| | | | |
|---|---|---|---|
| **Patient Name:** | Dummy | **Booking ID:** | XXX |
| **Age:** | 59 Years | **Sample Type:** | FFPE BLOCK |
| **Gender:** | Male | **Sample Collection Date:** | 30.12.2023 |
| **Referring Clinician:** | Dr. XXX | **Sample Receiving Date:** | 01.01.2024 |
| **Test Requested:** | SOMATIC CANCER HOTSPOT MUTATION PANEL BY NGS | **Reporting Date:** | 18.01.2024 |

# SOMATIC PANCREATIC CANCER NGS PANEL REPORT

## CLINICAL INFORMATION

Pancreatic mass biopsy show features of ductal adenocarcinoma (FFPE tissue block received HP no. H2305846).

## RESULT SUMMARY

**POSITIVE**
(clinically relevant variant were identified related to phenotype)

## KEY FINDINGS

| Genes & Transcript | Exons | Locus | Variants | Allele Frequency/Depth | ASCO/AMP Class* |
|---|---|---|---|---|---|
| *SMAD4 (+) NM_005359.6* | Exon 9 | chr18:48591897 | p.Val354Leu p.(V354L)/ c.1060G>C | 6.65%/1999x | Tier IIC |
| *APC (+)* NM_000038.6 | Exon 16 | chr5:112175589 | p.Pro1433Leu p.(P1433L)/ c.4298C>T | 8.90%/2000x | Tier IIC |
| *KRAS (-) NM_033360.4* | Exon 2 | chr12:25398284 | p.Gly12VAL, p.(G12V)/ c.35G>T | 6.73%/ 1975 | Tier IIC |

*Genetic test results are reported based on the recommendations of AMP-ASCO-CAP guidelines.
*Public data sources included in relevant therapies: FDA, NCCN, EMA, ESMO.

## ADDITIONAL FINDINGS

| Genes & Transcript | Exons | Location | Variants | Allele Frequency | ASCO/AMP Class | Pathway in which the gene functions |
|---|---|---|---|---|---|---|
| *RET (+) NM_020975.6* | Exon 15 | chr10:43615572 | p.Glu884Val, p.(E884V)/ c.2651A>T | 9.70%/1639 | Tier IIC | PI3K/AKT, RAS/RAF/MEK/ERK, and PLCγ/PKC pathways |
| *RB1 (+) NM_000321.3* | Exon 20 | chr13:49033902 | p.Ile680Thr, p.(I680T) c.2039T>C | 7.02%/ 1980 | Tier IIC | G1/S cell cycle regulation |

## DETAILED VARIANT INTERPRETATION & ITS CLINICAL CORRELATION

**1. Potential relevance of SMAD4 p.(V354L) c.1060G>C:** Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)[1]. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF-β signaling[4,5,6]. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers[6,7,8].

Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers[2,4,9,10,11]. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy[12,13]. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)[13]. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors[14].

**2. Potential relevance of APC p.(P1433L) c.4298C>T:**Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma[6,7,8]. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation[20,21]. Currently, no therapies are approved for APC aberrations.

**Potential relevance of KRAS p.(G12V) c.35G>T:** 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 cancer4. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q614,5,6. Mutations at A59, K117, and A146 have also been observed but are less frequent.

## CLINICAL SIGNIFICANCE

- ✓ Please correlate clinically.
- ✓ Genetic counseling for accurate interpretation oftest results is recommended.
- ✓ We recommend confirming the presence of this variants by alternate method like Sanger Sequencing.
- ✓ For about this report, or for assistance in locating nearby genetic counseling services, please contact the Laboratory: geneticcounselors@redcliffelabs.com, or ccsupport@redcliffelabs.com.

