

KRAS Target Dossier - Pancreatic Cancer

06-08-2024

Table of contents:

| | |
|---|-----------|
| 1. Target information..... | 3 |
| 1.1 Summary and characteristics..... | 3 |
| 1.2 Transmembrane Helix Prediction..... | 5 |
| 1.3 Subcellular location..... | 6 |
| 1.4 Expression..... | 7 |
| 1.5 Mutations..... | 11 |
| 1.6 Glycosylations..... | 15 |
| 1.7 Gene essentiality..... | 16 |
| 1.8 Protein-protein interactions..... | 19 |
| 1.9 Pathway enrichment..... | 20 |
| 1.10 SIGnaling Network..... | 21 |
| 1.11 Role in physiology..... | 25 |
| 1.12 Role in tumor progression..... | 25 |
| 1.13 Kaplan-Meier curves..... | 26 |
| 2. Disease information..... | 34 |
| 2.1 Disease description..... | 34 |
| 2.2 Disease statistics..... | 35 |
| 2.3 ESMO guidelines..... | 37 |
| 3. Competitive landscape..... | 43 |
| 3.1 Pancreatic cancer standard of care..... | 43 |
| 3.2 Pancreatic cancer current therapies..... | 44 |
| 3.3 Known drugs targeting KRAS..... | 45 |
| 4. Conclusion..... | 53 |
| 4.1 SWOT analysis..... | 53 |
| 4.2 Conclusion..... | 55 |

1. Target information

1.1 Summary and characteristics

This gene, a Kirsten ras oncogene homolog from the mammalian ras gene family, encodes a protein that is a member of the small GTPase superfamily. A single amino acid substitution is responsible for an activating mutation. The transforming protein that results is implicated in various malignancies, including lung adenocarcinoma, mucinous adenoma, ductal carcinoma of the pancreas and colorectal carcinoma. Alternative splicing leads to variants encoding two isoforms that differ in the C-terminal region. [provided by RefSeq, Jul 2008]

Source: NCBI Gene [1]



KRAS protein structure

Source: RCSB [2]

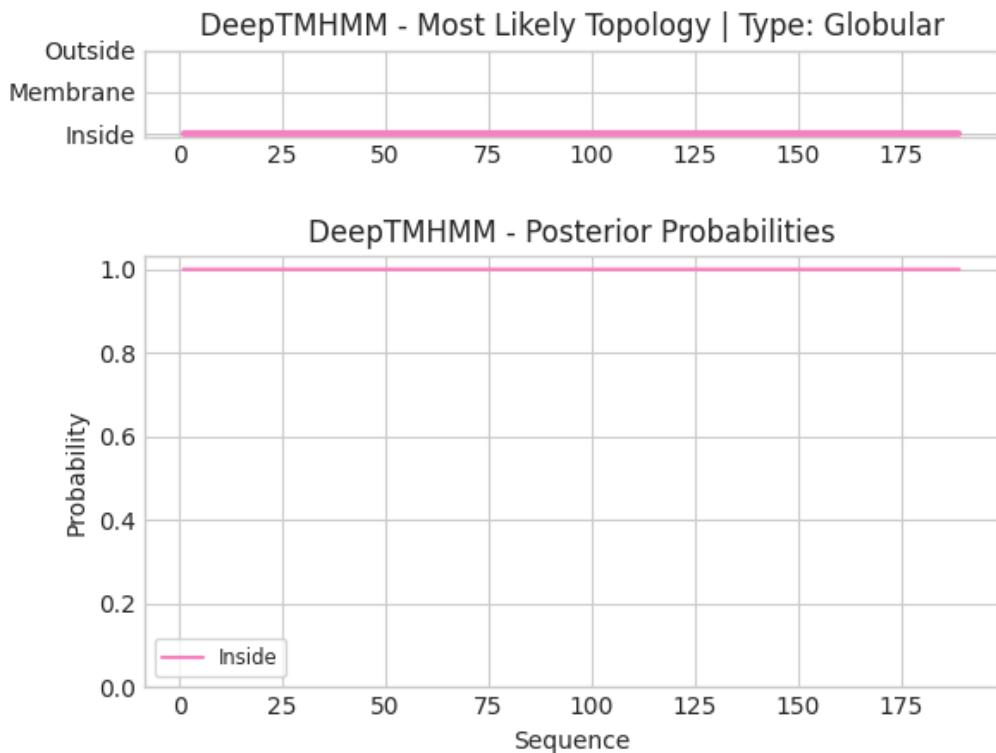
Target characteristics

| | |
|-----------------------------|---|
| Name | KRAS |
| Size | 21.66 kDa |
| Family | RAS, DI-RAS, AND RHEB FAMILY MEMBERS OF SMALL GTPASE SUPERFAMILY |
| Subcellular location | Cell membrane, Endomembrane system, Cytoplasm, cytosol |
| Isoforms | 2A, 2B |
| Human protein sequence | MTEYKLVVVGAGGVGKSALTIQLIQNHFVDEYDPTIEDSY RKQVVIDGETCLLDILDTAGQEEYSAMRDQYMRTGEGFL CVFAINNTKSFEDIHHYREQIKRVKDSEDVPMVLVGNKCD LPSRTVDTKQAQDLARSYGIPFIETSAKTRQRVEDAFYTL VREIRQYRLKKISKEEKTPGCVKIKKCIIM |
| AA sequence length | 189 |
| Similarity with rats | 98.94% |
| Similarity with monkeys | 97.01% |
| Similarity with mice | 98.94% |
| Similarity with rabbits | 98.94% |
| Similarity with dogs | 98.94% |
| Similarity with Guinea pigs | 100.0% |
| Protein function | Ras proteins regulate cell proliferation by binding GDP/GTP and inducing TSG silencing in CRC cells through ZNF304. |

Source: UniProt [3] and BLAST

1.2 Transmembrane Helix Prediction

The plot shows the protein prediction topology: the probabilities of the amino acids locations with respect to the membrane.



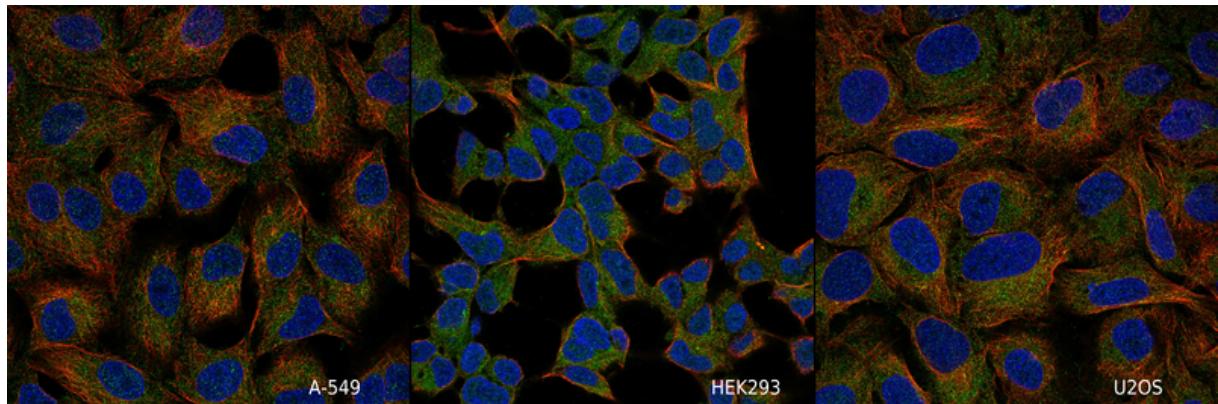
The prediction indicates that the entire KRAS protein sequence, consisting of 189 amino acids, is predicted to be located inside the membrane.

Source: DeepTMHMM [4]

1.3 Subcellular location

Localized to the cytosol.

Representative multi-color images showing the protein of interest in green are displayed below. The images also include markers for the nucleus (blue) and microtubules (red).



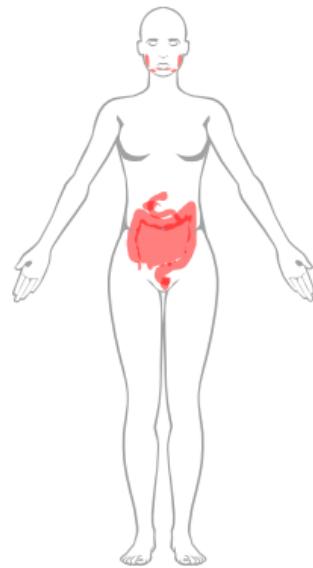
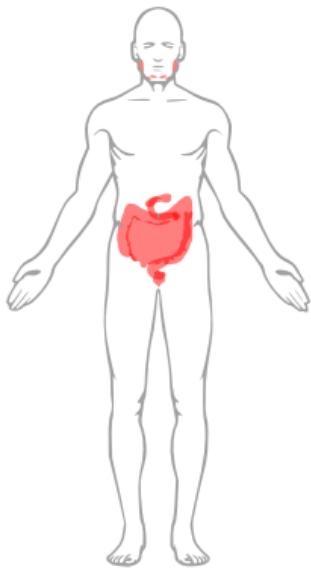
| Antibody | Cell line | Cell line origin | Location |
|-----------|-----------|--------------------------|----------|
| HPA072761 | A-549 | Lung | cytosol |
| HPA072761 | HEK293 | Kidney & Urinary bladder | cytosol |
| HPA072761 | U2OS | Mesenchymal | cytosol |

Source: Human Protein Atlas [5]

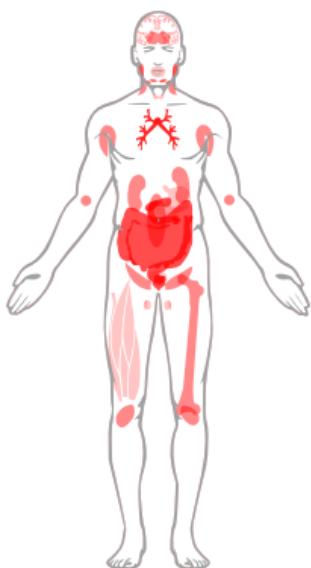
1.4 Expression

Wild type KRAS protein expression levels

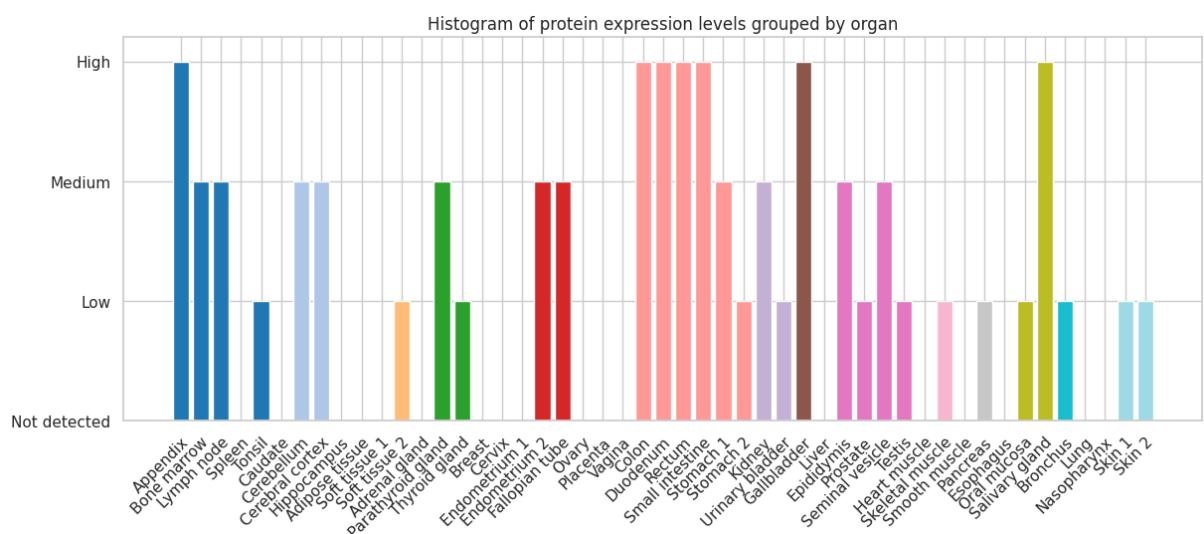
The following image shows organs in which KRAS protein expression level is high.



The following image shows KRAS protein expression level in the organs. The darker the colour, the higher the expression level.

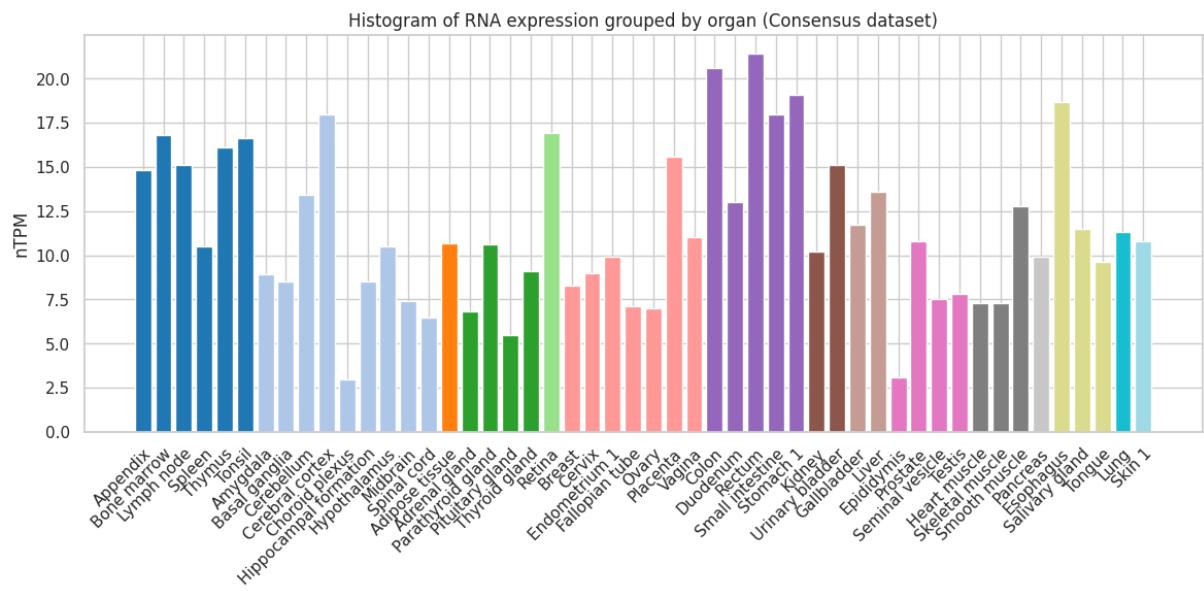


KRAS is highly expressed in Appendix, Colon, Duodenum, Gallbladder, Rectum, Salivary gland, Small intestine



Source: Human Protein Atlas [6]

Wild type KRAS RNA expression

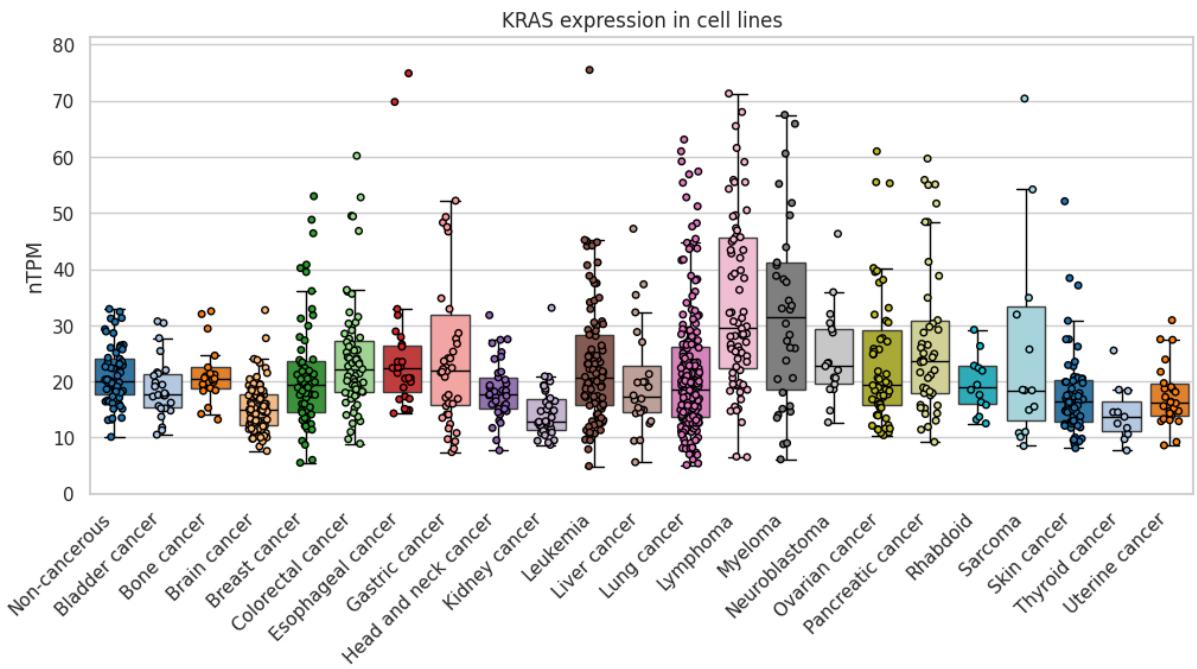


Potential toxicity

The tissues with the highest RNA expression of KRAS are: rectum, colon, stomach, esophagus and cerebral cortex.

