Clinical Case #2

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26.6.23

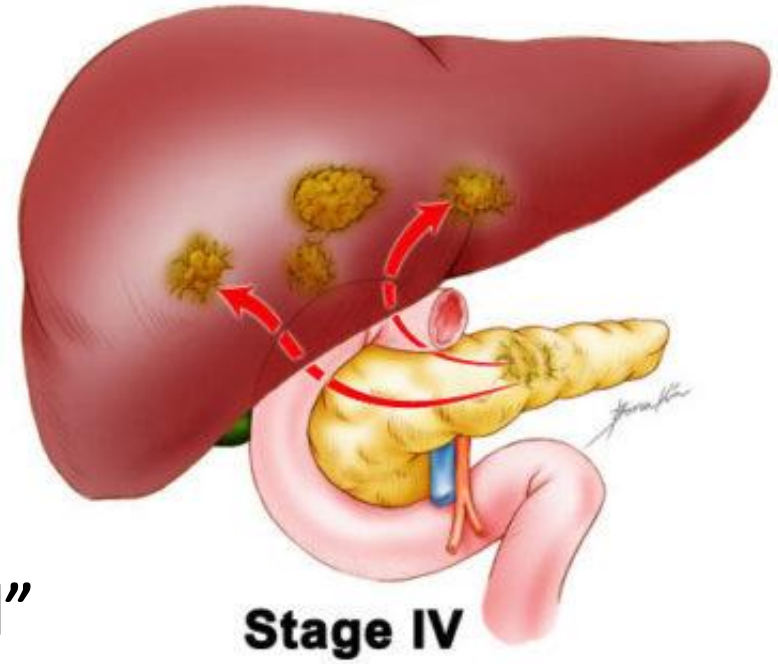
Introduction May 2022

A 58 year old man

Abdominal pain and weight loss

On imaging:

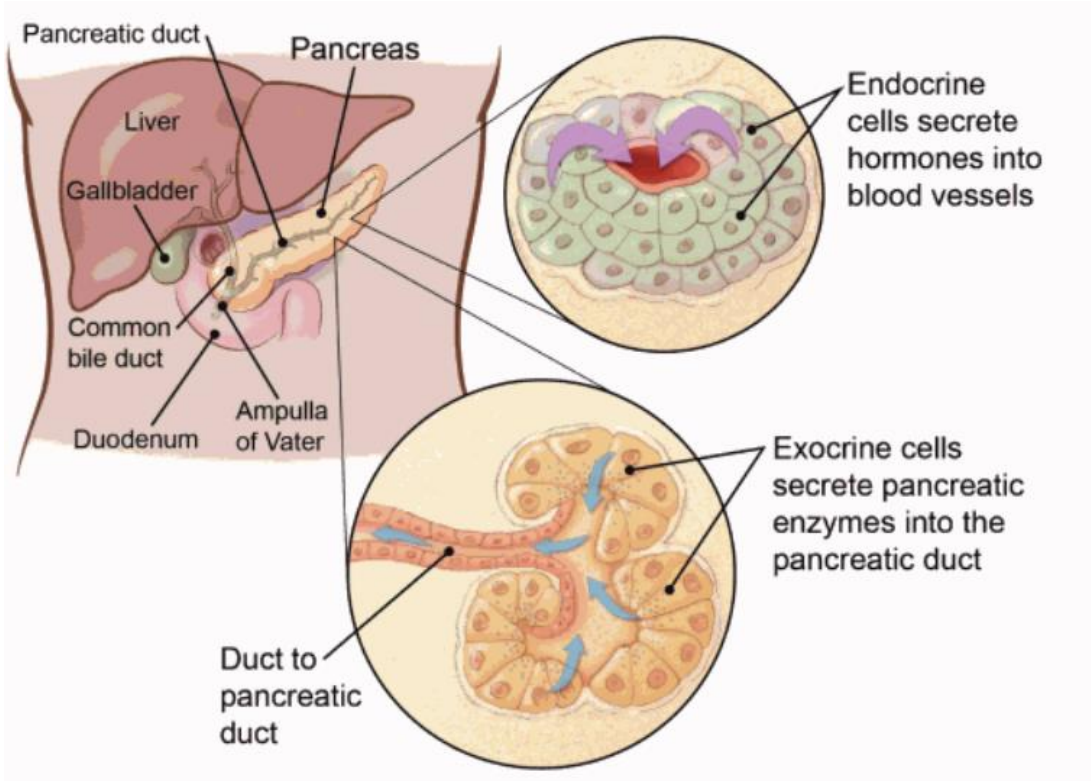
- Pancreatic mass
- Liver and peritoneal lesions



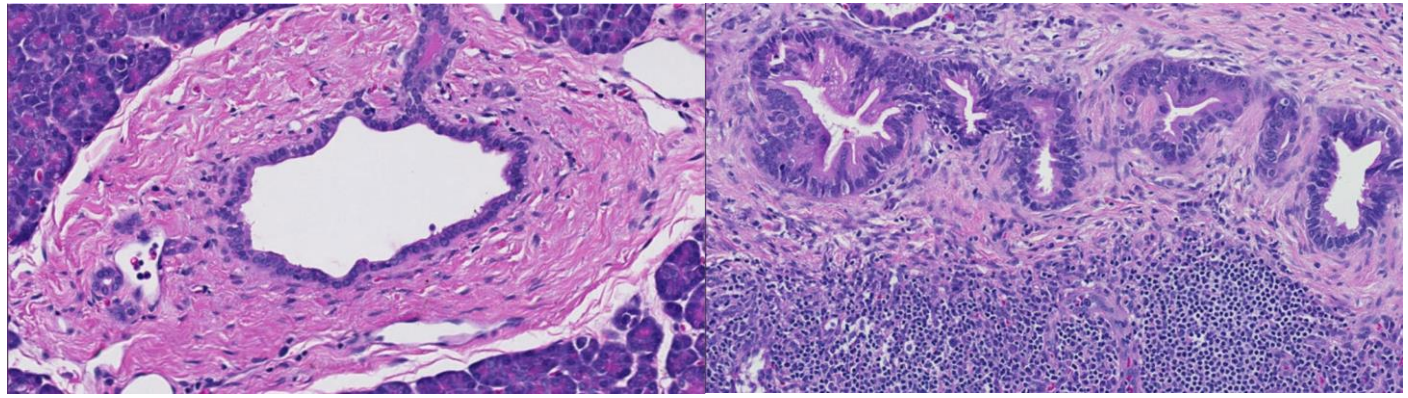
Pathology→ "Metastatic Pancreas adenocarcinoma, moderately differentiated"