## TEST DESCRIPTION

This somatic cancer hotspot gene panel through next generation sequencing (NGS) allows the identification of different type of variants i.e. targeted hot-spot mutations, Indels, copy number variations to understand their prognostic and therapeutic implications in various carcinomas of an affected individuals. Targeted regions of genes analysis by NGS method allows detection of specific mutations (SNVs, INDELs, CNVs that can provide treatment opportunities to the affected patients and their predictive response of therapy against the FDA/NCCN/ESMO approved drugs as per key findings. This gene panel with improved primer design and low input requirement of as 10-20 ng of DNA enable to sequence challenging samples such as Formalin fixed, paraffin embedded (FFPE) tissue which exhibit variable quality.

## TEST METHODOLOGY

Next Generation Sequencing: These 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 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 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

## 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.
- ✓ 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 scope of this assay limits to SNV and small deletions/duplication. Due to poor quality of FFPE DNA, indeterminate result due to low gene coverage or low variant depth cannot be ruled out. The sensitivity of the assays depends on the quality of the block, and tumor content.
- ✓ The sensitivity of this assay to detect small deletions/duplication is upto certain number of bases only. The CNVs if detected with this assay have to be confirmed by alternate method such as MLPA & Microarray.
- ✓ Variations with high minor allele frequencies which are benign/likely benign will be given upon request if required.
- ✓ 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 AMP-ASCO-CAP guidelines can be given upon request.
- ✓ Genes with pseudogenes, paralog 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).
- ✓ 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.
- ✓ Detailed clinical trial summary for clinically relevant variant is available with specific case and can be given upon request to authorized person.

## 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. Since only a portion of the tumor was tested, it is possible that this result may not represent the entire tumor population.

## VARIANT REPORTING CLASSIFICATION BASED ON AMP ASCOCAP 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)**<br>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;<br>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)**<br>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.<br>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**<br>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** |

Reviewed by
Imran Haider
Senior Scientific Officer
Onco-Genomics

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

**Patient Name: BHERLAL JAIN M** **Booking ID: XXX** **18.01.2024**

## Sample Cancer Type: Pancreatic Cancer

## 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 | *KRAS p.(G12V) c.35G>T*<br>KRAS proto-oncogene, GTPase<br>Allele Frequency: 6.73%<br>Locus: chr12:25398284<br>Transcript: NM_033360.4 | ⊘ (2) | ⊘ (2) | ⊘ (3) | ⚠ (6) | ● (45) |
| IIC | *RET p.(E884V) c.2651A>T*<br>ret proto-oncogene<br>Allele Frequency: 9.70%<br>Locus: chr10:43615572<br>Transcript: NM_020975.6 | ✖ | ✖ | ○ (1) | ○ (2) | ● (10) |
| IIC | *APC p.(P1433L) c.4298C>T*<br>APC regulator of WNT signaling pathway<br>Allele Frequency: 8.90%<br>Locus: chr5:112175589<br>Transcript: NM_000038.6 | ✖ | ✖ | ✖ | ✖ | ● (3) |
| IIC | *RB1 p.(I680T) c.2039T>C*<br>RB transcriptional corepressor 1<br>Allele Frequency: 7.02%<br>Locus: chr13:49033902<br>Transcript: NM_000321.3 | ✖ | ✖ | ✖ | ✖ | ● (1) |
| IIC | *SMAD4 p.(V354L) c.1060G>C*<br>SMAD family member 4<br>Allele Frequency: 6.65%<br>Locus: chr18:48591897<br>Transcript: NM_005359.6 | ✖ | ✖ | ✖ | ✖ | ● (1) |

**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.

## Biomarker Descriptions

**KRAS p.(G12V) c.35G>T**

*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[1,2,3].

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[4]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[4,5,6]. Mutations at A59, K117, and A146 have also been observed but are less frequent[7,8].