Source: Human Protein Atlas [6]

Wild type KRAS RNA expression in non cancerous and cancer cell lines



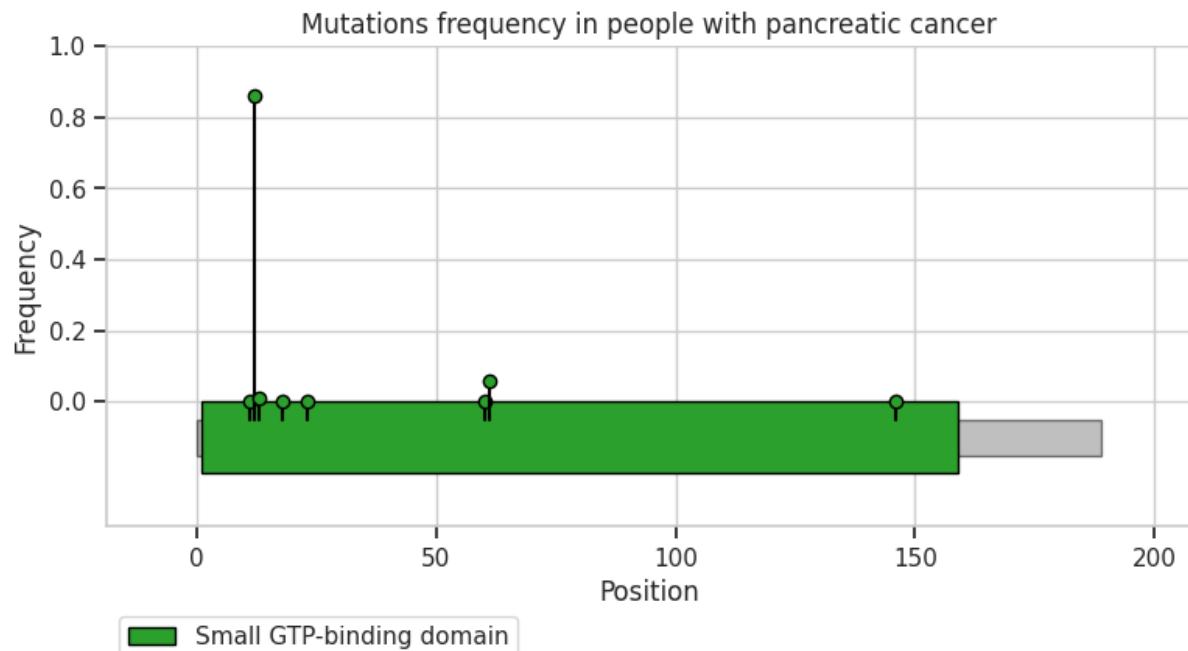
Source: Human Protein Atlas [7]

1.5 Mutations

Mutations frequency in people with pancreatic cancer

| Position | Mutation | Type | Frequency |
|----------|--------------------------|----------|-------------------------|
| 11 | G12R | Missense | 0.11% (1/881) |
| 11 | A11T | Missense | 0.11% (1/881) |
| | Total position 11 | | 0.23% (2/881) |
| 12 | G12D | Missense | 37.91% (334/881) |
| 12 | G12V | Missense | 29.85% (263/881) |
| 12 | G12R | Missense | 15.66% (138/881) |
| 12 | G12C | Missense | 1.36% (12/881) |
| 12 | G12S | Missense | 0.45% (4/881) |
| 12 | G12A | Missense | 0.34% (3/881) |
| 12 | G12L | Missense | 0.23% (2/881) |
| 12 | G12I | Missense | 0.11% (1/881) |
| 12 | G13H | Missense | 0.11% (1/881) |
| | Total position 12 | | 86.04% (758/881) |
| 13 | G13D | Missense | 0.34% (3/881) |
| 13 | G13P | Missense | 0.23% (2/881) |
| 13 | G13C | Missense | 0.23% (2/881) |
| 13 | G13R | Missense | 0.11% (1/881) |
| | Total position 13 | | 0.91% (8/881) |
| 18 | A18V | Missense | 0.11% (1/881) |
| | Total position 18 | | 0.11% (1/881) |
| 23 | L23V | Missense | 0.11% (1/881) |
| | Total position 23 | | 0.11% (1/881) |
| 60 | Q61K | Missense | 0.11% (1/881) |
| | Total position 60 | | 0.11% (1/881) |
| 61 | Q61H | Missense | 4.31% (38/881) |
| 61 | Q61R | Missense | 1.14% (10/881) |
| 61 | Q61K | Missense | 0.23% (2/881) |

| | | |
|------------|---------------------------|-----------------------|
| | Total position 61 | 5.68% (50/881) |
| 146 | A146T | Missense |
| | Total position 146 | 0.11% (1/881) |
| | | 0.11% (1/881) |



Mutations in the general population

| Mutation | Frequency | SNP ID |
|----------|--------------------|-----------|
| G12D | 0.0014% (2/142857) | 121913529 |
| G12V | 0.0014% (2/142857) | 121913529 |
| G12R | 0.0007% (1/142857) | 121913530 |

Mutations descriptions generated by the LLM

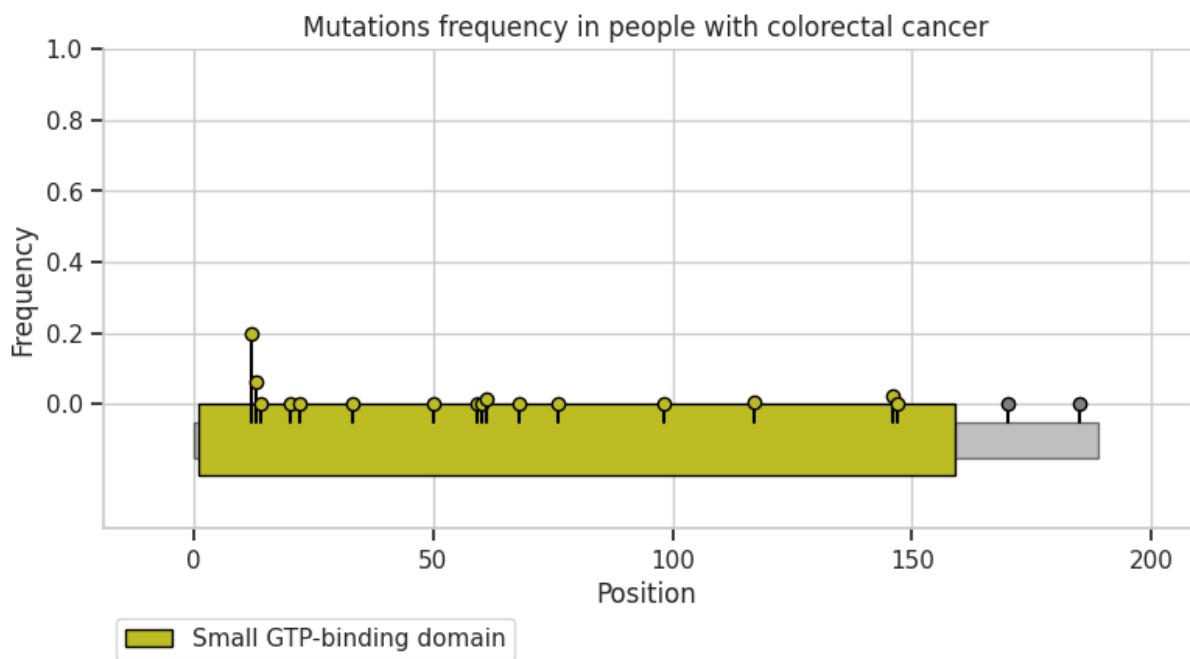
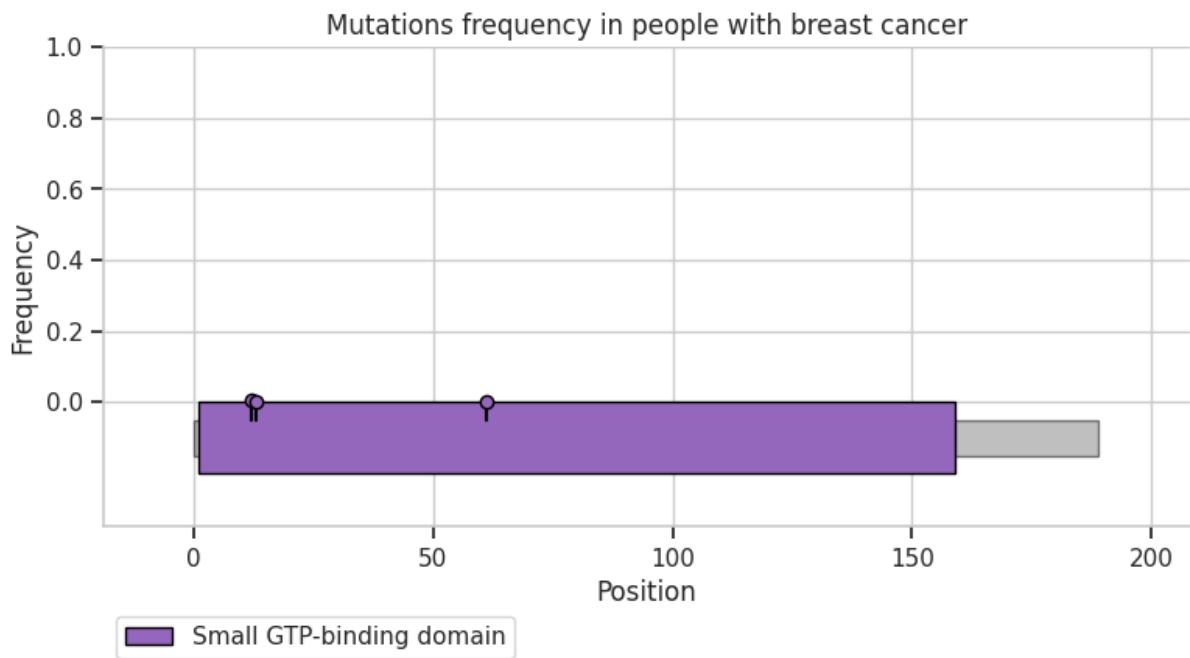
The KRAS G12D mutation is an activating mutation that is associated with increased proliferation and invasion in pancreatic ductal adenocarcinoma (PDAC). It is distinct from the KRAS G12R mutation, which is impaired in activating a key effector, p110 α PI3K, and instead relies on upregulated KRAS-independent PI3K γ activity to support macropinocytosis. The KRAS G12D mutation is present in both heterozygous and homozygous states and is linked to a poor prognosis in colorectal cancer (CRC), especially when combined with microsatellite instability (MSI) and a BRAF(V600E) mutation. In CRC, the presence of the KRAS G12D mutation is associated with decreased expression of E-cadherin, α -E-catenin, and increased expression of MMP-3, MMP-9, and

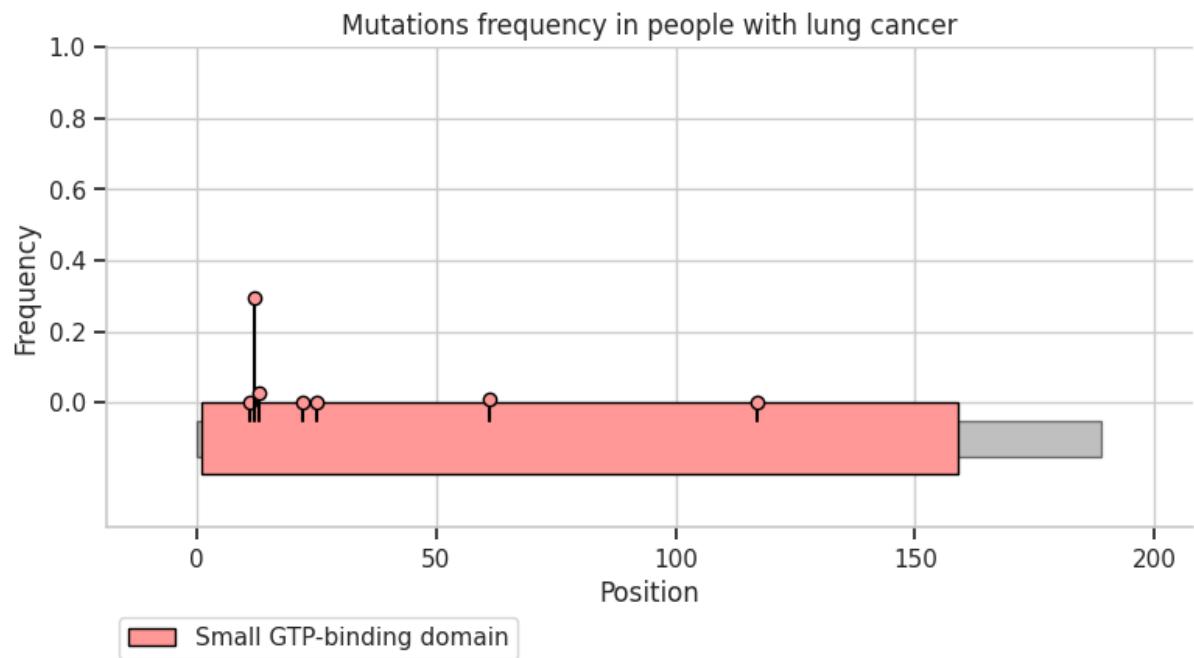
phosphorylated STAT3. In PDAC, the KRAS G12D mutation is linked to increased proliferation, invasion, and migration, as well as decreased expression of E-cadherin and α -E-catenin.

The KRAS G12V mutation is an activating mutation that is sufficient to induce brain arteriovenous malformations when expressed in the endothelium of both mice and zebrafish. This mutation leads to altered endothelial cell morphogenesis, increased cell size, ectopic sprouting, expanded vessel lumen diameter, and direct connections between arteries and veins. The lesions are not associated with altered endothelial growth dynamics or a lack of proper arteriovenous identity but instead seem to feature exuberant angiogenic signaling. In zebrafish, KRAS-dependent arteriovenous malformations are refractory to inhibition of the downstream effector PI3K but instead require active MEK signaling.

The KRAS G12R mutation is a rare mutation that is relatively common in pancreatic ductal adenocarcinoma (PDAC), but is rare in lung and colorectal cancers. Unlike the more common KRAS G12D and KRAS G12V mutations, KRAS G12R is impaired in activating a key effector, p110 α PI3K, due to structural perturbations in switch II. Instead, upregulated KRAS-independent PI3K γ activity is able to support macropinocytosis in KRAS G12R mutant PDAC. KRAS G12R mutant PDAC displays a distinct drug sensitivity profile compared with KRAS G12D mutant PDAC but is still responsive to the combined inhibition of ERK and autophagy. Patients with KRAS G12R mutant PDAC have longer overall survival (OS) and progression-free survival (PFS) compared with non-G12R mutant PDAC, but this advantage is offset by co-occurring PI3K alterations. KRAS G12R is associated with P+LD morphology in PDACs and longer OS when compared with G12D in both Kaplan-Meier analyses and in the adjuvant-only subset.

Mutations frequency in people with other cancers

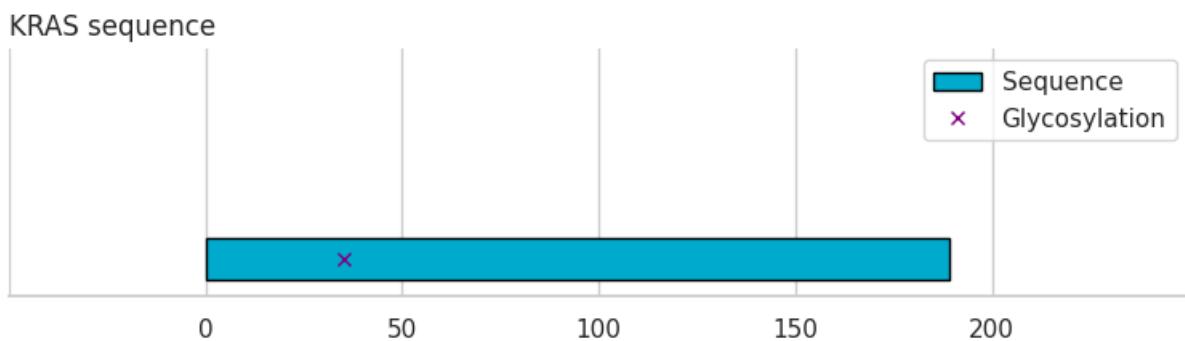




Source: cBioPortal and NCBI

1.6 Glycosylations

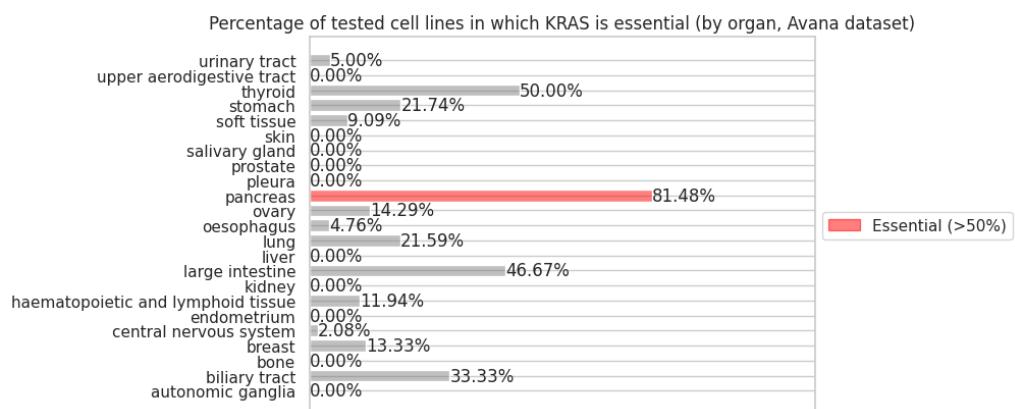
This plot shows the positions of glycosylations, i.e. the positions of all glycan groups covalently attached to the protein.



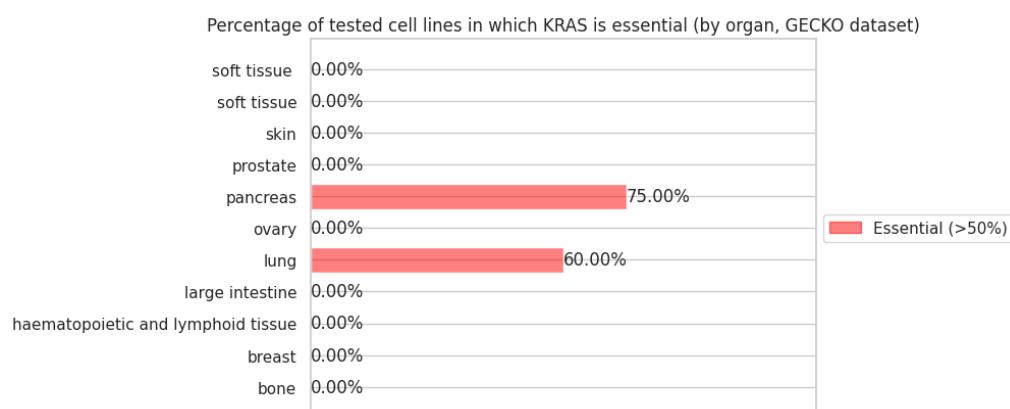
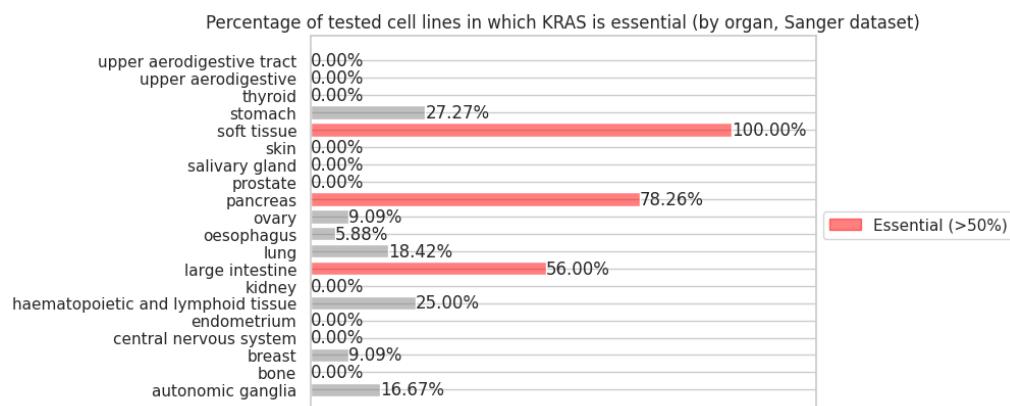
| Position | Type |
|----------|--------------------------|
| 35 | O-linked (Glc) threonine |

Source: UniProt [3]

1.7 Gene essentiality



Organs in which KRAS is essential (KRAS is essential in more than 50% of the tested cell lines, Avana dataset): pancreas



The scores of each dataset are converted into z-scores. The smaller the z-value associated with the cell line, the more essential KRAS is in that cell line.