Pancreas Adenocarcinoma

- 95% of pancreatic cancer.
- It begins when exocrine cells in the pancreas start to grow uncontrollably.

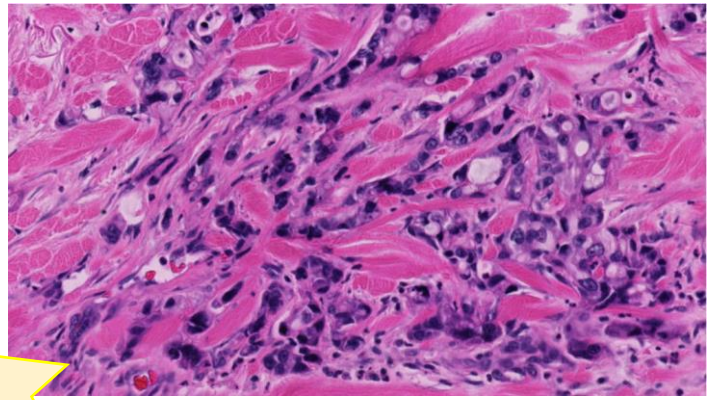


Understanding the Significance of Grade G2 in Tumor Classification



NORMAL DUCT
The normal cells in the pancreas form ducts ("tubes") that are lined by small uniform cells.

LOW-GRADE ADENOCARCINOMA
Well-differentiated adenocarcinomas form ducts that, like normal ducts, are lined by relatively uniform cells.



IGH-GRADE ADENOCARCINOMA
oorly-differentiated
enocarcinomas do not form well-
fined ducts, and the cells vary in
ze and shape.

Grade	What it Means
G1	Low-grade. Well differentiated. Generally less aggressive.
G2	Moderately differentiated
G3	High-grade. Poorly differentiated. Generally more aggressive.
GX	Cannot be assessed (for cases in which there isn't adequate material to evaluate microscopically)

JOHNS HOPKINS
MEDICINE
PATHOLOGY

Mutations

KRAS Alteration:

c.35G>T

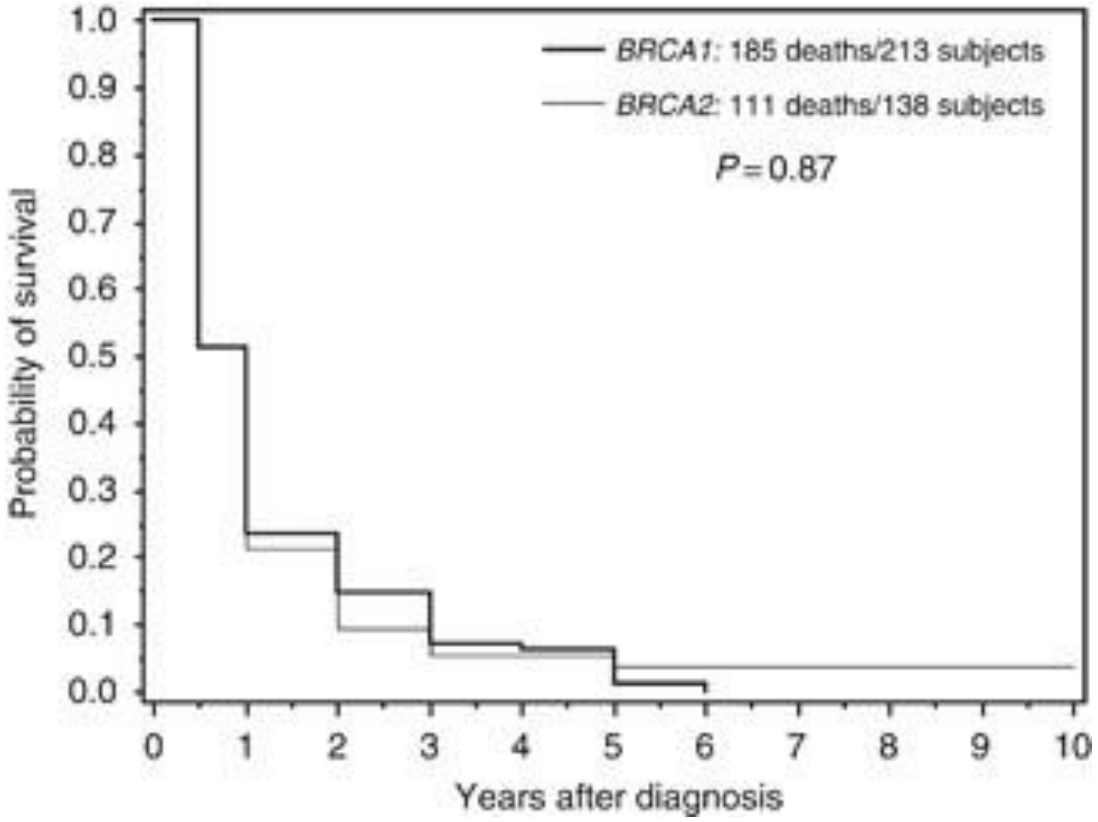
Amino acid change: p.Gly12Val

% of DNA sequence: 11.12% Transcript: NM_033360.4

BRCA1/2 - BRCA2 Transcript: : c.5946delT Amino acid change: p.Ser1982ArgfsTer22

% of DNA sequence: 57.42%

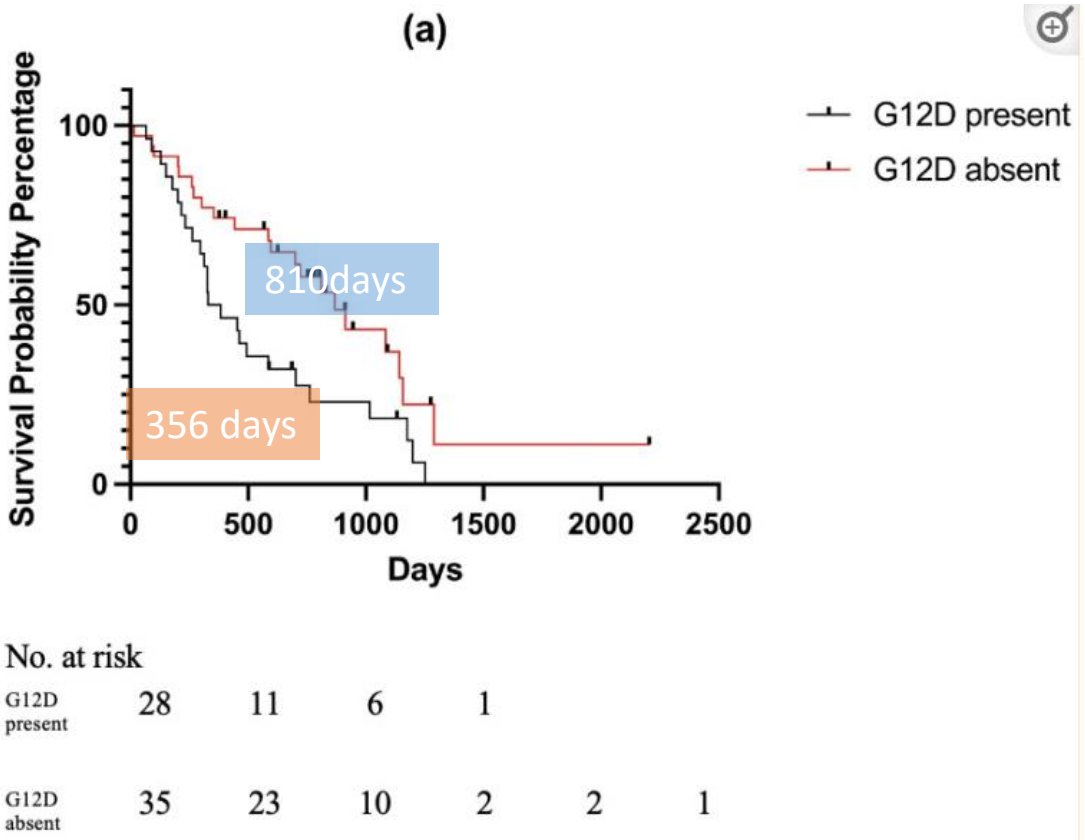
Survival After Pancreas Cancer by BRCA Mutation



- 84% diagnosed at age 50 or above (87% for BRCA1, 80% for BRCA2).
- 58% of cases in males, 42% in females.
- Mean survival: BRCA1=1.07 years, BRCA2=1.00 years.
- 5-year survival rate: BRCA1=6.1%, BRCA2=3.6%.

(Iqbal et al. 2012)

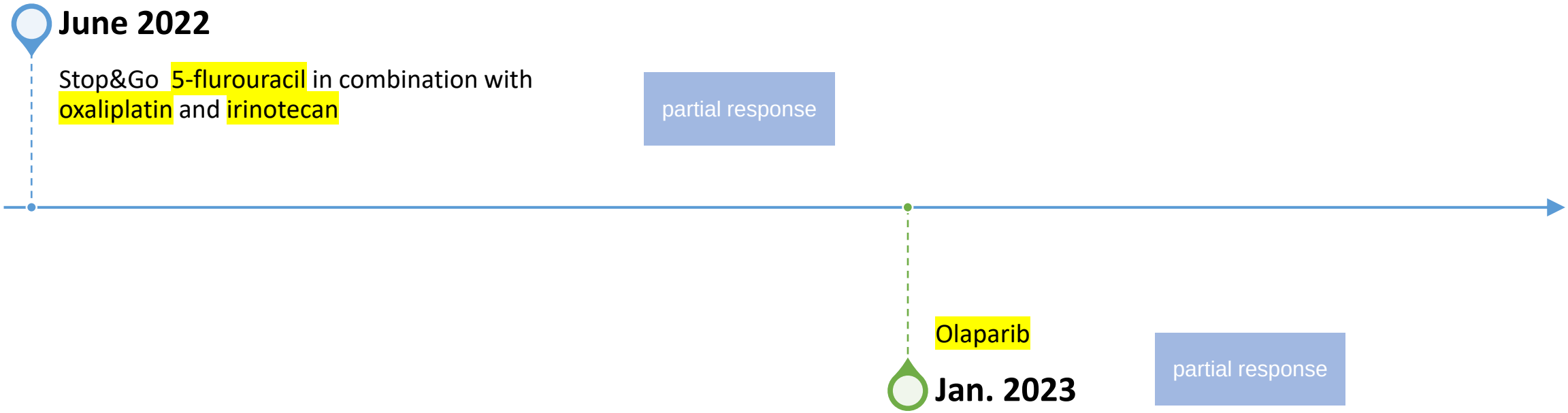
KRAS G12D Mutation in Pancreatic Ductal Adenocarcinoma: Impact on Prognosis and Disease Stage



- KRAS G12D mutation is found in over 40% of PDAC cases.
- Resectable PDAC patients with KRAS G12D mutation had shorter median survival compared to other genotypes.
- KRAS G12D mutation could be a valuable prognostic biomarker specifically for resectable PDAC patients.