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib[9] (2021) and adagrasib[10] (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036[11], for KRAS G12C mutation in non-small cell lung cancer. The small molecular inhibitor, RO-5126766, was granted breakthrough designation (2021) alone for KRAS G12V mutant non-small cell lung cancer or in combination with defactinib, for KRAS mutant endometrial carcinoma and KRAS G12V mutant non-small cell lung cancer[12]. The PLK1 inhibitor, onvansertib[13], 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). Additionally, the SHP2 inhibitor, BBP-398[14] was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC.The EGFR antagonists, cetuximab[15] and panitumumab[16], 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)[8]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[17].

**SMAD4 p.(V354L) c.1060G>C**

*SMAD family member 4*

Background: The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[18,19]. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF-β and BMP signaling pathways that are implicated in cancer initiation and progression[19,20,21]. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC[18,19]

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)[18]. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF-β signaling[7,21,22]. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers[4,7,23].

Potential relevance: Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers[19,21,24,25,26]. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy[27,28]. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)[28]. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors[29].

**APC p.(P1433L) c.4298C>T**

*APC regulator of WNT signaling pathway*

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β-catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation[30]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[31,32]. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine[30,33]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[34].

## Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma[4,7,23]. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation[35,36].

Potential relevance: Currently, no therapies are approved for APC aberrations.

**RET p.(E884V) c.2651A>T**

*ret proto-oncogene*

Background: The RET gene encodes the RET receptor tyrosine kinase which is activated by a ligand family of glial cell line-derived neurotrophic factors (GDNF)[37]. RET is the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact RET tyrosine kinase domain combined with several fusion partner genes. RET fusion kinases are constitutively activated and drive oncogenic transformation which can lead to activation of PI3K/AKT, RAS/RAF/MEK/ERK, and PLCγ/PKC pathways resulting in cell survival and proliferation[38].

Alterations and prevalence: RET fusions occur in approximately 55% of papillary thyroid carcinomas (PTC) with even higher frequencies observed in PTC patients with radiation exposure[39,40,41]. RET rearrangement is also present in 1-2% of non-small cell lung cancer (NSCLC)[42]. Point mutations in RET are relatively common in sporadic medullary thyroid cancer (MTC), with 6% of patients found to contain germline mutations[43]. Somatic mutations (specifically at codon 918), which leads to increased kinase activity, have been observed in at least 25% of MTC cases[43].

Potential relevance: The FDA approved small-molecule tyrosine kinase inhibitor, cabozantinib (2012), is recommended for the treatment of NSCLC patients with RET rearrangements[44]. Cabozantinib has also demonstrated clinical benefit in RET mutated medullary thyroid cancer patients[45]. Selpercatinib[46] is approved (2020) for RET fusion-positive NSCLC, thyroid cancer, and metastatic solid tumors that have progressed following systemic treatment. Selpercatinib[46] is also approved for RET-mutation positive medullary thyroid cancer (MTC). Additionally, the RET inhibitor, pralsetinib[47], was approved (2020) for RET fusion-positive NSCLC and thyroid cancer as well as RET mutation-positive MTC. Point mutations involving codons 804 and 806 have been shown to confer resistance to selective kinase inhibitors including vandetanib[48,49]. RET mutations at codon 918 are associated with high risk and adverse prognosis in patients diagnosed with MTC[50].

**RB1 p.(I680T) c.2039T>C**

*RB transcriptional corepressor 1*

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[51,52]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[53]. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation[51,52,54]. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma[55].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in urothelial carcinoma (approximately 16%), endometrial cancer (approximately 12%), and sarcomas (approximately 9%)[7]. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)[7]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[56,57,58].

Potential relevance: Currently, there are no therapies approved for RB1 aberrations.