Heatmap of Z-scores of most essential cell lines originated from pancreas

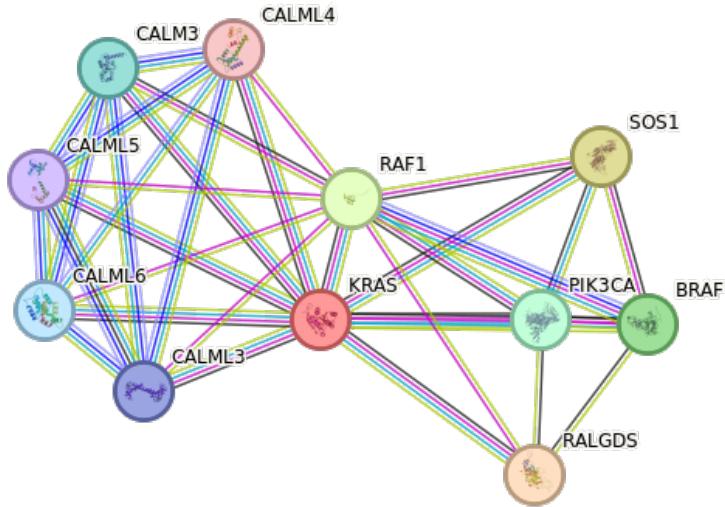


Heatmap of Z-scores of least essential cell lines originated from pancreas



Source: OGEE [8]

1.8 Protein-protein interactions



Red line - fusion evidence
Green line - neighborhood evidence
Blue line - cooccurrence evidence
Purple line - experimental evidence
Yellow line - textmining evidence
Light blue line - database evidence
Black line - coexpression evidence

Interaction scores

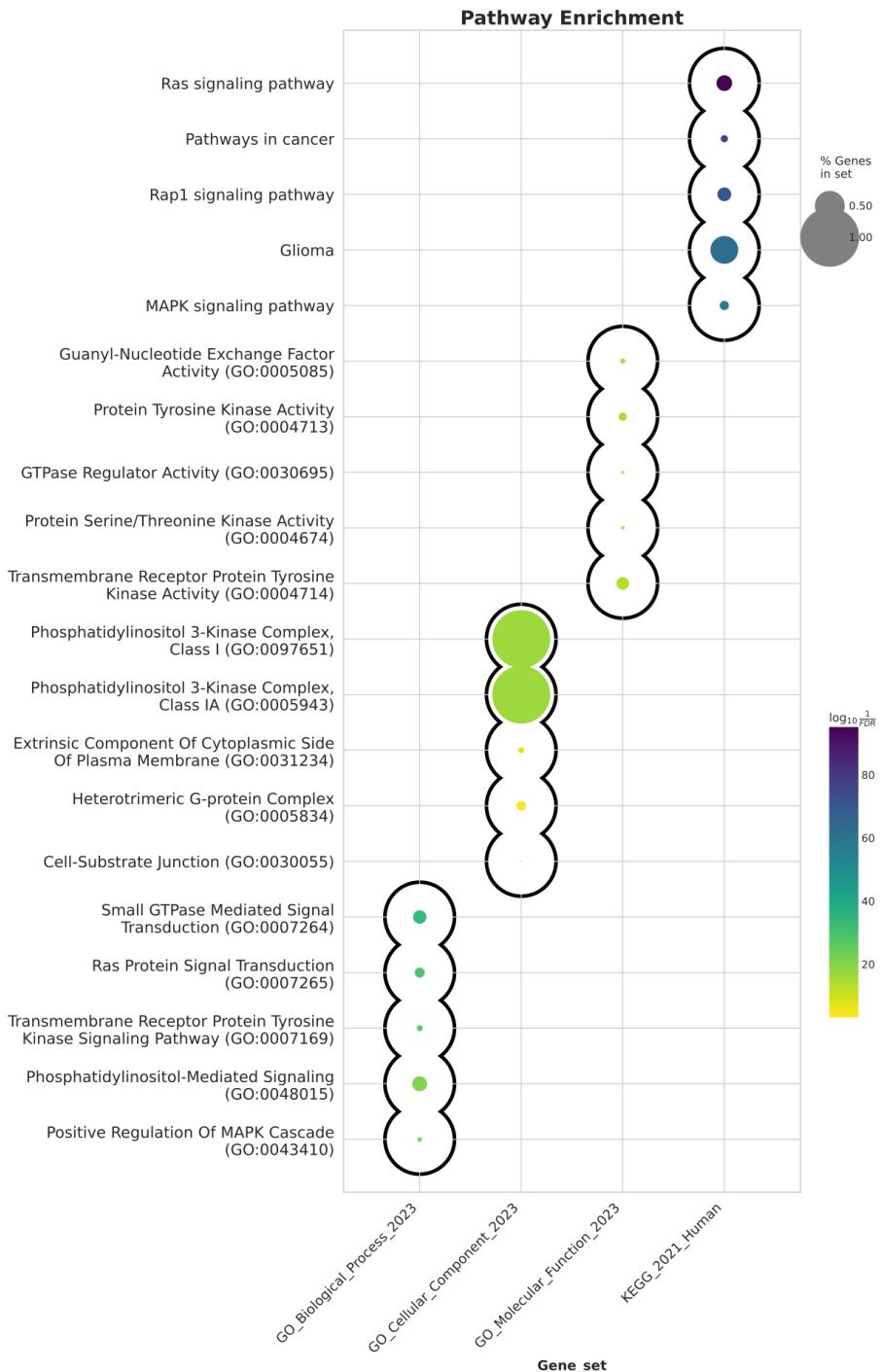
| Protein | Score |
|---------|-------|
| BRAF | 0.999 |
| RAF1 | 0.999 |
| RALGDS | 0.999 |
| SOS1 | 0.999 |
| CALM3 | 0.998 |
| CALML3 | 0.998 |
| CALML4 | 0.998 |
| CALML5 | 0.998 |
| CALML6 | 0.998 |
| PIK3CA | 0.998 |

The scores are from 0 to 1 and indicate the confidence: how likely STRING judges an interaction to be true, given the available evidence.

Source: STRING

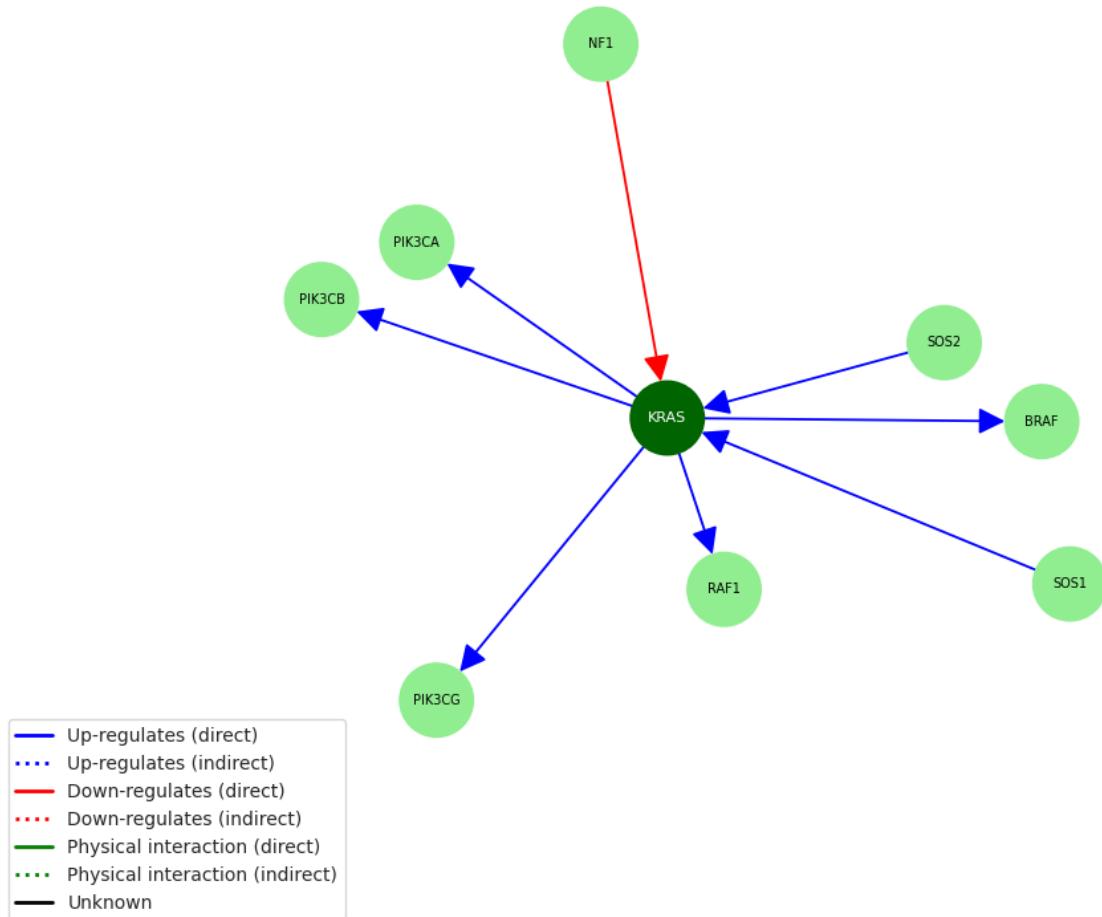
1.9 Pathway enrichment

Pathway enrichment analysis for the 100 genes that have the highest interaction score with KRAS.



Source: gseapy

1.10 SIGnaling Network



| Regulator | Effect | Mechanism | Direct | Target | Score |
|-----------|-----------------------|------------------------------------|--------|--------|-------|
| KRAS | up-regulates | binding | YES | PIK3CA | 0.907 |
| KRAS | up-regulates activity | binding | YES | BRAF | 0.872 |
| KRAS | up-regulates | binding | YES | RAF1 | 0.84 |
| KRAS | up-regulates | binding | YES | RAF1 | 0.84 |
| SOS1 | up-regulates | guanine nucleotide exchange factor | YES | KRAS | 0.82 |

| | | | | | |
|--------|-------------------------------------|------------------------------------|-----|------------|-------|
| SOS1 | up-regulates | guanine nucleotide exchange factor | YES | KRAS | 0.82 |
| SOS1 | up-regulates | guanine nucleotide exchange factor | YES | KRAS | 0.82 |
| SOS1 | up-regulates | guanine nucleotide exchange factor | YES | KRAS | 0.82 |
| KRAS | up-regulates | binding | YES | PIK3CG | 0.767 |
| KRAS | up-regulates | binding | YES | PIK3CG | 0.767 |
| KRAS | up-regulates | binding | YES | PI3K | 0.728 |
| NF1 | down-regulates activity | binding | YES | KRAS | 0.71 |
| SOS2 | up-regulates | guanine nucleotide exchange factor | YES | KRAS | 0.703 |
| KRAS | up-regulates | N/A | NO | Glycolysis | 0.7 |
| KRAS | up-regulates | binding | YES | PIK3CB | 0.7 |
| RASSF5 | up-regulates activity | binding | YES | KRAS | 0.68 |
| PTPN11 | up-regulates activity | dephosphorylation | YES | KRAS | 0.646 |
| SRC | up-regulates | phosphorylation | YES | KRAS | 0.644 |
| KRAS | up-regulates activity | binding | YES | RASSF1 | 0.637 |
| KRAS | up-regulates | binding | YES | PIK3CD | 0.618 |
| RIN1 | up-regulates | binding | YES | KRAS | 0.578 |
| DAB2IP | down-regulates activity | gtpase-activating protein | YES | KRAS | 0.495 |
| KRAS | up-regulates quantity by expression | transcriptional regulation | NO | NFE2L2 | 0.438 |
| FNTB | up-regulates activity | N/A | YES | KRAS | 0.429 |

| | | | | | |
|-----------------|---|---|------------|---------------|--------------|
| RAP1GDS1 | up-regulates | binding | YES | KRAS | 0.427 |
| RAPGEF5 | up-regulates | guanine nucleotide exchange factor | YES | KRAS | 0.412 |
| RASGEF1A | up-regulates | guanine nucleotide exchange factor | YES | KRAS | 0.399 |
| FNTA | up-regulates activity | N/A | YES | KRAS | 0.391 |
| KRAS | up-regulates | binding | YES | MAP3K1 | 0.375 |
| KRAS | up-regulates | phosphorylation | YES | MAP3K1 | 0.375 |
| KRAS | up-regulates | phosphorylation | YES | MAP3K1 | 0.375 |
| KRAS | up-regulates | phosphorylation | YES | TCF3 | 0.317 |
| RASGEF1B | up-regulates | binding | YES | KRAS | 0.301 |
| PTPN2 | down-regulates activity | dephosphorylation | YES | KRAS | 0.28 |
| KRAS | down-regulates activity | N/A | NO | CARM1 | 0.276 |
| TRiC | up-regulates quantity by stabilization | binding | YES | KRAS | 0.27 |
| LZTR1 | down-regulates activity | ubiquitination | YES | KRAS | 0.253 |
| LZTR1 | down-regulates quantity | ubiquitination | YES | KRAS | 0.253 |
| RASGEF1C | up-regulates | binding | YES | KRAS | 0.2 |
| KRAS | up-regulates | N/A | NO | NFIL3 | 0.2 |
| MVD | up-regulates quantity by stabilization | N/A | NO | KRAS | 0.2 |
| EFR3A | up-regulates quantity | binding | YES | KRAS | 0.2 |
| KRAS | up-regulates | N/A | NO | MINK1 | 0.2 |

| | | | | | |
|----------|--------------|-----|----|--------|-----|
| EML4-ALK | up-regulates | N/A | NO | KRAS | 0.2 |
| KRAS | up-regulates | N/A | NO | MAP4K5 | 0.2 |

Source: Signor [9]

1.11 Role in physiology

KRAS is a GTPase that plays a fundamental role in transducing signals from plasma membrane growth factor receptors to downstream signaling pathways controlling cell proliferation, survival, and migration. In normal cells, KRAS activity is tightly controlled, but specific mutations, such as those at codons 12, 13, or 61, disrupt the RAS protein's ability to transition between its active and inactive states, leading to persistent activation and uncontrolled cell growth, contributing to various cancers. KRAS signaling also plays an essential role in regulating the balance of secretory, ciliated, and squamous cell differentiation of the human airway epithelium. In the context of the provided study, siRNA-mediated knockdown of KRAS decreased differentiation of basal stem/progenitor cells into secretory and ciliated cells, while activation of KRAS signaling via lentivirus-mediated over-expression of the constitutively active G12V KRAS mutant had the opposite effect. Cigarette smoke exposure increases KRAS and RAS protein family activation in vitro and in vivo, contributing to airway epithelial remodeling.

Source: PubMed [10]

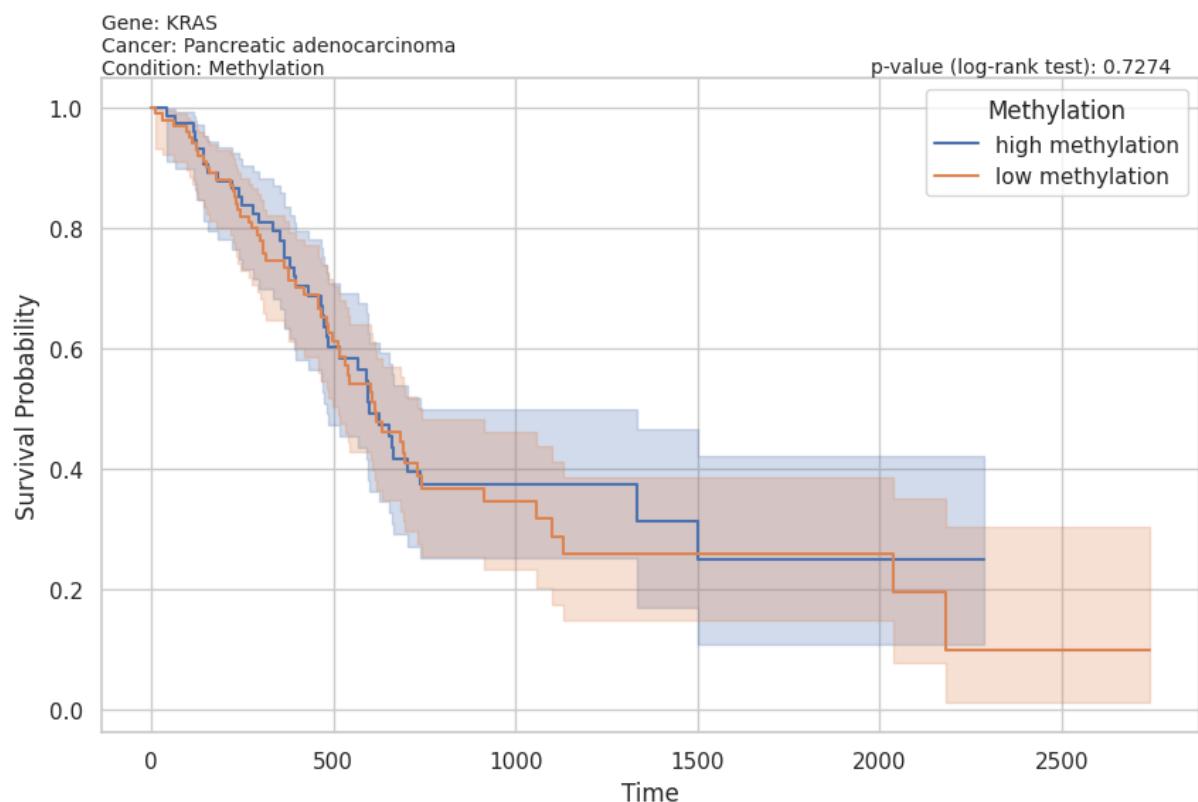
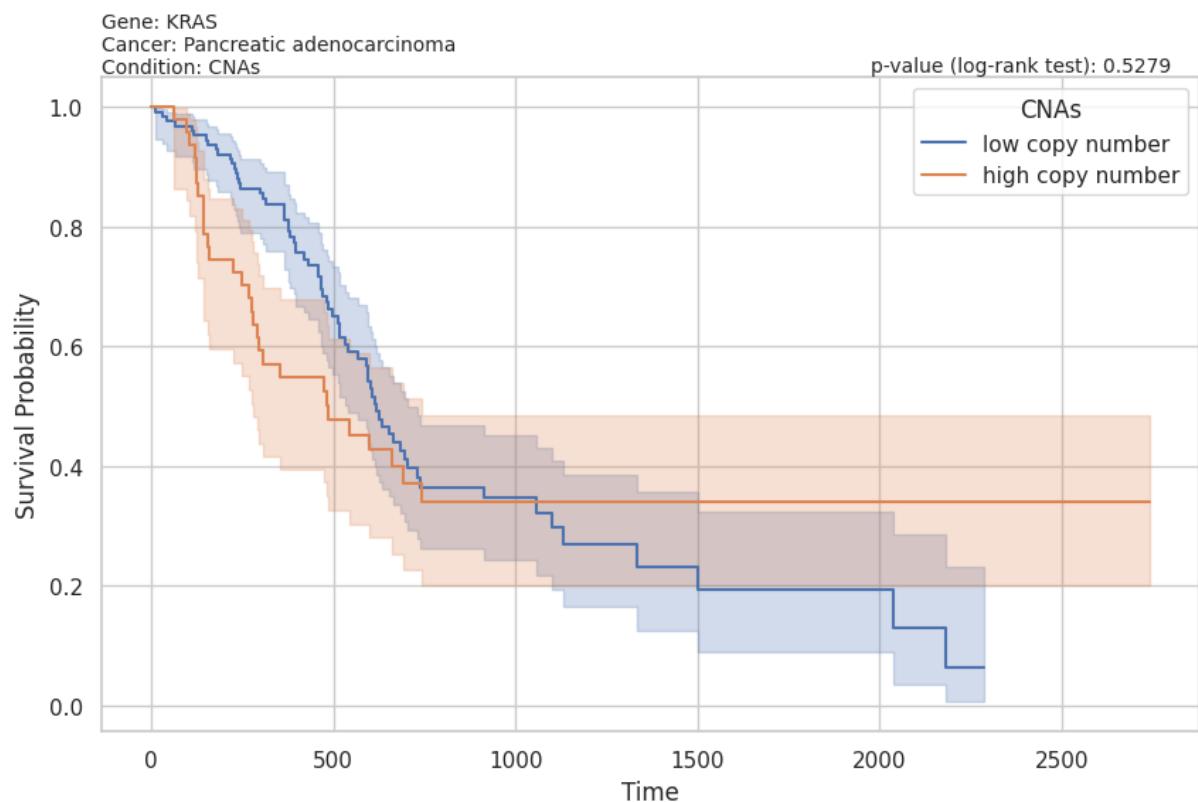
1.12 Role in tumor progression