(Shen et al. 2022)

Treatments


June 2022
Stop&Go 5-flurouracil in combination with oxaliplatin and irinotecan
partial response
Olaparib
Jan. 2023
partial response

Olaparib: A Novel Therapy for Patients With a BRCA 1/2 Mutation

- DNA repair pathways maintain genomic stability.
- Mutations in BRCA1/2 genes cause DNA double-strand breaks (DSBs) accumulation.
- PARP inhibitors exploit synthetic lethality in BRCA-deficient cells.

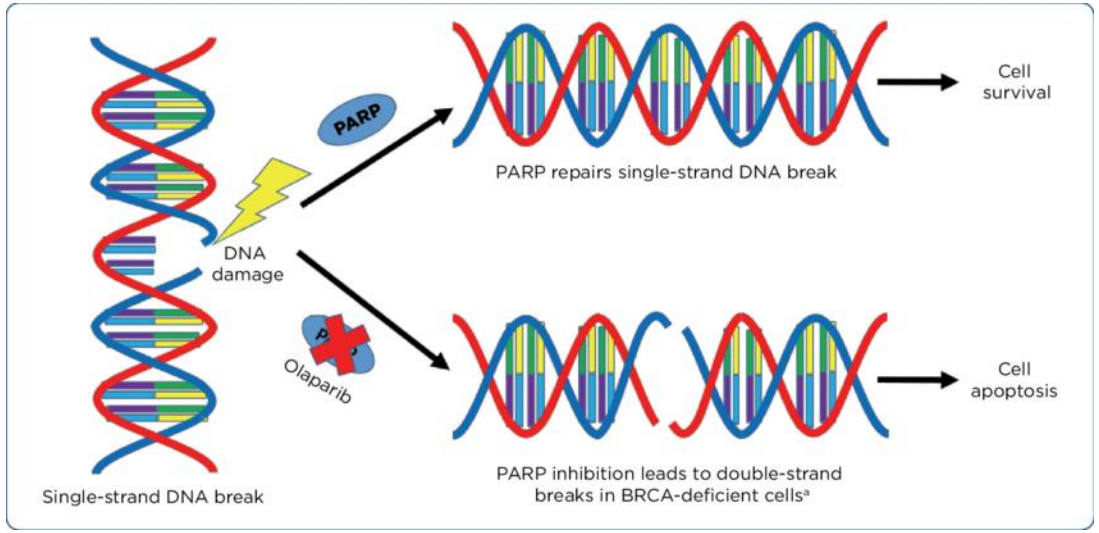
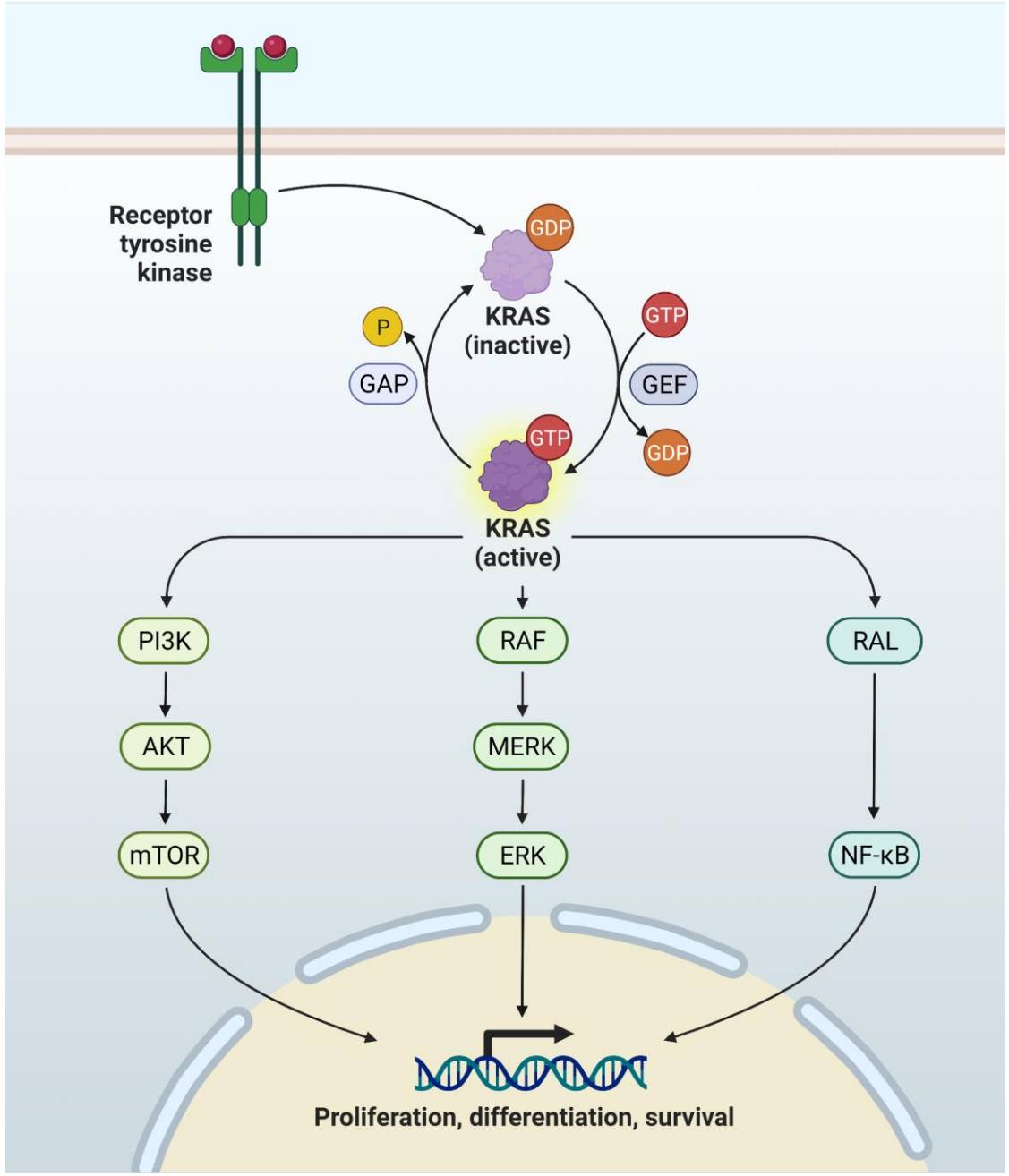