## Clinical Trials Summary

### KRAS p.(G12V) c.35G>T

| NCT ID | Title | Phase |
|---|---|---|
| NCT04146298 | Clinical Trial Evaluating the Safety and Activity of Mutant KRAS G12V-specific TCR Transduced T Cell Therapy for Advanced Pancreatic Cancer | I/II |

## Clinical Trials Summary (continued)

### KRAS p.(G12V) c.35G>T (continued)

| NCT ID | Title | Phase |
|---|---|---|
| NCT05846516 | A Phase Ib Study to Evaluate the Safety, Tolerability and Preliminary Efficacy of ATP150/ATP152, VSV-GP154 and Ezabenlimab (BI 754091) in Patients With KRAS G12D/G12V Mutated Pancreatic Ductal Adenocarcinoma (KISIMA-02) | I |
| NCT05379985 | A Multicenter Open-Label Study of RMC-6236 in Patients With Advanced Solid Tumors Harboring Specific Mutations in RAS | I |
| NCT05438667 | An Exploring clinical Research on Evaluating the Safety, Efficacy and Pharmacokinetics of KRAS Mutated Antigen-Specific TCR-T Cell Therapy for Advanced Pancreatic Cancer and Other Solid Tumors. | I |
| NCT04045496 | A Phase I, Multi-Center, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Evidence of Antitumor Activity of JAB-3312 in Adult Patients With Advanced Solid Tumors | I |
| NCT05631574 | A Phase I/Ib Dose Finding Study of BMF-219, an Oral Covalent Menin Inhibitor, in Adult Patients With Unresectable, Locally Advanced, or Metastatic Non-small Cell Lung Cancer (NSCLC), Pancreatic Cancer (PDAC), and Colorectal Cancer (CRC). | I |
| NCT04348045 | MAZEPPA: Phase II PRODIGE-GERCOR Study to Evaluate MAintenance Therapy With Olaparib or Selumetinib Plus Durvalumab According to BRCAness and KRAS Somatic Status Personalized in Metastatic Pancreatic Adenocarcinoma Patients | II |
| NCT05221320 | A Phase II Basket Trial of Ulixertinib (BVD-523) in Combination With Hydroxychloroquine in Patients With Advanced GI Malignancies Harboring Mitogen-activated Protein Kinase (MAPK) Pathway Mutations (BVD-523-HCQ) | II |
| NCT05039177 | A Phase Ib/II Study of Agents Targeting the Mitogen-Activated Protein Kinase Pathway in Patients With Advanced Gastrointestinal Malignancies (HERKULES-3) | I/II |
| NCT04892017 | A Phase I/II, First-in-human Study of Dcc-3116 as Monotherapy and in Combination with Ras/Mapk Pathway Inhibitors in Patients with Advanced or Metastatic Solid Tumors with Ras/Mapk Pathway Mutations | I/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 |
| 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 |
| NCT04615312 | Phase I Clinical Study on the Safety and Tolerability of a CDK4 / 6 Inhibitor and a MEK Inhibitor in the Treatment of Metastatic Digestive System Tumors | I |
| NCT06026410 | Phase I, First-in-Human, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Antitumor Activity of KO-2806 When Administered as Monotherapy and in Combination Therapy in Adult Patients With Advanced Solid Tumors | I |
| NCT04870034 | Perioperative Analysis of Binimetinib and Palbociclib in RAS-Driven Tumors | I |
| NCT04916236 | Phase I/Ib Study With the Combination of RMC-4630 (SHP2 Inhibitor) and LY3214996 (ERK Inhibitor) in Metastatic KRAS Mutant CRC, PDAC and NSCLC | I |
| NCT04303403 | Phase Ib Study Evaluating Safety and Tolerability of Combination Trametinib and Ruxolitinib in Patients with Advanced RAS Mutant Colorectal Cancer and Pancreatic Adenocarcinoma | I |
| NCT05866692 | A Phase I, Multicenter, Open-label Study of TY-2699a, Administered Orally in Adult Patients With Locally Advanced or Metastatic Solid Tumors | 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 |

