Solid Tumors With MAPK Signaling Pathway Mutations	I
NCT05557045	Phase I, FIH, Open-label, Nonrandomized, Multicenter Study of JZP815 in Participants With Advanced or Metastatic Solid Tumors Harboring Alterations in the MAPK Pathway	I

Clinical Trials Summary (continued)

KRAS p.(Q61H) c.183A>C (continued)

NCT ID	Title	Phase
NCT04551521	Continuous ReAssessment With Flexible ExTension in Rare Malignancies - CRAFT: The NCT-PMO-1602 Phase II Trial	II
NCT05580770	A Phase I/IIa Open-Label, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Efficacy of Mirdametinib in Combination With BGB-3245 in Patients With Advanced Solid Tumors	I/II
NCT04305249	A Phase I, Open-Label, Multi-Center Dose Finding Study to Investigate the Safety, Pharmacokinetics, and Preliminary Efficacy of ATG-017 Monotherapy or Combination Therapy With Nivolumab in Patients With Advanced Solid Tumors and Hematological Malignancies	I
NCT05354843	A Phase I, Open-Label, Multi-Center Dose Finding Study to Investigate the Safety, Pharmacokinetics, and Preliminary Efficacy of SHP2 Inhibitor ET0038 Monotherapy in Patients With Advanced Solid Tumors	I
NCT05488821	A Phase I Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Oral Pan-RAF Inhibitor QLH11906 in Subjects With Advanced Solid Tumors Harboring MAPK Pathway Alterations.	I

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
IDH1	p.(R132C)	c.394C>T	COSM28747	chr2:209113113	22.22%	NM_005896.4	missense
KRAS	p.(Q61H)	c.183A>C	COSM554	chr12:25380275	85.67%	NM_033360.4	missense

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