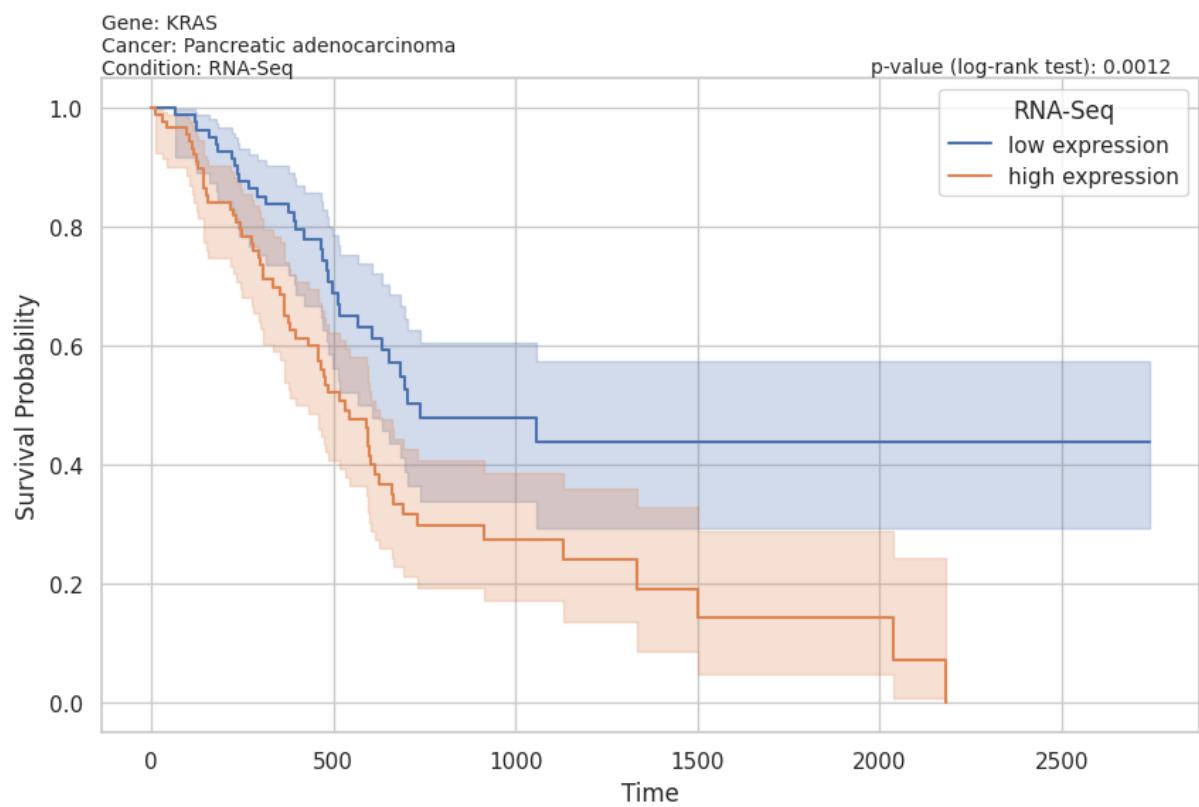
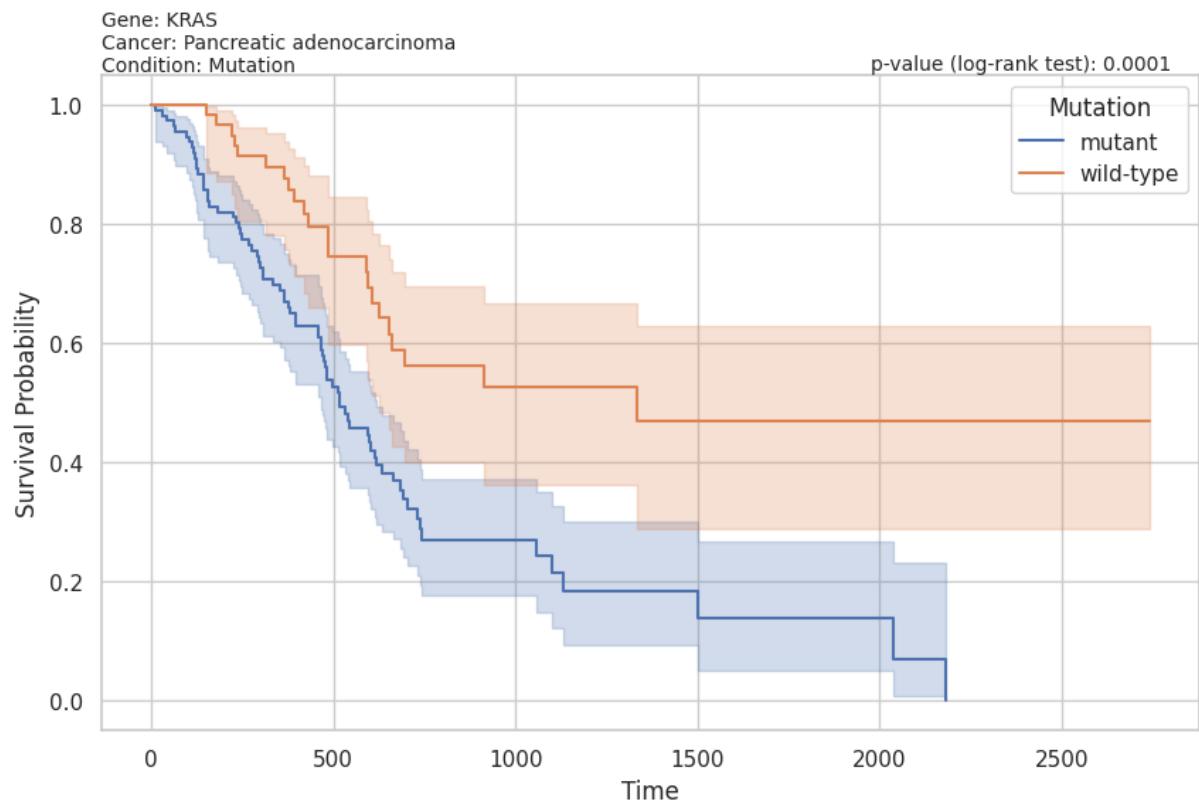
KRAS is a frequently mutated oncogene in human adenocarcinoma of the lung and pancreas. In pancreatic cancer, KRAS mutations are linked with poor clinical outcomes. Recent studies suggest that KRAS-driven tumor progression may not be completely independent of upstream signaling, as ERBB family receptor tyrosine kinases (RTKs) have been shown to play a role in KRAS-driven lung tumor development and progression. Similarly, in pancreatic ductal adenocarcinomas (PDAC), SMAD4 deficiency, which is associated with KRAS mutations, has been shown to accelerate PDAC development and alter tumor phenotype. Additionally, a non-receptor protein tyrosine phosphatase, SHP2, has been identified as an essential player in oncogenic KRAS-driven tumors, and its inhibition or deletion has been shown to delay tumor progression but not achieve tumor regression. Synergy is observed when both SHP2 and MEK are targeted, resulting in sustained tumor growth control in murine and human patient-derived organoids and xenograft models of pancreatic ductal adenocarcinoma. These findings suggest that KRAS plays a central role in pancreatic cancer progression and that targeting multiple signaling pathways may be an effective therapeutic approach for KRAS-mutant cancers.

Source: PubMed [11]

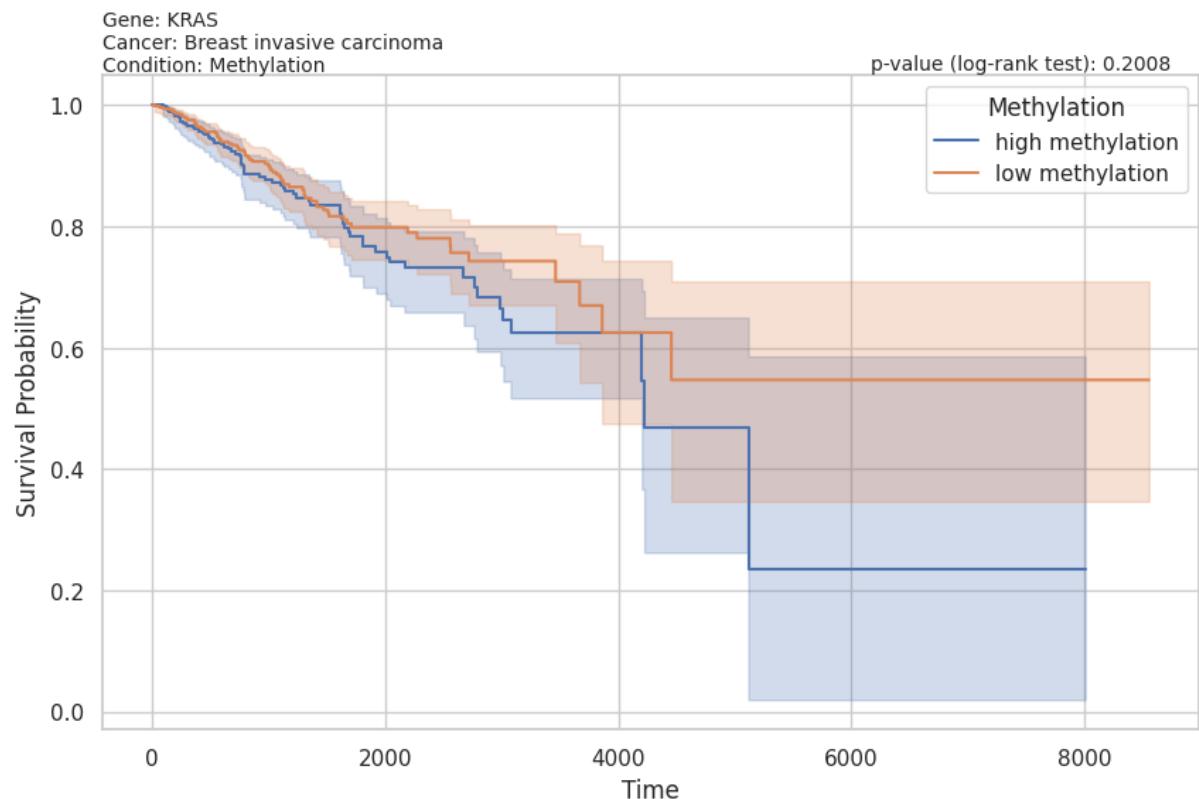
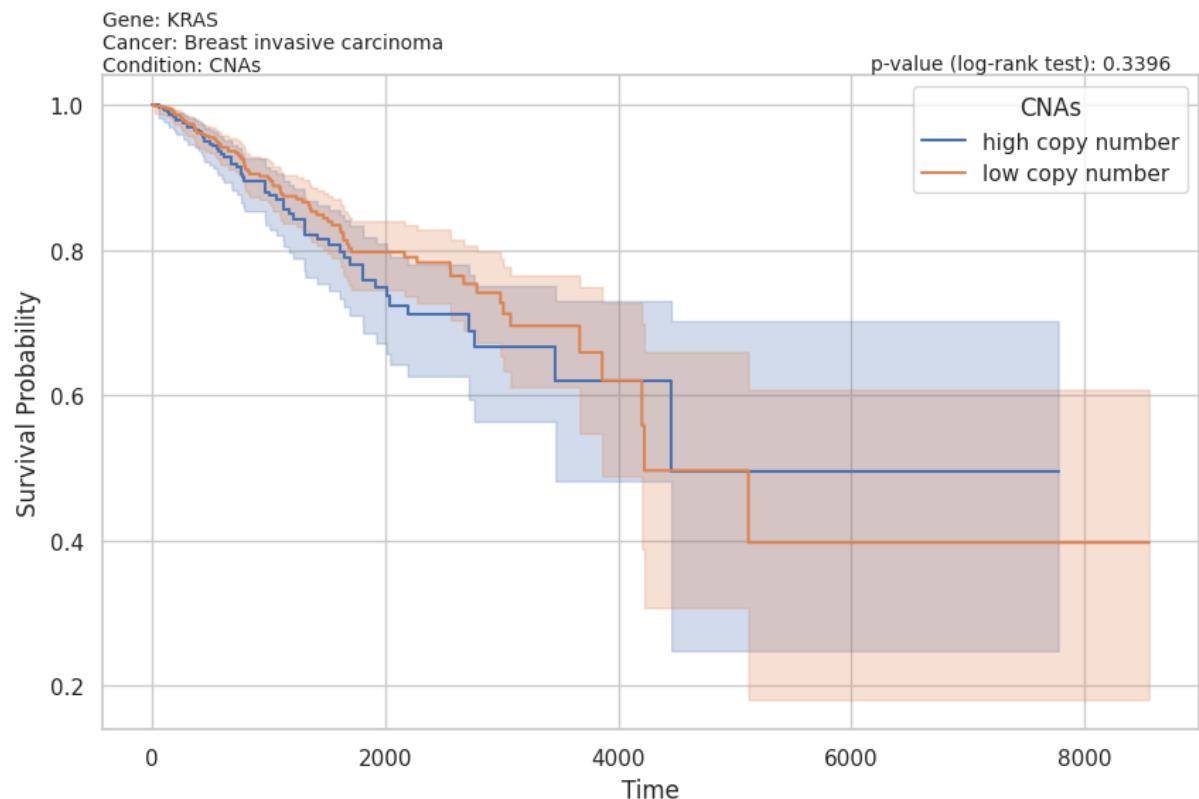
1.13 Kaplan-Meier curves

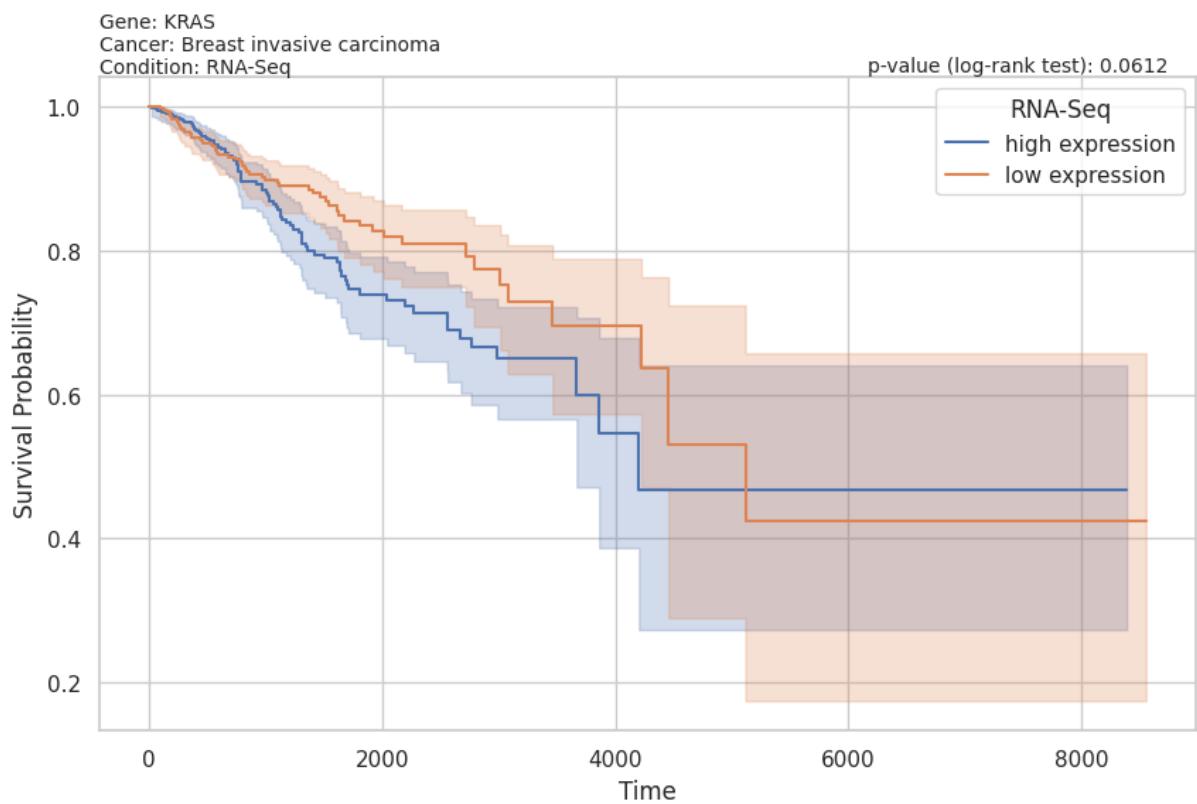
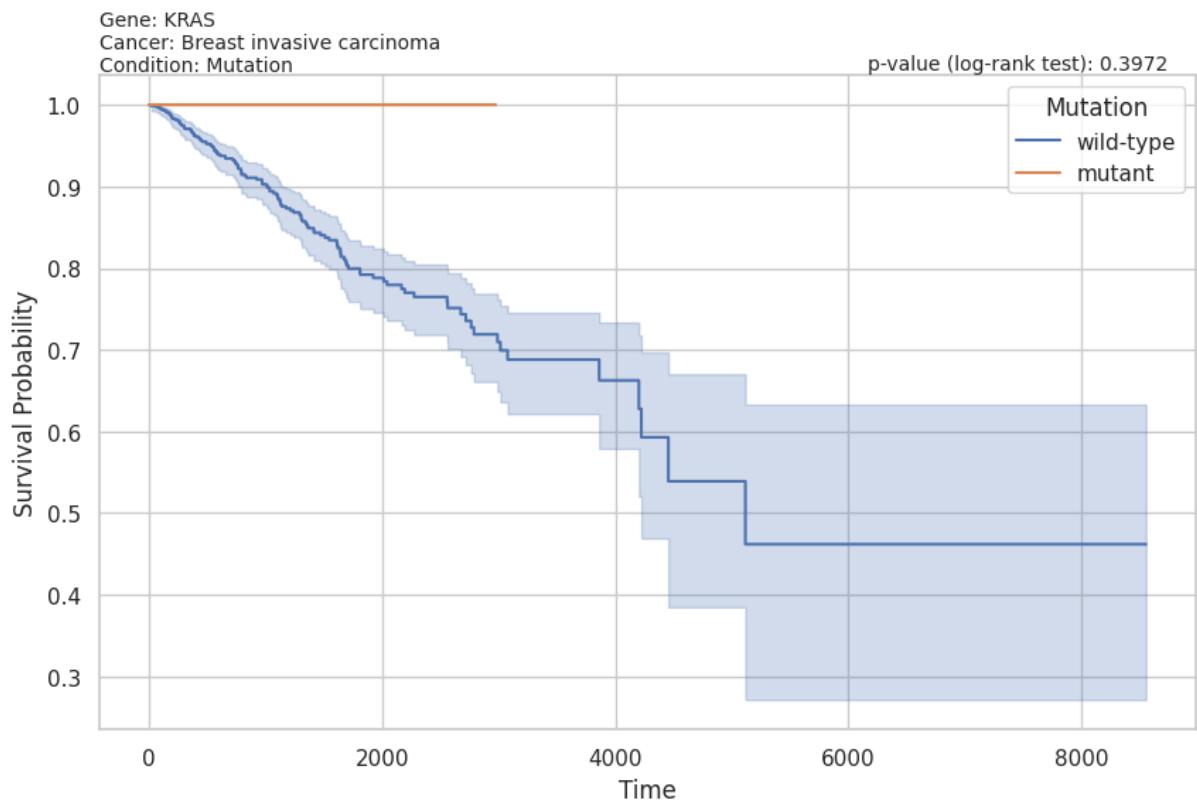
Pancreatic adenocarcinoma