Figure 1. Olaparib mechanism, specifically in BRCA-deficient cells compared to normal cells.

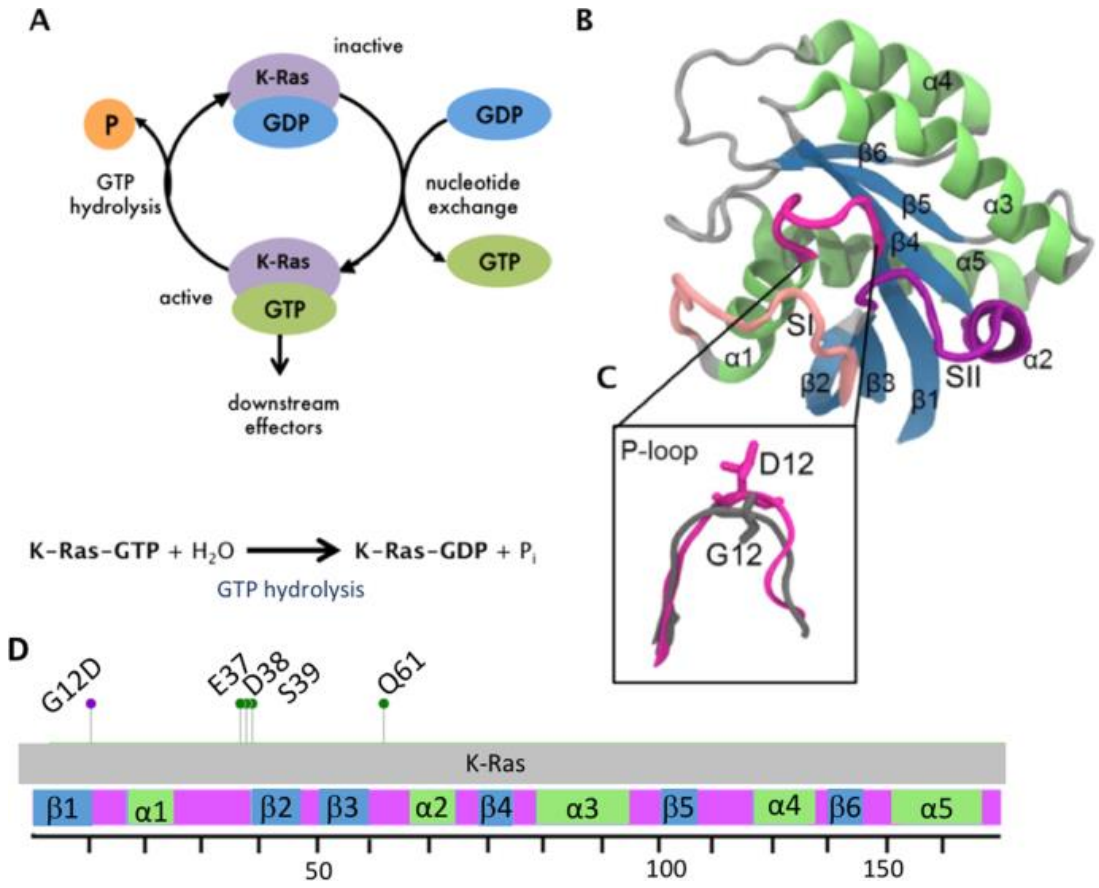
(Se, Cc, and Kf 2019)

KRAS Pathway



(Ras Signaling n.d.)