## Clinical Trials Summary (continued)

### KRAS p.(G12V) c.35G>T (continued)

| NCT ID | Title | Phase |
|---|---|---|
| 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 |
| NCT06054984 | To Investigate the Safety, Tolerability, Efficacy and Pharmacokinetics of T Cell Receptor T Cell Therapy in the Treatment of Advanced Pancreatic Cancer | I |
| NCT03190941 | A Phase I/II Study Administering Peripheral Blood Lymphocytes Transduced With a Murine T-Cell Receptor Recognizing the G12V Variant of Mutated RAS in HLA-A*11:01 Patients | 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 |
| NCT05631899 | A Pilot Clinical Trial of Autologous EphA-2-Targeting Chimeric Antigen Receptor Dendritic Cell Vaccine Loaded With KRAS Mutant Peptide in Combination With Anti-PD-1 Antibody for Local Advanced/ Metastatic Solid Tumors | 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 |
| 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 |
| 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 |
| NCT05111561 | A Phase I Study of ZEN003694 in Combination With Binimetinib in Solid Tumors With RAS Pathway Alterations and Triple Negative Breast Cancer | I |
| 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 |
| 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 |
| NCT05010694 | A Phase I Study Evaluating the Safety, Tolerability, Pharmacokinetic Characteristics, and Primary Antitumor Activity of GH35 in Patients With Advanced Solid Tumors With KRAS Mutation | 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 |
| 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 |
| NCT05340621 | NAUTILUS: A Phase I b/II Study of OKI-179 Plus Binimetinib in Patients With Advanced Solid Tumors and Activating Mutations in the RAS Pathway (Phase 1b) and in Patients With Advanced NRAS-Mutated Melanoma (Phase 2) | I/II |
| 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 |

## Clinical Trials Summary (continued)

### KRAS p.(G12V) c.35G>T (continued)

| NCT ID | Title | Phase |
|---|---|---|
| No NCT ID | A Phase I/II Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics Characteristics and Efficacy of Oral Administration of GH55 in Patients with Advanced Solid Tumors with Mutations in MAPK Signaling Pathway | 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 |
| 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 |
| NCT04551521 | Continuous ReAssessment With Flexible ExTension in Rare Malignancies - CRAFT: The NCT-PMO-1602 Phase II Trial | II |
| NCT03520075 | A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors | I/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 |
| NCT04528836 | A Phase I/IB First-in-Human Study of the SHP2 Inhibitor BBP-398 (Formerly Known as IACS-15509) 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 |

### RET p.(E884V) c.2651A>T

| NCT ID | Title | Phase |
|---|---|---|
| NCT03239015 | Efficacy and Safety of Precision Therapy in Refractory Tumor (Long March Pathway) | II |
| NCT02693535 | Targeted Agent and Profiling Utilization Registry (TAPUR) Study | II |
| No NCT ID | An open-label, multicenter phase I/II clinical study evaluating the safety, tolerability, pharmacokinetics and efficacy of BYS10 tablets in the treatment of advanced solid tumors with RET gene fusion or mutation | I/II |
| NCT05451602 | Phase I/II Study of the Highly-selective RET Inhibitor,HEC169096 in Participants With Thyroid Cancer, Non-Small Cell Lung Cancer, and Other Advanced Solid Tumors | I/II |
| NCT05265091 | An Open, Multi-Center Phase I/II Clinical Study To Evaluate The Safety, Tolerability, Pharmacokinetic Characteristics And Effectiveness Of KL590586 Capsules In Patients With Advanced Solid Tumors Carrying RET Fusion Or Mutant Genes | I/II |
| NCT05278364 | A Phase I/II, Open-Label, Single-arm, Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antineoplastic Activity of SY-5007 in Patients With RET-altered Advanced Solid Tumor. | I/II |
| No NCT ID | A Phase I Study Investigating the Safety, Tolerability, Pharmacokinetics and Initial Efficacy of APS03118 in Adults with Unresectable, Locally Advanced, or Metastatic Solid Tumors with RET Mutations or Fusions | I |
| NCT05675605 | A Phase I/II Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of Selective RET Inhibitor TY-1091 Capsules in Patients with Advanced Solid Tumors | I |