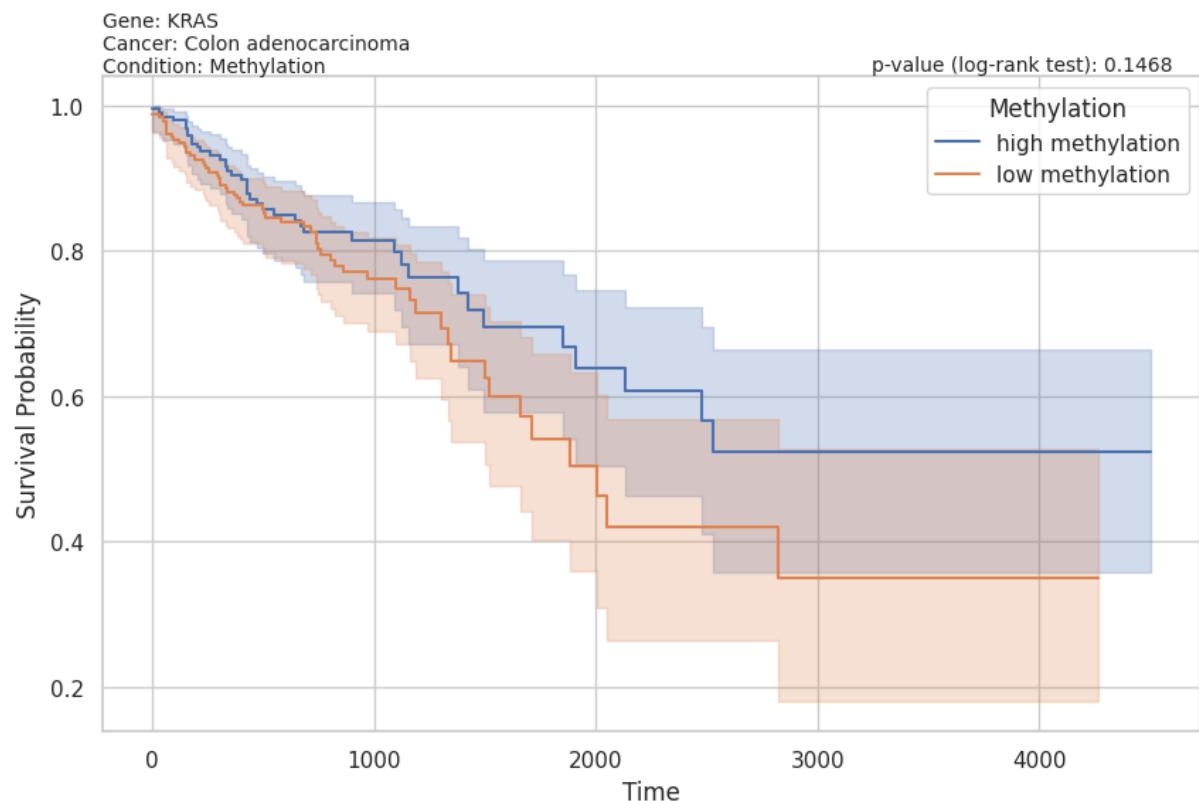
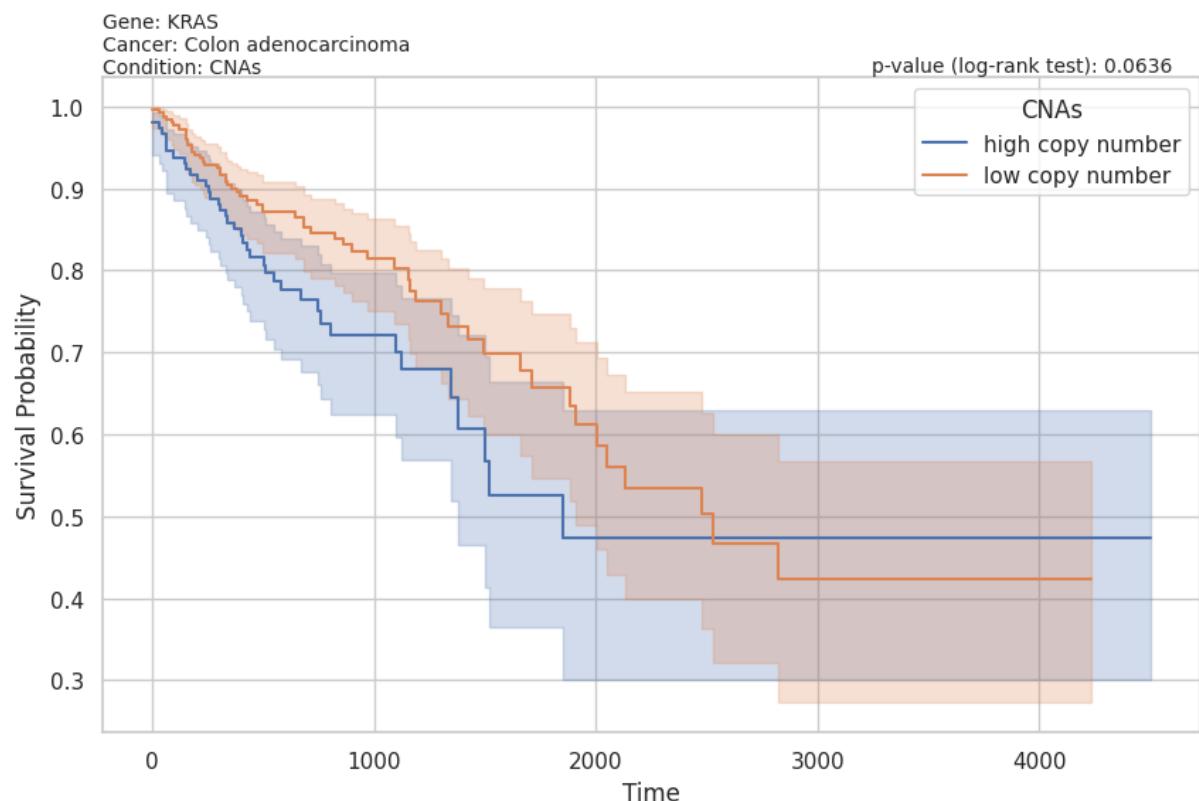


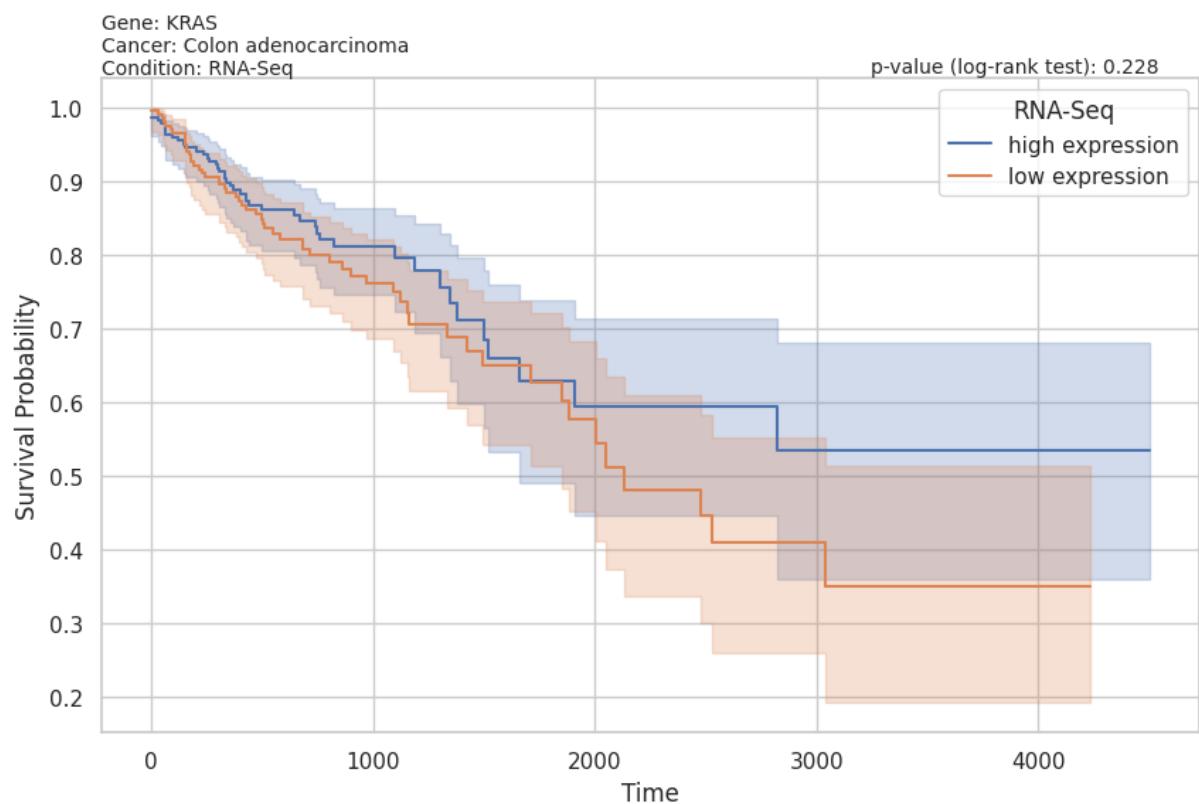
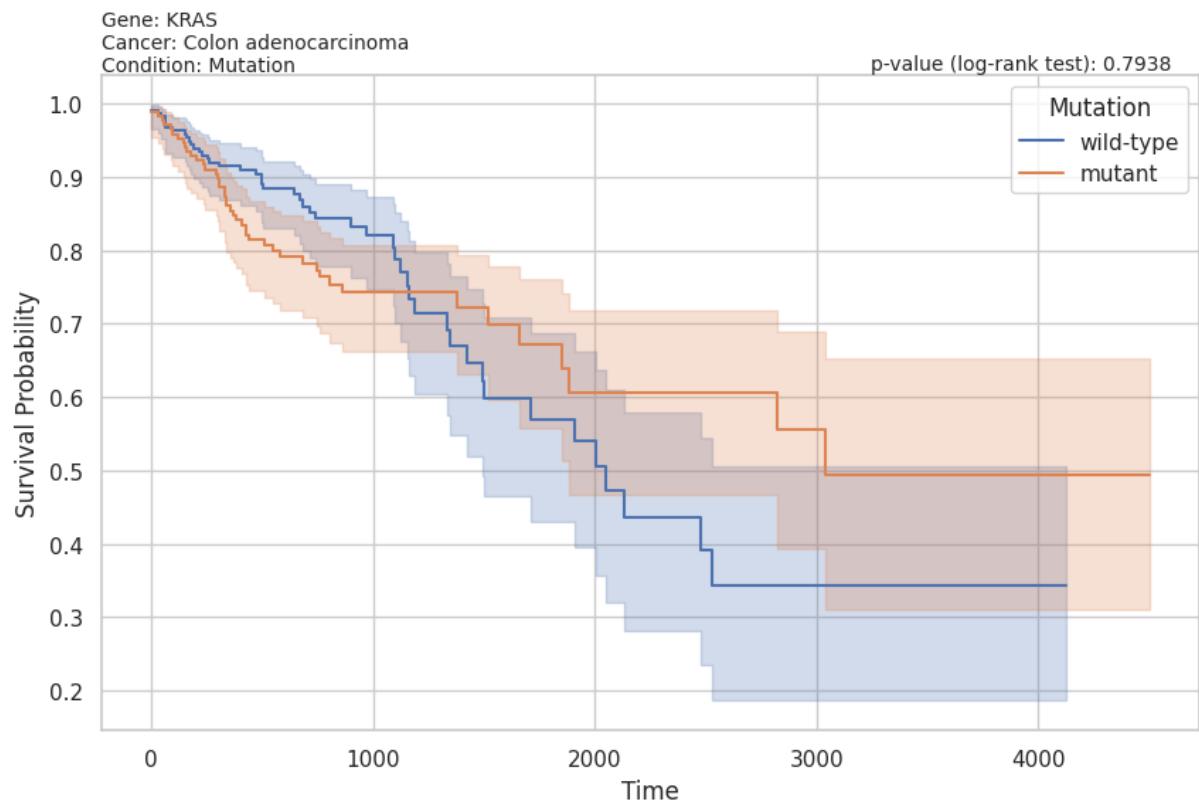
Breast invasive carcinoma



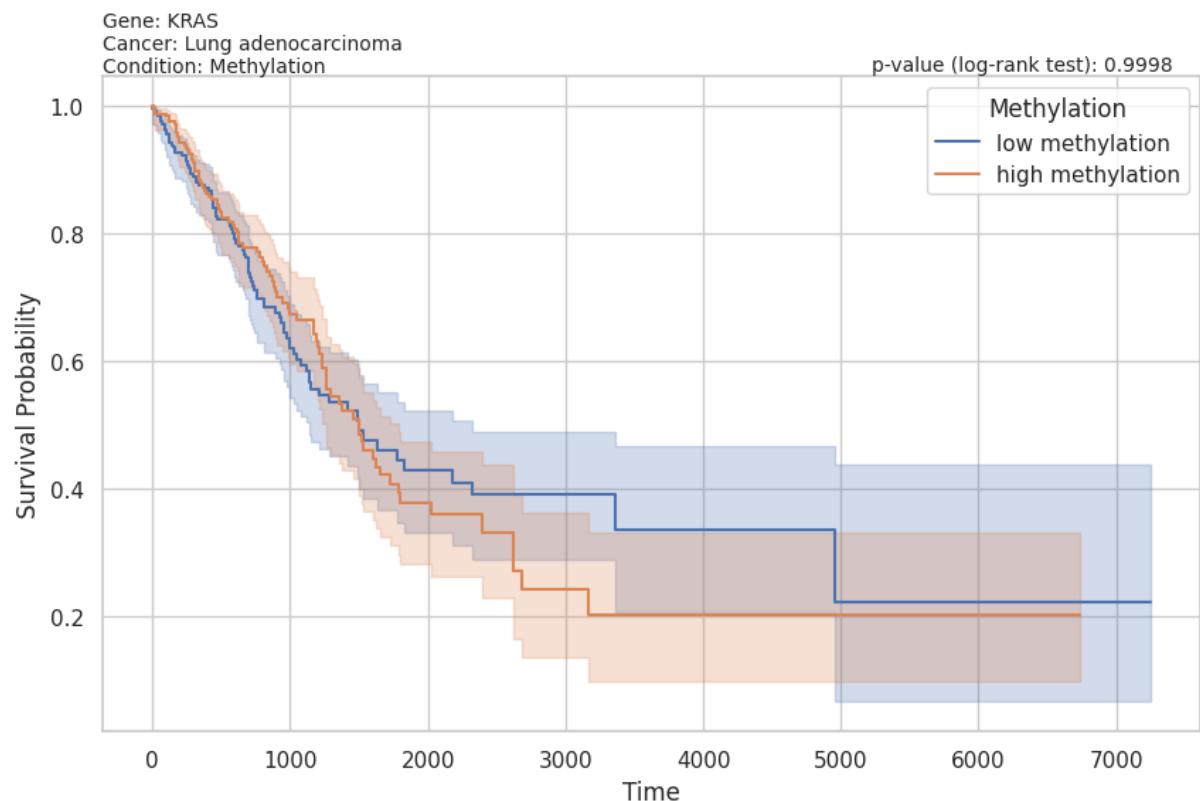
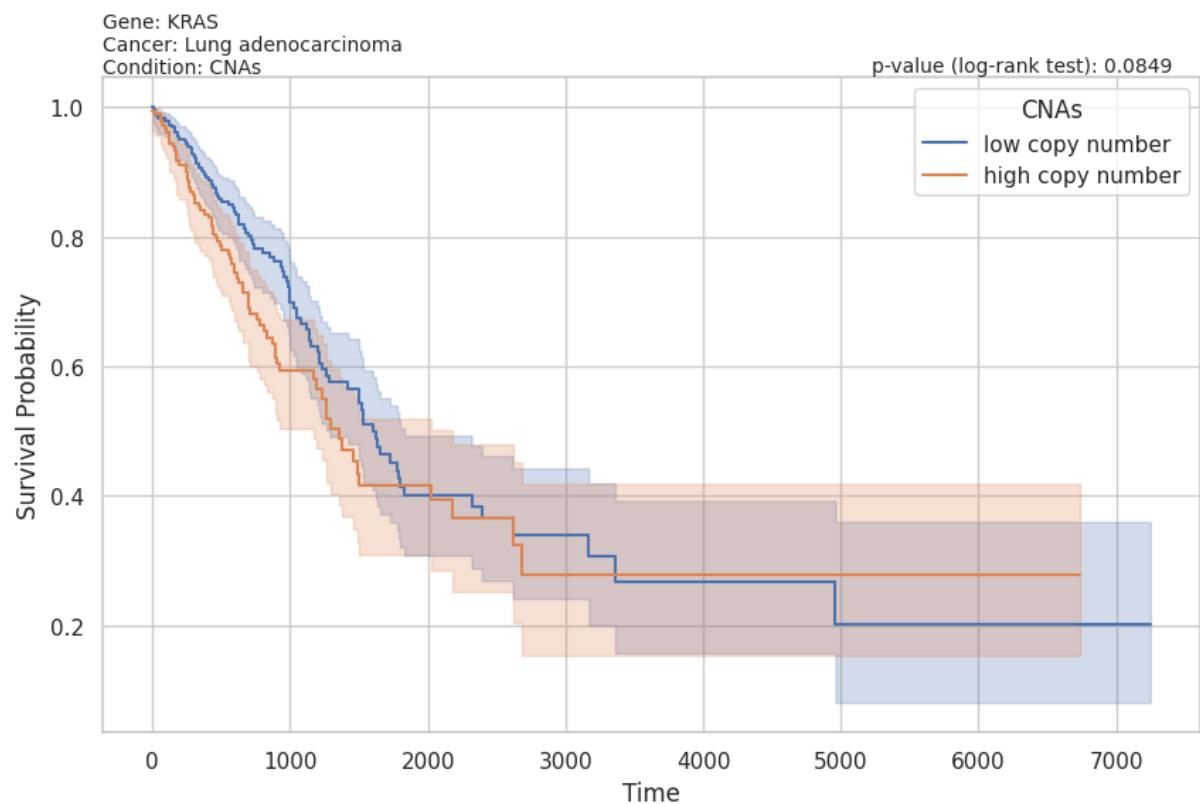