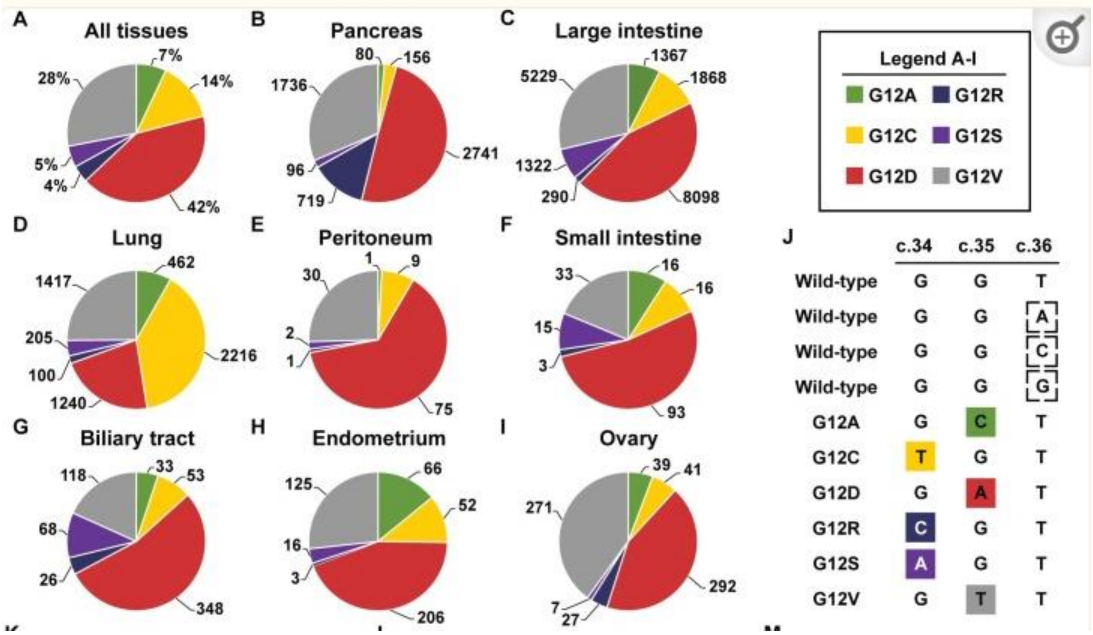
The Impact of the G12D Mutation in KRAS



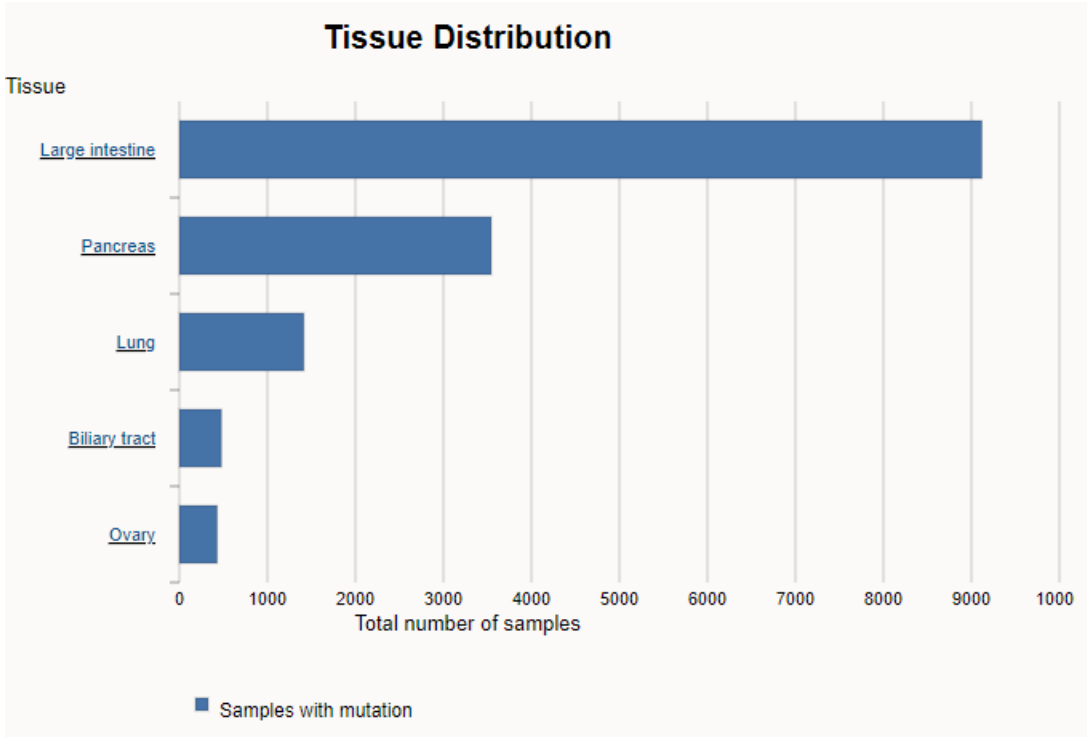
- The G12D mutation in KRAS leads to constitutive activation of the protein.
- It freezes KRAS in its active state, resulting in uncontrolled cellular growth and evasion of apoptosis.
- The mutation alters the distribution of conformational states in a nucleotide-specific manner.
- Understanding these changes can aid in developing targeted therapies for KRAS G12D.

(Vatansever, Erman, and Gümüş 2019)