## Clinical Trials Summary (continued)

### RET p.(E884V) c.2651A>T (continued)

| NCT ID | Title | Phase |
|---|---|---|
| NCT05443126 | A Modular, Open-label, Phase I/II Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of EP0031 in Patients With Advanced RET-altered Malignancies | I/II |
| NCT05207787 | A Phase I, Open-label, Multicenter Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Single and Multiple Doses of Oral Administration of HS-10365 in Patients With Locally Advanced or Metastatic Solid Tumors Who Have Progressed Following Prior Therapy | I |

### APC p.(P1433L) c.4298C>T

| NCT ID | Title | Phase |
|---|---|---|
| NCT04851119 | A Phase I/II Study of Tegavivint (NSC#826393) in Children, Adolescents, and Young Adults With Recurrent or Refractory Solid Tumors, Including Lymphomas and Desmoid Tumors | I/II |
| NCT03833700 | An Open-label Phase I Study of E7386 in Subjects With Advanced Solid Tumor Including Colorectal Cancer | I |
| NCT05848739 | A Phase 1-2 Dose-escalation and Expansion Study of ST316 in Subjects With Selected Advanced Unresectable and Metastatic Solid Tumors | I/II |

### RB1 p.(I680T) c.2039T>C

| NCT ID | Title | Phase |
|---|---|---|
| NCT05866692 | A Phase I, Multicenter, Open-label Study of TY-2699a, Administered Orally in Adult Patients With Locally Advanced or Metastatic Solid Tumors | I |

### SMAD4 p.(V354L) c.1060G>C

| NCT ID | Title | Phase |
|---|---|---|
| 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 |

## Variant Details

### DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| APC | p.(P1433L) | c.4298C>T | . | chr5:112175589 | 8.90% | NM_000038.6 | missense |
| RET | p.(E884V) | c.2651A>T | . | chr10:43615572 | 9.70% | NM_020975.6 | missense |
| KRAS | p.(G12V) | c.35G>T | COSM520 | chr12:25398284 | 6.73% | NM_033360.4 | missense |
| RB1 | p.(I680T) | c.2039T>C | . | chr13:49033902 | 7.02% | NM_000321.3 | missense |
| SMAD4 | p.(V354L) | c.1060G>C | . | chr18:48591897 | 6.65% | NM_005359.6 | missense |