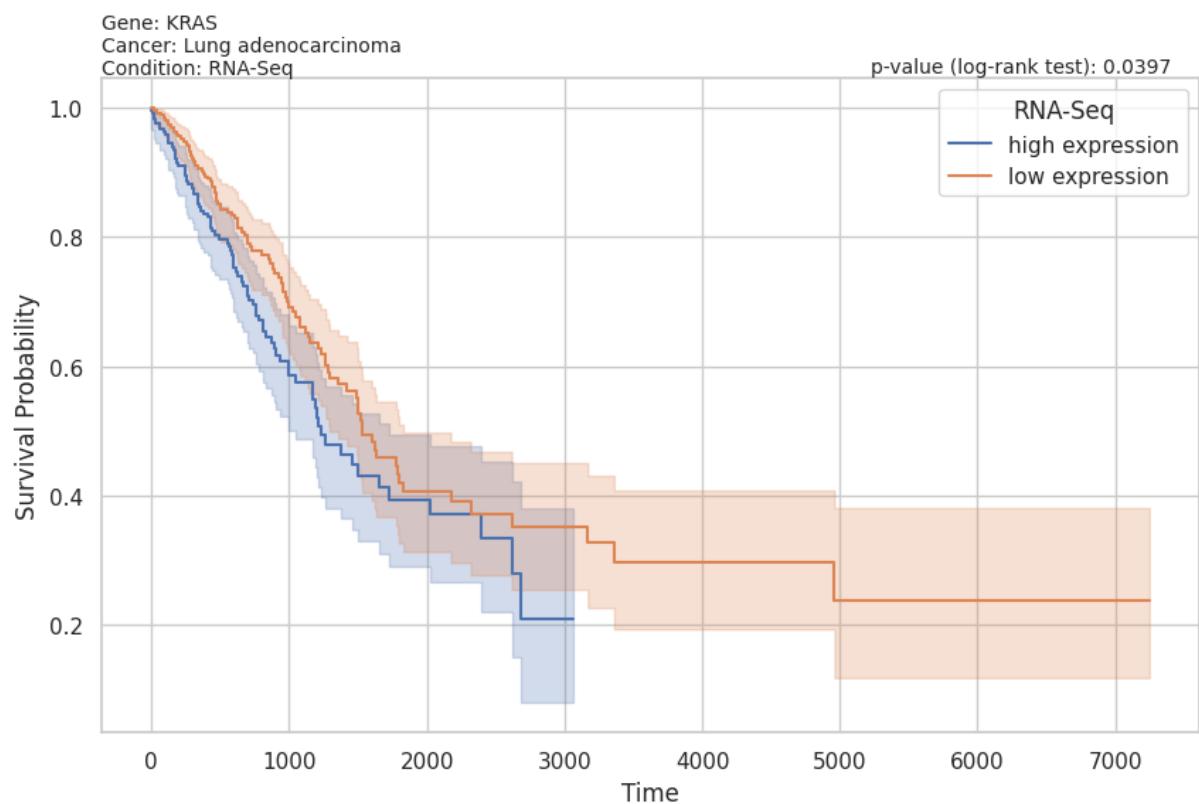
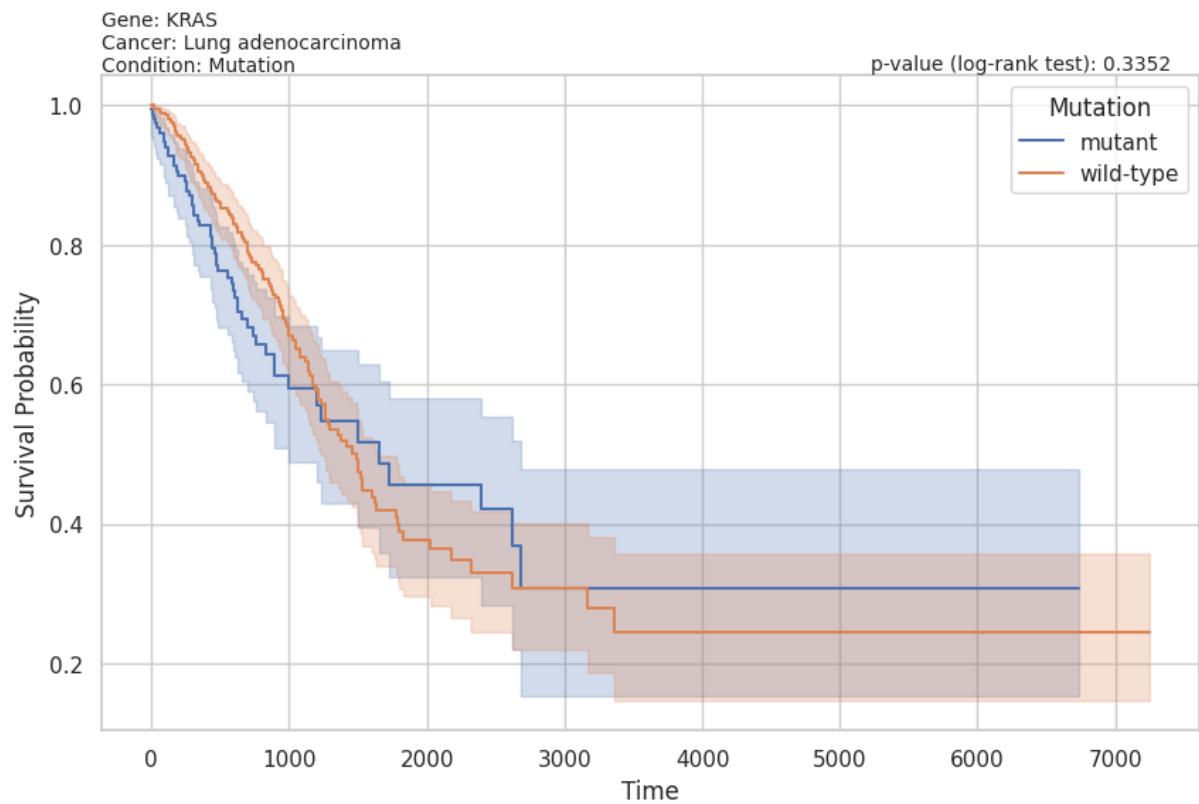
Colon adenocarcinoma





Lung adenocarcinoma





Source: TCGA Survival [12]

2. Disease information

2.1 Disease description

Pancreatic cancer is a highly malignant tumor of the digestive system. Its incidence is increasing rapidly, making it a significant health concern. Early diagnosis remains challenging, and most patients are diagnosed with advanced stage disease. The prognosis for pancreatic cancer patients is poor, with a 5-year relative survival rate of less than 8%. Therapy failure is often due to distant metastasis before surgical intervention and limited efficiency of chemotherapy or radiation therapy.

The relationship between pancreatic cancer and hyperglycemia has been established clinically. Diabetes mellitus increases the incidence of pancreatic cancer compared to the non-diabetes population. The mortality rate for pancreatic cancer patients with diabetes mellitus is significantly higher than those without diabetes. Additionally, pancreatic cancer patients with diabetes mellitus often present with larger tumors and reduced median survival. However, the precise role and molecular mechanisms of hyperglycemia in pancreatic cancer progression have yet to be elucidated.

The immune system plays a crucial role in the development of pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer. Despite significant advances in cancer research, pancreatic cancer remains a deadly disease, with a 5-year survival rate of only 8%. Among patients with pancreatic cancer, 90% carry a KRAS mutation, which is considered a driver gene for pancreatic cancer progression. Inactivating mutations in TP53, CDKN2A, and SMAD4 are also common. The pancreatic cancer microenvironment, consisting of cancer cells, stromal cells, and extracellular components, plays a significant role in the disease's progression.

Pancreatic cancer is one of the leading causes of cancer-related mortality worldwide. The 5-year survival rate remains below 10%. Despite advances in new systemic treatments and the increased availability of active agents, median overall survival in metastatic pancreatic cancer is less than one year. Multiple combinations of somatic gene mutations have been identified as causes of pancreatic cancer, with mutational activation of oncogenic KRAS and inactivation of tumor suppressor genes such as TP53, CDKN2A, and SMAD4 being the four major driver genes. Up to 10% of pancreatic cancers are related to inherited genes. Hereditary pancreatic cancer syndromes and familial pancreatic cancer (FPC) are two broad risk categories for inherited pancreatic cancer. Most hereditary pancreatic cancers have autosomal dominant inheritance, presenting a 50% probability that the pathogenic variant will be passed on to the next generation.

Source: PMC [13]

2.2 Disease statistics

Pancreatic cancer, specifically pancreatic ductal adenocarcinoma (PDAC), is a highly aggressive and deadly cancer. According to the International Agency for Research on Cancer (IARC) GLOBOCAN statistics from 2020, there were 496,000 newly diagnosed cases and 466,000 related deaths worldwide. PDAC accounts for over 90% of all pancreatic cancer cases. Despite being the 10th most prevalent cancer, it is the seventh leading cause of cancer-related deaths due to its poor prognosis. The 5-year survival rate of pancreatic cancer is less than 10% globally.

The incidence rate of pancreatic cancer has been rising in recent decades, and it accounts for 4.9% and 4.5% of worldwide cancer incidence and related deaths, respectively. The primary reasons for the low survival rate are that the disease remains asymptomatic until advanced stages due to the anatomical position of the pancreas in the retroperitoneum and the lack of valuable biomarkers for early stages.

PDAC arises from acinar and ductal cells in the pancreas. The tumor microenvironment (TME) of PDAC plays a role in enabling chemotherapeutic resistance, cancer cell proliferation, invasion, migration, and metastasis. It is characterized by a dense extracellular matrix (ECM) structure, stromal cells, cancer-associated fibroblasts, and immune cells. The overexpression of ECM proteins exacerbates PDAC tumorigenesis, fostering tumor growth. Pancreatic cancer cells secreting ECM proteins such as collagen and fibronectin were found to have increased proliferation and were desensitized to chemotherapeutic drugs such as gemcitabine.

The need for prompt diagnosis and treatment of pancreatic cancer is recognized globally due to its dismal prognosis. Clinical biomarkers play a pivotal role in diagnosing and managing various cancers, including pancreatic cancer. CA-19-9 is one such biomarker commonly used for pancreatic cancer. It is a carbohydrate antigen that can be detected in the blood of some pancreatic cancer patients.

The prevalence and incidence of pancreatic neuroendocrine tumors (PNET) have gradually increased over the past 40 years and can be as high as 10% in autopsy studies. The 5-year survival rate of pancreatic tumor (PT), which includes PDAC and PNET, is roughly 10 percent across the world, with minimal change throughout the past few decades. The primary reasons for the low survival rate are that the disease remains asymptomatic until advanced stages, the low resectability rate at the time of diagnosis, early metastasis nature, and high resistance rate to neoadjuvant therapy.

In multiracial countries such as the United States of America, African Americans have increased incidence and poorer survival rates compared to other ethnicities, although this has been largely attributed to social factors such as smoking, alcohol consumption, obesity, and diabetes mellitus. Current studies

have determined genetics as an underlying factor.

In summary, pancreatic cancer, specifically PDAC, is a highly aggressive and deadly cancer with a poor prognosis. The incidence rate has been rising, and it accounts for a significant percentage of cancer-related deaths. The low survival rate is due to late detection, lack of valuable biomarkers for early stages, and the tumor microenvironment's role in enabling chemotherapeutic resistance and metastasis. The need for prompt diagnosis and treatment is recognized globally, and clinical biomarkers such as CA-19-9 play a crucial role in diagnosing and managing the disease.

Source: PMC [14]

2.3 ESMO guidelines

Management of local and locoregional disease

The ESMO guidelines for pancreatic cancer provide a treatment algorithm for local and locoregional disease. Surgical resection is the only potentially curative treatment for pancreatic cancer, and patients with a high probability of surgical resection with no tumor at the margin (R0) are good candidates for upfront surgery. The NCCN criteria are widely used to define tumor resectability, and these criteria have been adopted in the NCCN guidelines.

For resectable tumors, initial surgery remains the standard of care. The location and size of the tumor determine the type of surgery, with **pancreatoduodenectomy (Whipple procedure)** for tumors in the head of the pancreas and **distal pancreatectomy** for tumors in the body or tail. Minimally invasive techniques can reduce morbidity but have insufficient data regarding oncological results.

Lymphadenectomy should involve the removal of **/C2116 nodes**, and extended lymphadenectomy is not recommended. Age alone is not a determinant for selecting patients for pancreatectomy, but severe comorbidities or severe malnutrition may warrant avoidance of surgery. Preoperative biliary drainage is recommended for patients with a total bilirubin level >250 mmol/l, those planned to receive neoadjuvant treatment, or those for whom surgery will be delayed for longer than 2 weeks.

Neoadjuvant therapy, including neoadjuvant chemotherapy (ChT), neoadjuvant chemoradiotherapy (CRT), and neoadjuvant ChT followed by neoadjuvant CRT, is not well-established, and literature-based meta-analyses have reported conflicting data on R0 resection rate and potential survival benefit. A few randomized trials comparing neoadjuvant therapy with initial surgery and adjuvant therapy have been completed in selected patients with resectable PC or borderline resectable PC (BRPC).

For BRPC, induction treatment over upfront surgery is supported by evidence, with a significant improvement in OS in a recent meta-analysis of five studies. The most appropriate induction strategy, ChT and/or CRT, is a controversial issue, and patients with BRPC should be enrolled in clinical trials whenever possible.

For locally advanced PC (LAPC), the purpose of conversion (or induction) therapy is to induce tumor downsizing to facilitate resection in patients with initial unresectable disease. Reviews have demonstrated that induction therapy increases the possibility of an R0 resection and that OS is prolonged. A few randomized trials have been completed, with CRT producing mixed results.

Recommendations include frozen section analysis of pancreatic neck transection and common bile duct transection margins, tumor clearance definition for all margins identified by the surgeon, radical antegrade modular pancreatectomy with dissection of the left hemi-circumference of the SMA to the left of the coeliac trunk for patients with tumors in the body or tail, and the use of the UICC TNM eighth edition staging system to classify the anatomical spread of the tumor. Standard lymphadenectomy is recommended, and patients undergoing surgery should receive perioperative thromboprophylaxis. If the bilirubin level is >250 mmol/l, endoscopic drainage is recommended in patients with cholangitis, those planned to receive neoadjuvant treatment, or those in whom surgery will be delayed for longer than 2 weeks. Neoadjuvant therapy is not recommended for resectable PC, and following resection of PC, completion of 6 months of adjuvant ChT is strongly recommended. In patients who are not candidates for mFOLFIRINOX, gemcitabine capecitabine is an alternative option. Patients with BRPC have a high probability of an R1 resection and should be considered for induction treatment, and if inclusion in a clinical trial is not feasible, induction therapy is recommended over initial surgery. A period of induction ChT followed by CRT on a case-by-case basis and subsequent surgery is suggested, and following induction therapy, medically fit patients without disease progression and with a decrease in CA 19-9 should undergo surgical exploration. For LAPC, all patients must be evaluated by the local MDTB for resectability every 2-3 months, and patients with LAPC should be included in clinical trials whenever possible. A conversion surgery strategy utilizing the standard of care of (up to) 6 months of combination ChT can be chosen, and exploration for resection could be discussed if there is a significant decrease in CA 19-9 level, clinical improvement, and tumor downstaging. Arterial resection after induction therapy is not recommended but can be considered as a possibility in experienced centers on a case-by-case basis in selected patients.

Management of advanced disease

The standard of care for first-line treatment of metastatic pancreatic cancer (PC) was established as gemcitabine monotherapy in 1997. However, the addition of targeted agents to gemcitabine and combination regimens such as FOLFIRINOX and capecitabine-cisplatin have not shown significant benefits.

FOLFIRINOX has demonstrated superior efficacy over gemcitabine alone in patients with ECOG PS 0-1 and bilirubin level <1.5 times the upper limit of normal (ULN) in a randomized trial. Another trial showed that gemcitabine and nab-paclitaxel (GN) is superior to gemcitabine alone in patients with metastatic disease. However, there are no prospective randomized data comparing FOLFIRINOX and GN in the metastatic setting.

In the second-line setting, the combination of nanoliposomal irinotecan with 5-FU eLV showed an improvement in OS, PFS, and ORR over 5-FU eLV in the

randomized phase III NAPOLI-1 trial. This combination is an active and tolerable second-line treatment option for patients with metastatic disease who have received a prior gemcitabine-based treatment.

In the third-line setting, most patients are considered unsuitable for treatment due to poor nutritional status and/or poor performance status (PS), and best supportive care (BSC) is the appropriate treatment choice. In patients with good PS, inclusion in a clinical trial is the first option when available.

Precision medicine plays an important role in the management of metastatic PC. BRCA mutations occur in about 5-7% of Caucasian patients and make the tumors more susceptible to treatment with DNA crosslinking agents such as platinum compounds and PARP inhibitors. The POLO trial demonstrated that maintenance treatment with olaparib improved median PFS but not OS in patients with metastatic PC and gBRCA variants.

Microsatellite instability high/mismatch repair deficient (MSI-H/dMMR) occurs in about 0.8% of PC cases, mostly due to Lynch syndrome. Checkpoint inhibitors have shown some benefit in this population. In a prospective non-randomized trial, 22 patients with MSI-H/dMMR PC were treated with pembrolizumab, resulting in one complete responder and three partial responders.

Pancreatic acinar-cell carcinomas contain RAF fusions and frequent inactivation of DNA repair genes, which may be potentially targetable. NTRK fusions occur in KRAS-wt tumors and in >1% of all PCs and are targetable with specific inhibitors such as larotrectinib or entrectinib.

A treatment algorithm for the use of precision medicine in metastatic disease is provided in Figure 4.

Recommendations for first-line treatment include FOLFIRINOX or GN for patients with ECOG PS 0-1 and bilirubin level <1.5 times the ULN, GN for patients with ECOG PS 2, KPS /C2170 and bilirubin level /C201.5 times the ULN, and gemcitabine monotherapy for patients with ECOG PS 3-4. The efficacy of treatment should be evaluated every 8-12 weeks and based on clinical status, CA 19-9 trajectory, and imaging. Patients with BRCA mutations should receive platinum-based chemotherapy.