The occurrences of specific KRAS G12X mutations vary among different tissues



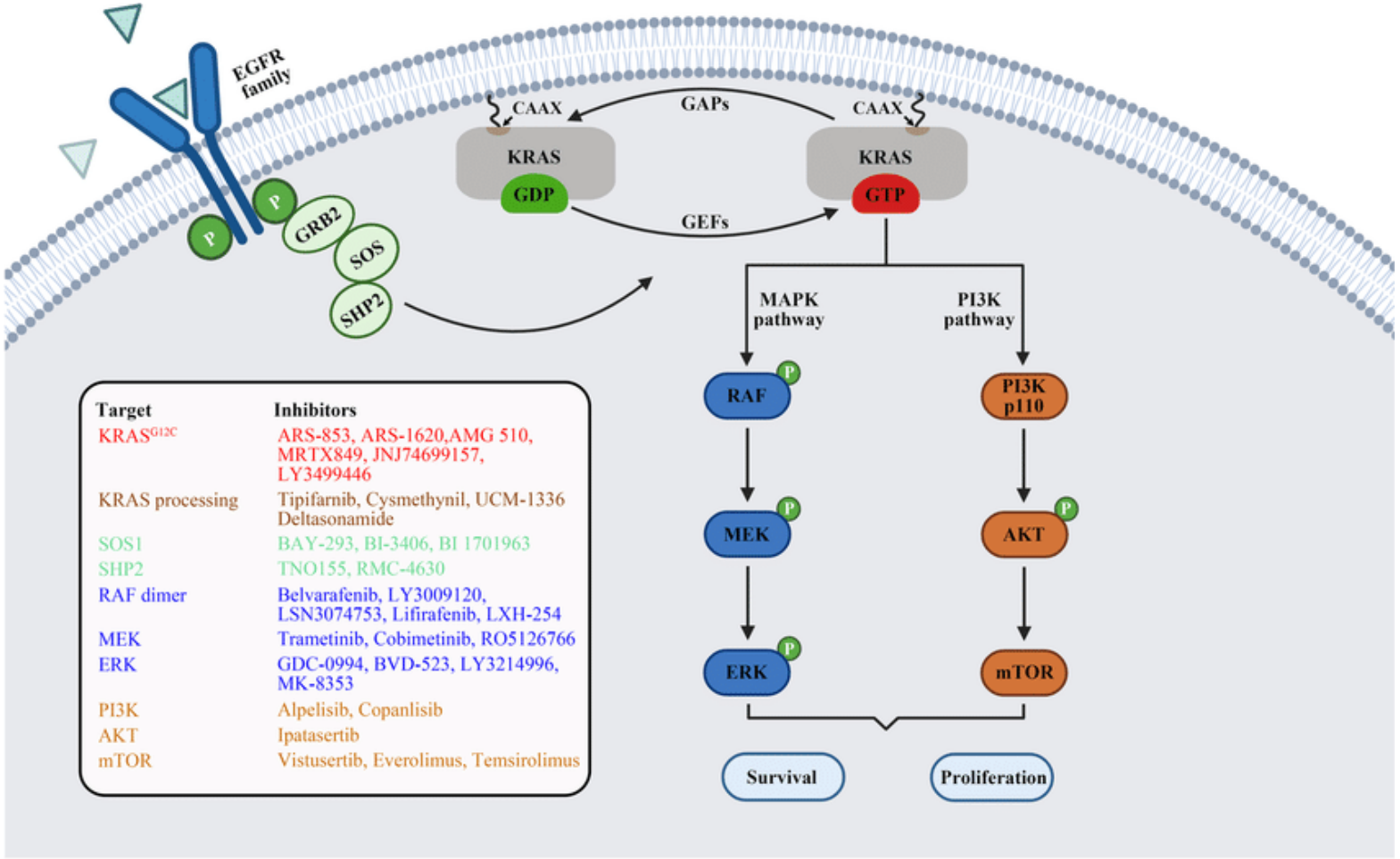
(Pantsar et al. 2018)



COSMIC
Catalogue Of Somatic Mutations In Cancer

KRAS Signaling Pathway: Specific Inhibitors

- Receptor tyrosine kinase activation leads to GRB2-SOS interaction and subsequent activation of KRAS.
- GTP-GDP cycling of KRAS is regulated by GEFs and GAPs.
- Mutated KRAS disrupts the cycling process, accumulating active KRAS and continuously activating MAPK and PI3K signaling pathways.



(Zhu et al. 2021)

Exploring Additional Treatment Options: Beyond the Standard Therapies

A Phase 1/2 Multiple Expansion Cohort Trial of MRTX1133 in Patients With Advanced Solid Tumors Harboring a KRAS G12D Mutation

TCR gene therapy targeting the KRAS G12D driver mutation

Clinical Trial:
The First G12D KRAS Inhibitor

3	☐	Recruiting	Study of MRTX1133 in Patients With Advanced Solid Tumors Harboring a **KRAS G12D Mutation**	• Solid Tumor • Advanced Solid Tumor • Non-small Cell Lung Cancer • (and 2 more...)	• Drug: MRTX1133

Intervention/treatment ⓘ

Drug: MRTX1133

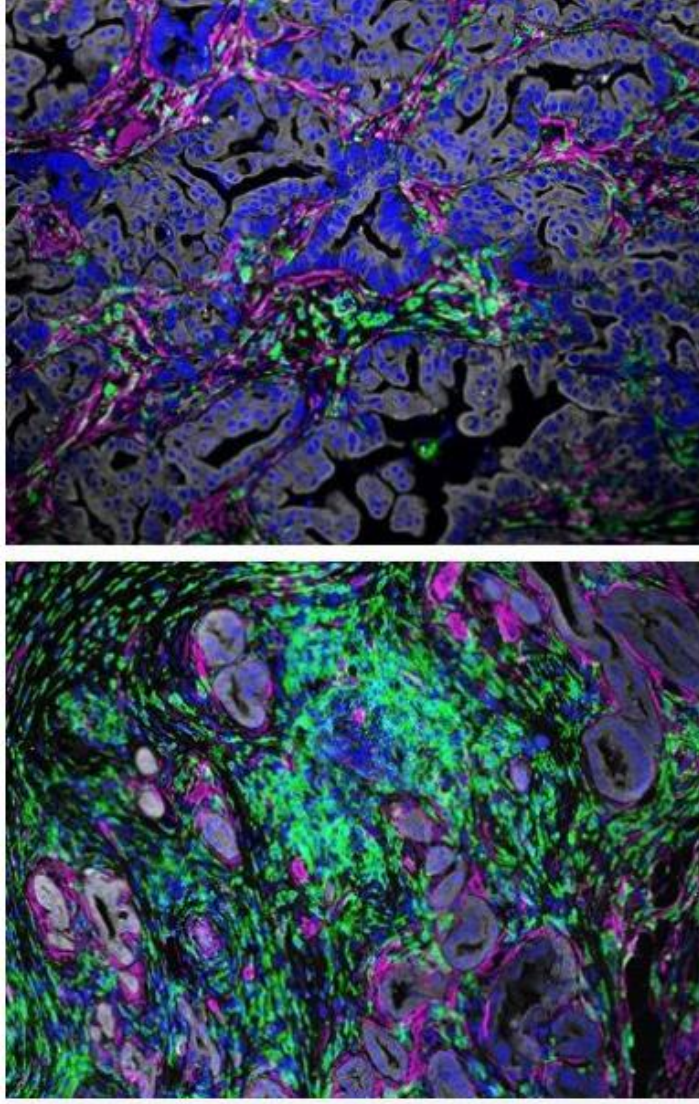
KRAS G12D Inhibitor

ClinicalTrials.gov Identifier: NCT05737706

Recruitment Status ⓘ : Recruiting
First Posted ⓘ : February 21, 2023
Last Update Posted ⓘ : June 8, 2023