## References


1. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. Nat. Rev. Cancer. 2011 Oct 13;11(11):761-74. PMID: 21993244
2. Karnoub et al. Ras oncogenes: split personalities. Nat. Rev. Mol. Cell Biol. 2008 Jul;9(7):517-31. PMID: 18568040
3. Scott et al. Therapeutic Approaches to RAS Mutation. Cancer J. 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.0000000000000187. PMID: 27341593
4. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
5. Román et al. KRAS oncogene in non-small cell lung cancer: clinical perspectives on the treatment of an old target. Mol Cancer. 2018 Feb 19;17(1):33. doi: 10.1186/s12943-018-0789-x. PMID: 29455666
6. Dinu et al. Prognostic significance of KRAS gene mutations in colorectal cancer--preliminary study. J Med Life. 2014 Oct-Dec;7(4):581-7. PMID: 25713627
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
8. Allegra et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J. Clin. Oncol. 2016 Jan 10;34(2):179-85. PMID: 26438111
9. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214665s004lbl.pdf
10. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/216340Orig1s000Corrected_lbl.pdf
11. https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf
12. https://investor.verastem.com//news-releases/news-release-details/verastem-oncology-reports-third-quarter-2022-financial-results
13. https://cardiffoncology.investorroom.com/2020-05-28-Cardiff-Oncology-Announces-Fast-Track-Designation-Granted-by-the-FDA-to-Onvansertib-for-Second-Line-Treatment-of-KRAS-Mutated-Colorectal-Cancer
14. https://bridgebio.com/news/bridgebio-pharma-announces-first-lung-cancer-patient-dosed-in-phase-1-2-trial-and-us-fda-fast-track-designation-for-shp2-inhibitor-bbp-398-in-combination-with-amgens-lumakras-sotorasib/
15. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
16. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125147s210lbl.pdf
17. Slebos et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. N. Engl. J. Med. 1990 Aug 30;323(9):561-5. PMID: 2199829
18. Ahmed et al. The TGF-β/Smad4 Signaling Pathway in Pancreatic Carcinogenesis and Its Clinical Significance. J Clin Med. 2017 Jan 5;6(1). PMID: 28067794
19. Zhao et al. The role of TGF-β/SMAD4 signaling in cancer. Int. J. Biol. Sci. 2018;14(2):111-123. PMID: 29483830
20. Cicenas et al. KRAS, TP53, CDKN2A, SMAD4, BRCA1, and BRCA2 Mutations in Pancreatic Cancer. Cancers (Basel). 2017 Apr 28;9(5). PMID: 28452926
21. Miyaki et al. Role of Smad4 (DPC4) inactivation in human cancer. Biochem. Biophys. Res. Commun. 2003 Jul 11;306(4):799-804. PMID: 12821112
22. Mehrvarz et al. Association of SMAD4 mutation with patient demographics, tumor characteristics, and clinical outcomes in colorectal cancer. PLoS ONE. 2017;12(3):e0173345. PMID: 28267766
23. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
24. Yan et al. Reduced Expression of SMAD4 Is Associated with Poor Survival in Colon Cancer. Clin. Cancer Res. 2016 Jun 15;22(12):3037-47. PMID: 26861460
25. Voorneveld et al. A Meta-Analysis of SMAD4 Immunohistochemistry as a Prognostic Marker in Colorectal Cancer. Transl Oncol. 2015 Feb;8(1):18-24. PMID: 25749173
26. Shugang et al. Prognostic Value of SMAD4 in Pancreatic Cancer: A Meta-Analysis. Transl Oncol. 2016 Feb;9(1):1-7. PMID: 26947875
27. Boulay et al. SMAD4 is a predictive marker for 5-fluorouracil-based chemotherapy in patients with colorectal cancer. Br. J. Cancer. 2002 Sep 9;87(6):630-4. PMID: 12237773
28. Kozak et al. Smad4 inactivation predicts for worse prognosis and response to fluorouracil-based treatment in colorectal cancer. J. Clin. Pathol. 2015 May;68(5):341-5. PMID: 25681512
29. Ozawa et al. SMAD4 Loss Is Associated with Cetuximab Resistance and Induction of MAPK/JNK Activation in Head and Neck Cancer Cells. Clin. Cancer Res. 2017 Sep 1;23(17):5162-5175. PMID: 28522603