In the second-line setting, GN or gemcitabine alone may be offered to patients with ECOG PS 0-1 and a favorable comorbidity profile, and oxaliplatin-based second-line treatment remains controversial but may be considered as an alternative in patients with ECOG PS 0-2 if not given previously. For patients with ECOG PS 3-4, symptom-directed care is recommended.

In the third-line setting, most patients are considered unsuitable for treatment and BSC is the appropriate treatment choice. In patients with a good PS, inclusion in a clinical trial is the first option when available.

Precision medicine recommendations include BRCA genetic testing for all patients with metastatic PC to determine eligibility for platinum-based chemotherapy and maintenance with olaparib, pembrolizumab for patients with MSI-H/dMMR pancreatic tumors, and larotrectinib or entrectinib for patients with an NTRK fusion.

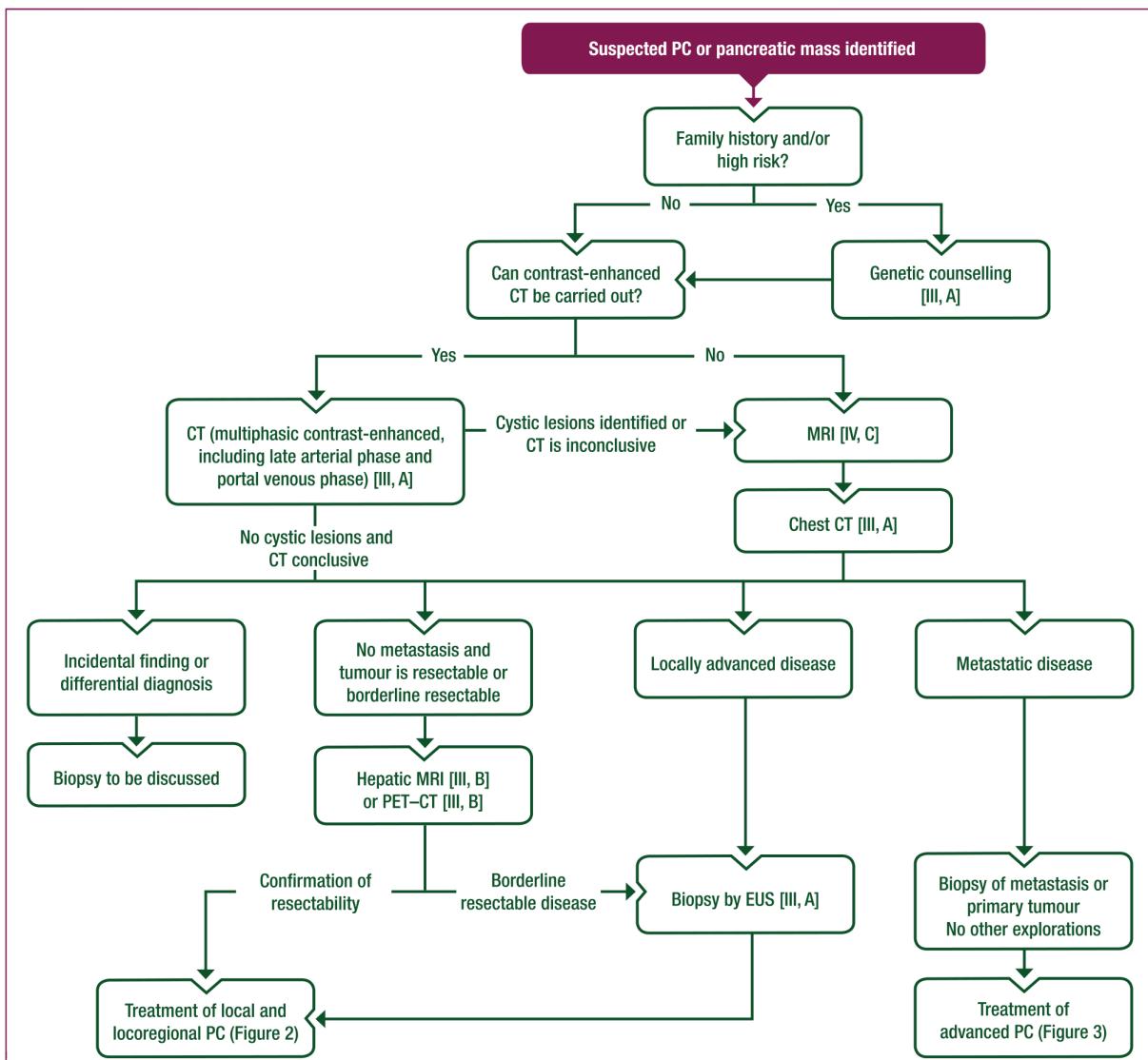


Figure 1. Diagnostic work-up of suspected PC.

Purple: general categories or stratification; white: management.

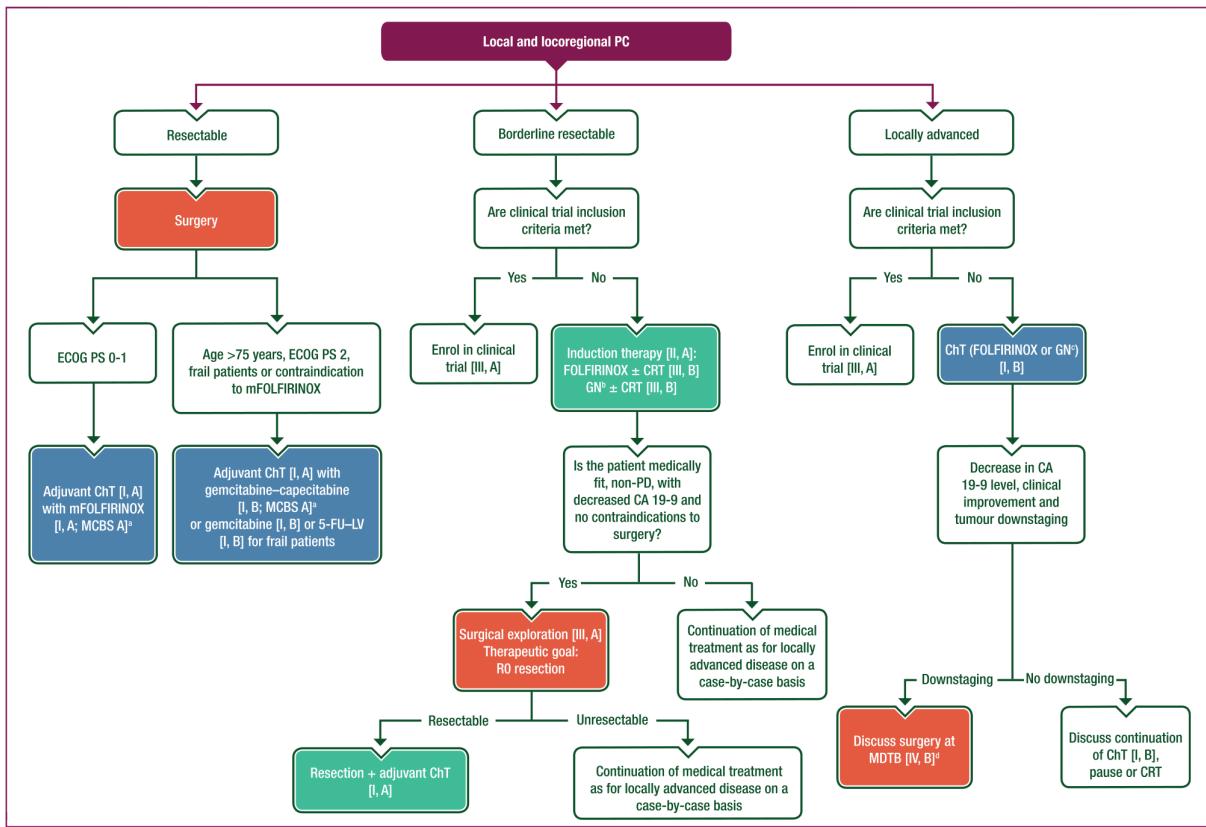


Figure 2. Treatment algorithm for local and locoregional PC.

Purple: general categories or stratification; red: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments; white: other aspects of management.

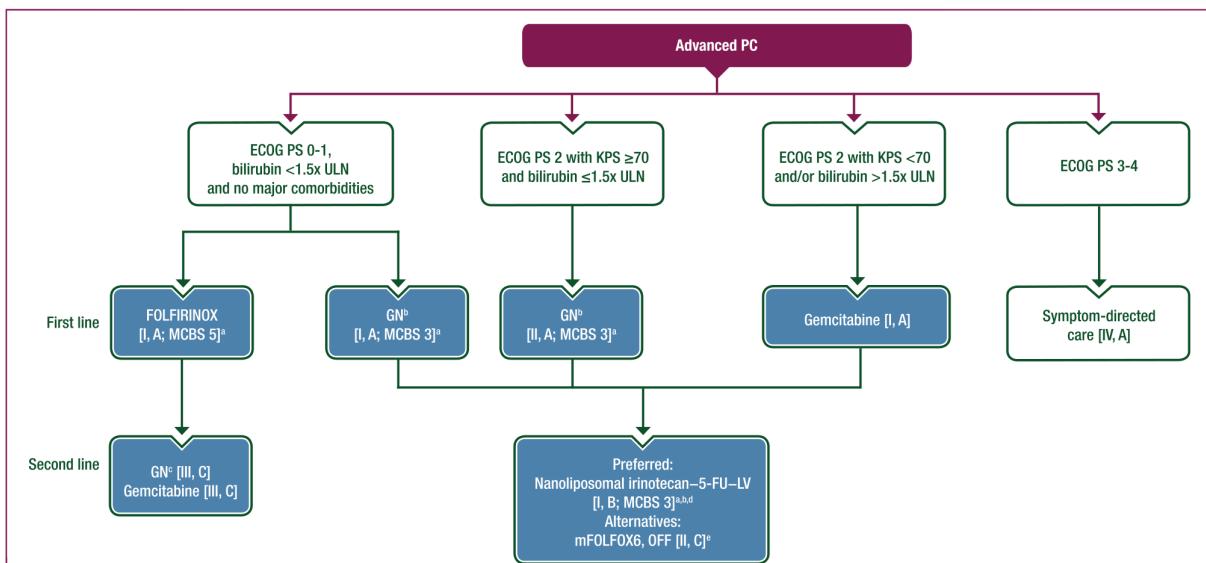


Figure 3. Systemic treatment of advanced PC.

Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

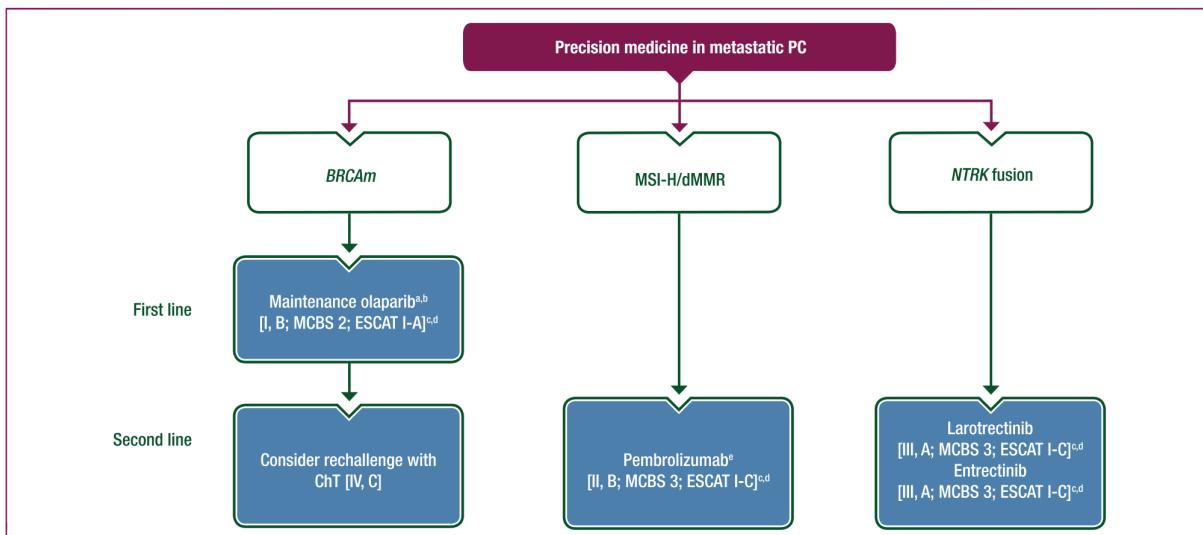


Figure 4. Precision medicine in metastatic PC.

Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

Source: ESMO

3. Competitive landscape

3.1 Pancreatic cancer standard of care

Pancreatic cancer is a lethal malignancy with a very poor prognosis, and most patients are diagnosed at an advanced stage, missing the opportunity for R0 surgery. In China, it is the seventh leading cause of cancer-related death, with nearly as many deaths as new cases each year. The standard treatment for metastatic and advanced pancreatic cancer is chemotherapy. Two regimens, Nab-paclitaxel plus gemcitabine (AG) and modified FOLFIRINOX, have been recommended as the first-line treatment options based on clinical trials.

The PRODIGE4/ACCORD11 clinical trial in 2011 demonstrated that the FOLFIRINOX regimen showed better survival benefits in metastatic pancreatic cancer patients compared to gemcitabine monotherapy. In 2013, the MPACT trial showed that the combination of gemcitabine and nab-paclitaxel also showed significant survival benefits compared to gemcitabine monotherapy. Therefore, these two regimens are now considered the standard first-line treatment for metastatic pancreatic cancer.

Gemcitabine monotherapy has been the standard treatment for metastatic pancreatic cancer for over two decades. However, various GEM-based combination regimens have not shown additional survival benefits, except for erlotinib, which, when combined with GEM, provides a statistically significant improvement in overall survival, although the absolute difference at median survival time is only marginal.

In a phase II/III study in 2011, Conroy et al. showed a significant improvement in overall survival and quality of life with FOLFIRINOX compared to gemcitabine in patients with metastatic pancreatic cancer. Since then, FOLFIRINOX has become the standard treatment for patients with pancreatic cancer with a good performance status in North America and Europe.

In summary, the standard treatment for pancreatic cancer is chemotherapy, with Nab-paclitaxel plus gemcitabine (AG) and modified FOLFIRINOX being the recommended first-line treatment options based on clinical trials. Gemcitabine monotherapy has been the standard treatment for over two decades, but more effective treatment options are urgently needed. FOLFIRINOX has shown significant improvements in overall survival and quality of life compared to gemcitabine in patients with metastatic pancreatic cancer.

Source: PMC [15]

3.2 Pancreatic cancer current therapies

1. **Gemcitabine:** Although gemcitabine is the standard of care for pancreatic cancer treatment, its therapeutic efficacy is limited, and the median survival remains dismal. The primary mechanism of action involves the triple phosphorylation within the cell by deoxycytidine kinase (dCK) to an active form, followed by intercalation into the DNA of the cell, leading to inhibition of DNA synthesis and cellular proliferation. However, the modest beneficial outcome in a clinical setting necessitates the exploration of combination therapies and alternative treatment options.
2. **Single agent chemotherapy:** In the past, single agent chemotherapy has been the mainstay treatment for advanced pancreatic cancer. However, the limitations of this approach include the absence of effective biomarkers, the late diagnosis of the disease, and the aggressive nature of pancreatic cancer, which often results in poor response to chemotherapy.
3. **Combination chemotherapy:** Several combination therapies utilizing gemcitabine and other drugs or antibodies have been explored to enhance the therapeutic effects of gemcitabine. However, all have shown dismal outcomes. The challenges in developing effective combination therapies include the complex nature of pancreatic cancer, the presence of a desmoplastic tumor microenvironment, and the lack of effective biomarkers to guide treatment.
4. **Immunotherapy:** Immunotherapy is an emerging treatment modality for various types of cancer, including pancreatic cancer. However, the limitations of current immunotherapies for pancreatic cancer include the lack of effective immune checkpoints, the presence of a desmoplastic tumor microenvironment that inhibits immune cell infiltration, and the absence of effective biomarkers to guide treatment.
5. **EUS-guided injectable treatment:** EUS-guided injectable treatment is a promising approach for the local delivery of anti-tumor agents to pancreatic ductal adenocarcinoma (PDAC) under real-time visualization and minimal invasiveness. However, the limited literature and heterogeneity in methodologies and outcomes necessitate a systematic review of the present literature to guide future research in this area. The challenges in developing effective EUS-guided injectable treatments include the complex nature of PDAC, the presence of a desmoplastic tumor microenvironment, and the lack of effective biomarkers to guide treatment.

Source: PMC [16]

3.3 Known drugs targeting KRAS

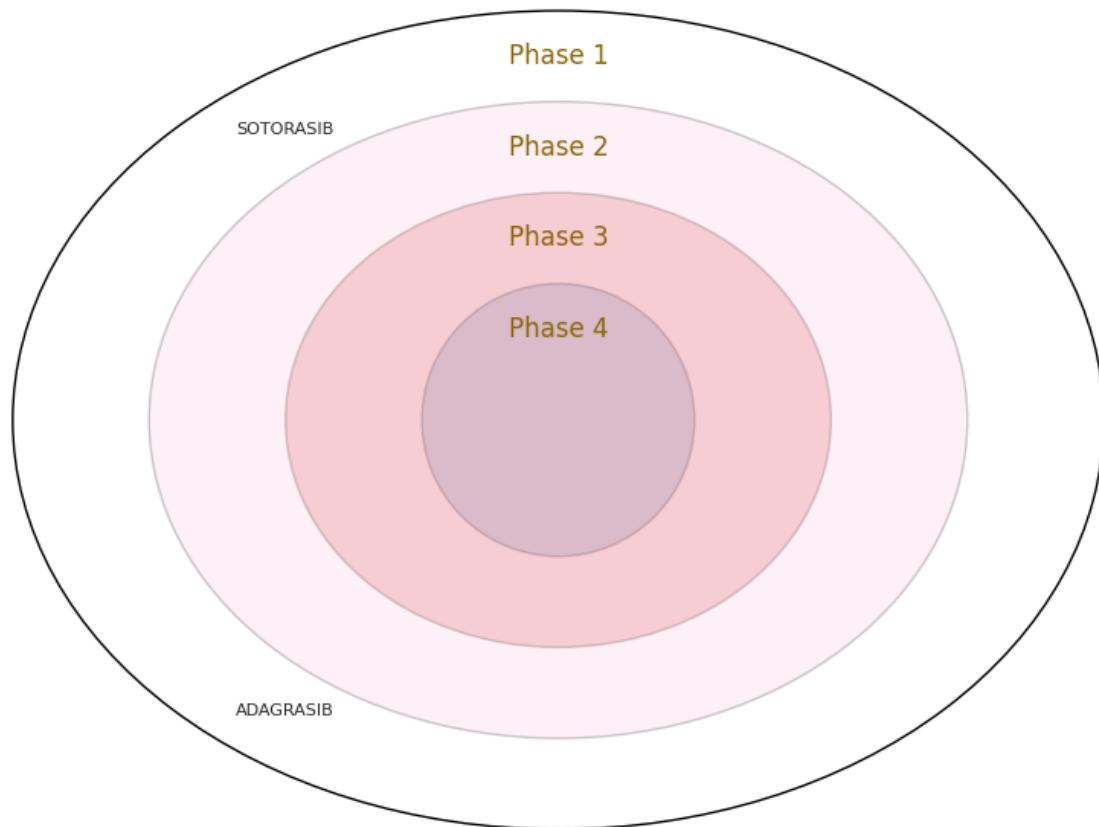
There are 2 different known drugs:

SOTORASIB (Drug type: Small molecule, Action type: Inhibitor)

ADAGRASIB (Drug type: Small molecule, Action type: Inhibitor)

In total, there are 12 drugs in phase 1, 20 drugs in phase 2, 7 drugs in phase 3, 4 drugs in phase 4.