## References (continued)

30. Wang et al. Loss of Tumor Suppressor Gene Function in Human Cancer: An Overview. Cell. Physiol. Biochem. 2018;51(6):2647-2693. PMID: 30562755
31. Stamos et al. The β-catenin destruction complex. Cold Spring Harb Perspect Biol. 2013 Jan 1;5(1):a007898. PMID: 23169527
32. Minde et al. Messing up disorder: how do missense mutations in the tumor suppressor protein APC lead to cancer?. Mol Cancer. 2011 Aug 22;10:101. doi: 10.1186/1476-4598-10-101. PMID: 21859464
33. Aoki et al. Adenomatous polyposis coli (APC): a multi-functional tumor suppressor gene. J. Cell. Sci. 2007 Oct 1;120(Pt 19):3327-35. PMID: 17881494
34. Miyoshi et al. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. Hum. Mol. Genet. 1992 Jul;1(4):229-33. PMID: 1338904
35. Rowan et al. APC mutations in sporadic colorectal tumors: A mutational "hotspot" and interdependence of the "two hits". Proc. Natl. Acad. Sci. U.S.A. 2000 Mar 28;97(7):3352-7. PMID: 10737795
36. Laurent-Puig et al. APC gene: database of germline and somatic mutations in human tumors and cell lines. Nucleic Acids Res. 1998 Jan 1;26(1):269-70. PMID: 9399850
37. Knowles et al. Structure and chemical inhibition of the RET tyrosine kinase domain. J. Biol. Chem. 2006 Nov 3;281(44):33577-87. PMID: 16928683
38. Ibáñez. Structure and physiology of the RET receptor tyrosine kinase. Cold Spring Harb Perspect Biol. 2013 Feb 1;5(2). PMID: 23378586
39. Santoro et al. Central role of RET in thyroid cancer. Cold Spring Harb Perspect Biol. 2013 Dec 1;5(12):a009233. PMID: 24296167
40. Elisei et al. RET/PTC rearrangements in thyroid nodules: studies in irradiated and not irradiated, malignant and benign thyroid lesions in children and adults. J. Clin. Endocrinol. Metab. 2001 Jul;86(7):3211-6. PMID: 11443191
41. Ciampi et al. RET/PTC rearrangements and BRAF mutations in thyroid tumorigenesis. Endocrinology. 2007 Mar;148(3):936-41. PMID: 16946010
42. Kohno et al. KIF5B-RET fusions in lung adenocarcinoma. Nat. Med. 2012 Feb 12;18(3):375-7. PMID: 22327624
43. Wohllk et al. Relevance of RET proto-oncogene mutations in sporadic medullary thyroid carcinoma. J. Clin. Endocrinol. Metab. 1996 Oct;81(10):3740-5. PMID: 8855832
44. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2023]
45. Sherman et al. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. Cancer. 2016 Dec 15;122(24):3856-3864. PMID: 27525386
46. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213246s008lbl.pdf
47. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213721s009lbl.pdf
48. Carlomagno et al. Disease associated mutations at valine 804 in the RET receptor tyrosine kinase confer resistance to selective kinase inhibitors. Oncogene. 2004 Aug 12;23(36):6056-63. PMID: 15184865
49. Carlomagno et al. Identification of tyrosine 806 as a molecular determinant of RET kinase sensitivity to ZD6474. Endocr Relat Cancer. 2009 Mar;16(1):233-41. doi: 10.1677/ERC-08-0213. Epub 2008 Nov 24. PMID: 19029224
50. NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 4.2023]
51. Korenjak et al. E2F-Rb complexes regulating transcription of genes important for differentiation and development. Curr Opin Genet Dev . 2005 Oct;15(5):520-7. doi: 10.1016/j.gde.2005.07.001. PMID: 16081278
52. Sachdeva et al. Understanding pRb: toward the necessary development of targeted treatments for retinoblastoma. J. Clin. Invest. 2012 Feb;122(2):425-34. PMID: 22293180
53. Dyson. RB1: a prototype tumor suppressor and an enigma. Genes Dev. 2016 Jul 1;30(13):1492-502. PMID: 27401552
54. Cobrinik. Pocket proteins and cell cycle control. Oncogene. 2005 Apr 18;24(17):2796-809. PMID: 15838516
55. Dommering et al. RB1 mutations and second primary malignancies after hereditary retinoblastoma. Fam. Cancer. 2012 Jun;11(2):225-33. PMID: 22205104
56. Anasua et al. Acute lymphoblastic leukemia as second primary tumor in a patient with retinoblastoma. . Oman J Ophthalmol . May-Aug 2016;9(2):116-8. PMID: 27433042
57. Tanaka et al. Frequent allelic loss of the RB, D13S319 and D13S25 locus in myeloid malignancies with deletion/translocation at 13q14 of chromosome 13, but not in lymphoid malignancies. Leukemia. 1999 Sep;13(9):1367-73. PMID: 10482987
58. Gombos et al. Secondary acute myelogenous leukemia in patients with retinoblastoma: is chemotherapy a factor?. Ophthalmology. 2007 Jul;114(7):1378-83. PMID: 17613328

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