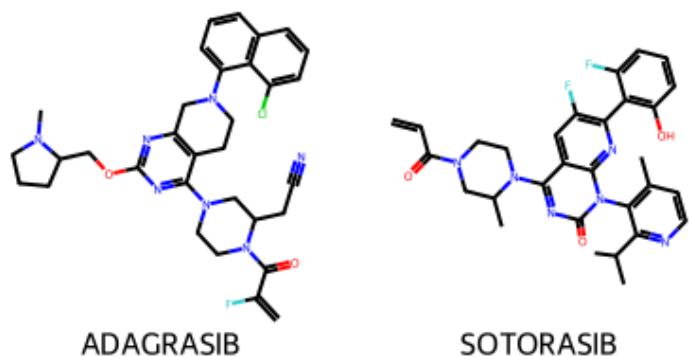
KRAS competitive landscape (pancreatic cancer)



| Drug | Type | Action type | Disease | Phase |
|------------------|----------------|-------------|-------------------------------|-------|
| SOTORASIB | Small molecule | Inhibitor | neoplasm | 4 |
| ADAGRASIB | Small molecule | Inhibitor | non-small cell lung carcinoma | 4 |
| ADAGRASIB | Small molecule | Inhibitor | neoplasm | 4 |

| | | | | |
|-----------|----------------|-----------|-------------------------------|---|
| SOTORASIB | Small molecule | Inhibitor | non-small cell lung carcinoma | 4 |
| ADAGRASIB | Small molecule | Inhibitor | non-small cell lung carcinoma | 3 |
| ADAGRASIB | Small molecule | Inhibitor | metastatic colorectal cancer | 3 |
| SOTORASIB | Small molecule | Inhibitor | metastatic colorectal cancer | 3 |
| SOTORASIB | Small molecule | Inhibitor | colorectal adenocarcinoma | 3 |
| SOTORASIB | Small molecule | Inhibitor | non-small cell lung carcinoma | 3 |
| SOTORASIB | Small molecule | Inhibitor | Fallopian Tube Carcinoma | 2 |
| SOTORASIB | Small molecule | Inhibitor | lung cancer | 2 |
| ADAGRASIB | Small molecule | Inhibitor | neoplasm | 2 |
| SOTORASIB | Small molecule | Inhibitor | neoplasm | 2 |
| SOTORASIB | Small molecule | Inhibitor | colorectal cancer | 2 |
| SOTORASIB | Small molecule | Inhibitor | non-small cell lung carcinoma | 2 |
| SOTORASIB | Small molecule | Inhibitor | ovarian carcinoma | 2 |
| SOTORASIB | Small molecule | Inhibitor | primary peritoneal carcinoma | 2 |
| ADAGRASIB | Small molecule | Inhibitor | non-small cell lung carcinoma | 2 |
| SOTORASIB | Small molecule | Inhibitor | lung adenocarcinoma | 2 |
| ADAGRASIB | Small molecule | Inhibitor | metastatic neoplasm | 2 |
| ADAGRASIB | Small molecule | Inhibitor | metastatic malignant neoplasm | 2 |
| SOTORASIB | Small molecule | Inhibitor | endometrial carcinoma | 2 |
| ADAGRASIB | Small molecule | Inhibitor | lung cancer | 1 |
| SOTORASIB | Small molecule | Inhibitor | non-small cell lung carcinoma | 1 |
| SOTORASIB | Small molecule | Inhibitor | pancreatic carcinoma | 1 |
| ADAGRASIB | Small molecule | Inhibitor | pancreatic carcinoma | 1 |

| | | | | |
|------------------|-----------------------|------------------|--------------------------------------|----------|
| ADAGRASIB | Small molecule | Inhibitor | malignant colon neoplasm | 1 |
| ADAGRASIB | Small molecule | Inhibitor | neoplasm | 1 |
| SOTORASIB | Small molecule | Inhibitor | neoplasm | 1 |
| SOTORASIB | Small molecule | Inhibitor | liver disease | 1 |
| ADAGRASIB | Small molecule | Inhibitor | non-small cell lung carcinoma | 1 |



Source: OpenTargets [17] and NCBI PubChem Compound

Adagrasib

Description:

Adagrasib (MRTX849) is an oral, small-molecule KRAS inhibitor developed by Mirati Therapeutics. KRAS mutations are highly common in cancer and account for approximately 85% of all RAS family mutations. However, the development of KRAS inhibitors has been challenging due to their high affinity for guanosine triphosphate (GTP) and guanosine diphosphate (GDP), as well as the lack of a clear binding pocket. Adagrasib targets KRAS G12C, one of the most common KRAS mutations, at the cysteine 12 residue and inhibits KRAS-dependent signalling. In a phase I/IB clinical study that included patients with KRAS G12C-mutated advanced solid tumors (NCT03785249), adagrasib exhibited anti-tumor activity. The phase II of the same study showed that in patients with KRAS G12C-mutated non-small-cell lung cancer (NSCLC), adagrasib was efficient without new safety signals.

In February 2022, the FDA accepted a new drug application (NDA) for adagrasib for the treatment of patients with previously treated KRAS G12C-positive NSCLC. In December 2022, the FDA granted accelerated approval to adagrasib for the treatment of KRAS G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy. Adagrasib joins [sotorasib] as another KRAS G12C inhibitor approved by the FDA.

CAS number:

2326521-71-3

State:

solid

Average mass:

604.13

Indication:

Adagrasib is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial(s).

Pharmacodynamics:

The exposure-response relationship and pharmacodynamic response time course of adagrasib have not been elucidated. The use of adagrasib can cause QTc interval prolongation. The increase in QTc is concentration-dependent. In patients given 600 mg of adagrasib twice daily, the mean QTcF change from baseline (Δ QTcF) was 18 ms at the mean steady-state maximum concentration.

The use of adagrasib can also lead to severe gastrointestinal adverse reactions, hepatotoxicity and interstitial lung disease/pneumonitis.

Mechanism of action:

In normal cells, KRAS is activated by binding to guanosine triphosphate (GTP), and this promotes the activation of the MAP kinase pathway and intracellular signal transduction. When GTP is hydrolyzed to guanosine diphosphate (GDP), KRAS is inactivated. This mechanism works as an "on"/"off" system that regulates cell growth. The substitution of Gly12 by cysteine in KRAS (KRAS G12C) impairs GTP hydrolysis, and maintains KRAS in its active form. Therefore, the presence of this mutation leads to uncontrolled cellular proliferation and growth, as well as malignant transformation. Adagrasib is a covalent inhibitor of KRAS G12C that irreversibly and selectively binds and locks KRAS G12C in its inactive, guanosine diphosphate-bound state. Therefore, the use of adagrasib inhibits tumor cell growth and viability in cancers with KRAS G12C mutations with minimal off-target activity.

Toxicity:

Toxicity information regarding adagrasib is not readily available. Patients experiencing an overdose are at an increased risk of severe adverse effects such as hepatotoxicity, gastrointestinal adverse reactions and QTc interval prolongation. Symptomatic and supportive measures are recommended.

The carcinogenicity of adagrasib has not been evaluated. In an in vitro bacterial reverse mutation (Ames) assay, adagrasib was not mutagenic. An in vitro chromosomal aberration assay and an in vivo micronucleus assay in rats showed that it was not genotoxic. Studies evaluating the effects of adagrasib on fertility have not been performed. The oral administration of adagrasib to rats for up to 13 weeks induced phospholipidosis at doses higher than 150 mg/kg (approximately 2 times the human exposure at the recommended dose based on AUC). The presence of phospholipidosis led to the increased vacuolation of multiple organs.

Metabolism:

Following single-dose administration, adagrasib is mainly metabolized by CYP3A4. However, since adagrasib inhibits CYP3A4 following multiple dosing, other enzymes such as CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2D6 contribute to its metabolism at steady-state.

Absorption:

The AUC and C_{max} of adagrasib increase in a dose-proportional manner between 400 mg and 600 mg (0.67 to 1 times the approved recommended dose). At the recommended dose, adagrasib reached steady-state within 8 days, with a 6-fold accumulation. The T_{max} of adagrasib is approximately 6 hours. The administration of a high-fat and high-calorie meal (900-1000 calories, 50% from fat) did not have a clinically significant effect on the pharmacokinetics of adagrasib. Adagrasib has high oral bioavailability and is able to penetrate the central nervous system.

Half-life:

Adagrasib has a terminal elimination half-life of 23 hours.

Protein binding:

In vitro, adagrasib has a human plasma protein binding of 98%.

Route of elimination:

Adagrasib is eliminated through feces and urine. In patients given a single dose of radiolabeled adagrasib, 75% of the dose was recovered in feces (14% as unchanged), while 4.5% was recovered in urine (2% as unchanged).

Volume of distribution:

Adagrasib has an apparent volume of distribution of 942 L.

Clearence:

Adagrasib has an apparent oral clearance (CL/F) of 37 L/h.

Sotorasib

Description:

Sotorasib, also known as AMG-510, is an acrylamide-derived KRAS inhibitor developed by Amgen. It is indicated in the treatment of adult patients with KRAS G12C mutant non-small cell lung cancer. This mutation makes up >50% of all KRAS mutations. Mutant KRAS discovered in 1982 but was not considered a druggable target until the mid-2010s. It is the first experimental KRAS inhibitor. The drug [MRTX849] is also currently being developed and has the same target.

Sotorasib was granted FDA approval on May 28, 2021, followed by the European Commission's approval on January 10, 2022.

CAS number:

2252403-56-6

State:

solid

Average mass:

560.606

Indication:

Sotorasib is indicated in the treatment of KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) in adults who have received at least one prior systemic therapy.

Pharmacodynamics:

Sotorasib is indicated in the treatment of adults with KRAS G12C mutant non small cell lung cancer. It has a moderate duration of action as it is given daily. Patients should be counselled regarding the risks of hepatotoxicity, interstitial lung disease and pneumonitis; and to avoid breastfeeding during treatment and up to 1 week after the last dose.

Mechanism of action:

Normally GTP binds to KRAS, activating the protein and promoting effectors to the MAP kinase pathway. GTP is hydrolyzed to GDP, and KRAS is inactivated. KRAS G12C mutations impair hydrolysis of GTP, leaving it in the active form.

Sotorasib binds to the cysteine residue in KRAS G12C mutations, holding the protein in its inactive form. The cysteine residue that sotorasib targets is not present in the wild type KRAS, which prevents off-target effects. This mutation is present in 13% of non small cell lung cancer, 3% of colorectal and appendix cancer, and 1-3% of solid tumors.

Toxicity:

Data regarding overdoses of sotorasib are not readily available. However, in clinical trials, signs of dose limiting toxicity were not found. Patients

experiencing an overdose may experience and increased risk and severity of adverse effects such as diarrhea, nausea, vomiting, fatigue, and elevated aminotransferase.

Metabolism:

Sotorasib is predominantly metabolized through conjugation or by CYP3As.

Absorption:

A 960 mg once daily dose of sotorasib reaches a C max of 7.50 µg/mL, with a median T max of 2.0 hours, and an AUC 0-24h of 65.3 h*µg/mL.

Half-life:

Sotorasib has a terminal elimination half life of 5.5 ± 1.8 hours.

Protein binding:

Sotorasib is 89% protein bound in plasma.

Route of elimination:

Sotorasib is 74% eliminated in the feces and 6% eliminated in the urine. 53% of the dose recovered in the feces and 1% of the dose recovered in the urine is in the form of the unchanged parent compound.

Volume of distribution:

The volume of distribution of sotorasib is 211 L.

Clearence:

Sotorasib has an apparent clearance at steady state of 26.2 L/h.

Source: DrugBank

4. Conclusion

4.1 SWOT analysis

Strengths

1. **Competitive advantage:** KRAS is a frequently mutated oncogene in human adenocarcinoma of the lung and pancreas, and inactivating mutations in TP53, CDKN2A, and SMAD4 are also common. Targeting KRAS could potentially address a significant portion of pancreatic cancer cases.
2. **Resources:** The availability of KRAS mutation data and the understanding of its role in pancreatic cancer progression provide a solid foundation for drug development efforts.
3. **Performing well:** KRAS signaling plays a central role in pancreatic cancer progression, and targeting multiple signaling pathways may be an effective therapeutic approach for KRAS-mutant cancers.

Threats

1. **Operational risks:** Developing a drug for KRAS is a complex and challenging process due to the presence of a desmoplastic tumor microenvironment and the lack of effective biomarkers to guide treatment.
2. **Competitors:** Several companies are already working on KRAS-targeted therapies, increasing the competition in this area.
3. The low survival rate of pancreatic cancer and the lack of effective treatments contribute to a high mortality rate and a limited market size.

Weaknesses

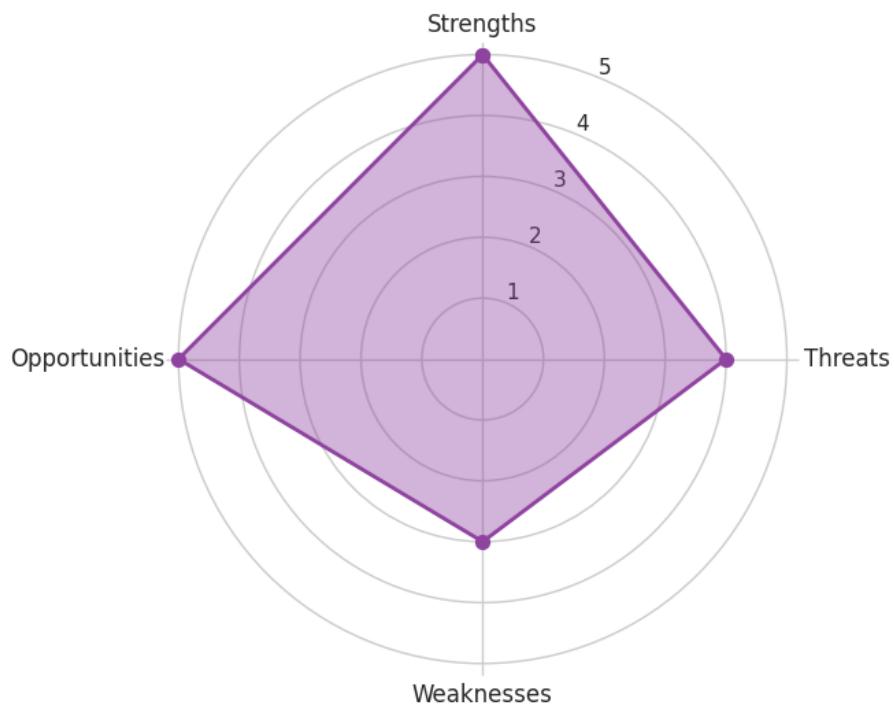
1. **Improvement:** The modest beneficial outcome of gemcitabine, the current standard of care, necessitates the exploration of combination therapies and alternative treatment options.
2. **High risk:** The complex nature of pancreatic cancer and the presence of a desmoplastic tumor microenvironment increase the risk of drug development efforts.
3. The lack of effective biomarkers to guide treatment and the absence of a clear understanding of the mechanisms underlying KRAS-driven tumor progression pose challenges in developing effective KRAS-targeted therapies.

Opportunities

1. **Improvement:** The availability of KRAS mutation data and the understanding of its role in pancreatic cancer progression provide opportunities for developing targeted therapies with improved efficacy.
2. **Efficiency:** Utilizing precision medicine, such as BRCA mutations, MSI-H/dMMR, and NTRK fusions, can make drug development efforts more

efficient by focusing on specific patient populations.

3. Exploration: The potential therapeutic area segments, such as combination therapies and immunotherapy, offer opportunities for expanding the scope of KRAS-targeted drug development.



Radar chart of the scores assigned by the LLM to each section of the SWOT analysis in the range 1-5.

4.2 Conclusion

KRAS is a promising therapeutic target for pancreatic cancer due to its frequent mutation in this disease and its central role in pancreatic cancer progression. The availability of KRAS mutation data and the understanding of its role in pancreatic cancer provide a solid foundation for drug development efforts. However, the complex nature of pancreatic cancer and the presence of a desmoplastic tumor microenvironment increase the risk of drug development efforts. The lack of effective biomarkers to guide treatment and the absence of a clear understanding of the mechanisms underlying KRAS-driven tumor progression pose challenges in developing effective KRAS-targeted therapies. Despite these challenges, the potential therapeutic area segments, such as combination therapies and immunotherapy, offer opportunities for expanding the scope of KRAS-targeted drug development. Overall, the potential benefits of targeting KRAS in pancreatic cancer outweigh the challenges, making it a worthwhile therapeutic pursuit.

Sources

- [1] NCBI Gene: <https://www.ncbi.nlm.nih.gov/gene/3845>
- [2] RCSB: https://cdn.rcsb.org/images/structures/7vvb_assembly-1.jpeg
- [3] UniProt: <https://www.uniprot.org/uniprotkb/P01116/entry>
- [4] DeepTMHMM: <https://dtu.biolib.com/DeepTMHMM>
- [5] Human Protein Atlas: <https://www.proteinatlas.org/ENSG00000133703-KRAS/subcellular>
- [6] Human Protein Atlas: <https://www.proteinatlas.org/ENSG00000133703-KRAS/tissue>
- [7] Human Protein Atlas: <https://www.proteinatlas.org/ENSG00000133703-KRAS/cell+line>
- [8] OGEE: <https://v3.ogee.info/?#/gene/human/KRAS>
- [9] Signor: https://signor.uniroma2.it/relation_result.php?id=P01116
- [10] PubMed Abstracts: PMIDs 31399087, 29748135, 33082413, 38570452, 30041673, 37121193
- [11] PubMed Abstracts: PMIDs 29956571, 29925636, 27494869, 17114584, 29808009, 17690114
- [12] TCGA Survival: https://www_tcga-survival_com/data-table?view=gene&gene=KRAS
- [13] PMC Articles: PMIDs 6518784, 6065152, 8835700
- [14] PMC Articles: PMIDs 7553299, 10551021, 10632485
- [15] PMC Articles: PMIDs 9869579, 6718524, 4462360
- [16] PMC Articles: PMIDs 3590245, 4849685, 9185216
- [17] Open Targets: <https://platform.opentargets.org/target/ENSG00000133703>



Contact us

**Oncodesign
Precision Medicine**

18 rue Jean Mazen
21000 Dijon France

+33 (0)310 451 820

oncodesign.com