See **Contacts and Locations**

View this study on the modernized ClinicalTrials.gov



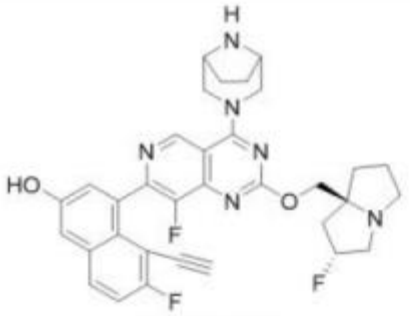
Microscopic image of a mouse pancreatic tumor before (top) and after (bottom) treatment with MRTX1133. The image taken after treatment shows more white blood cells called macrophages (green) and fewer cancer cells (gray).
Credit: Used with permission from Dr. Samantha Kemp/University of Pennsylvania

(MRTX1133 Targets Tumors with KRAS G12D Mutations - NCI 2023)

Identification of MRTX1133, a Noncovalent, Potent, and Selective KRAS^{G12D} Inhibitor

CONCLUSION

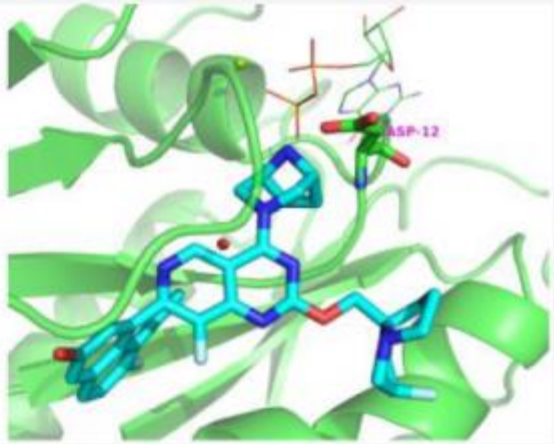
Through extensive structure-based drug design, MRTX1133 was identified as a noncovalent, potent, and selective inhibitor of KRAS^{G12D}. MRTX1133 suppresses KRAS^{G12D} signaling in cells and *in vivo*, and its antitumor benefit was demonstrated in a murine animal model. To the best of our knowledge, this is the first report in the literature of a small molecule inhibitor of KRAS^{G12D} that exhibits robust *in vivo* efficacy. These data support the potential for the advancement of an effective therapeutic against this "undruggable" target. The optimization process was facilitated by high-resolution X-ray crystal structures. In-depth binding mode analysis derived from cocrystal structures allowed the optimization of lipophilic contact of the inhibitor in the binding pocket and the identification of nonclassical hydrogen bonding and ion pair interactions, ultimately increasing selective binding affinity for KRAS^{G12D} by more than 1,000,000-fold relative to the initial hit **5B**. MRTX1133 binds to the switch II pocket and inhibits the protein−protein interactions necessary for activation of the KRAS pathway. MRTX1133 not only possesses single-digit nM potency in a cellular proliferation assay, but also demonstrates tumor regressions in the Panc 04.03 xenograft model. A more comprehensive *in vitro* and *in vivo* pharmacological characterization of MRTX1133 will be disclosed in due course.



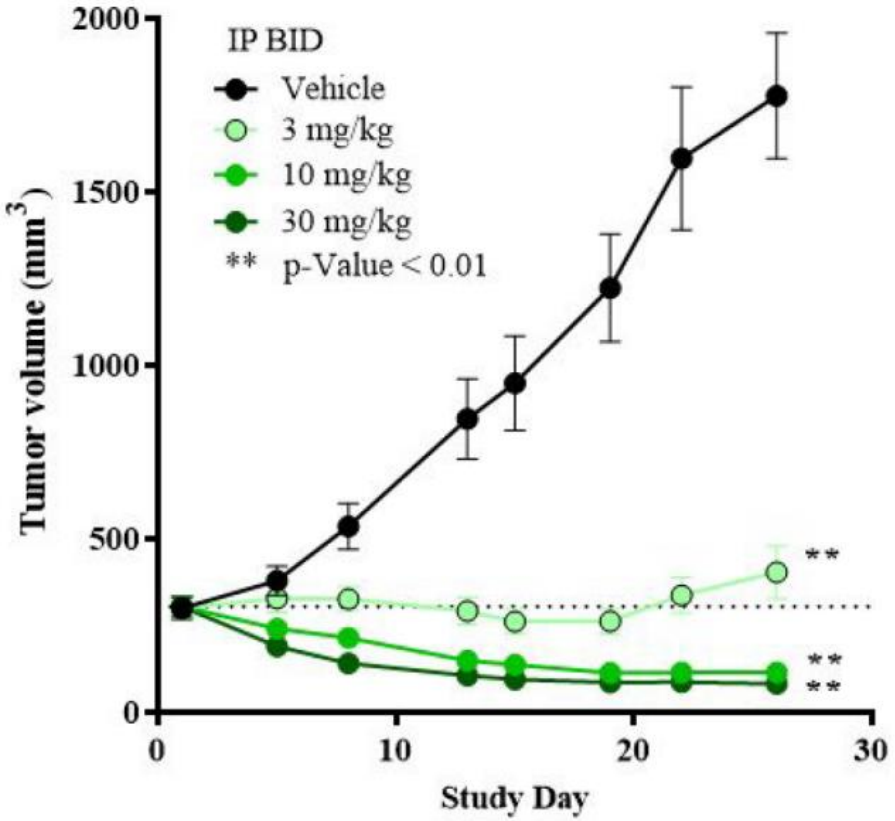
MRTX1133

AGS pERK IC_{50}: 2 nM

Panc 04.03: -70% Tumor regression (30 mg/kg IP BID)



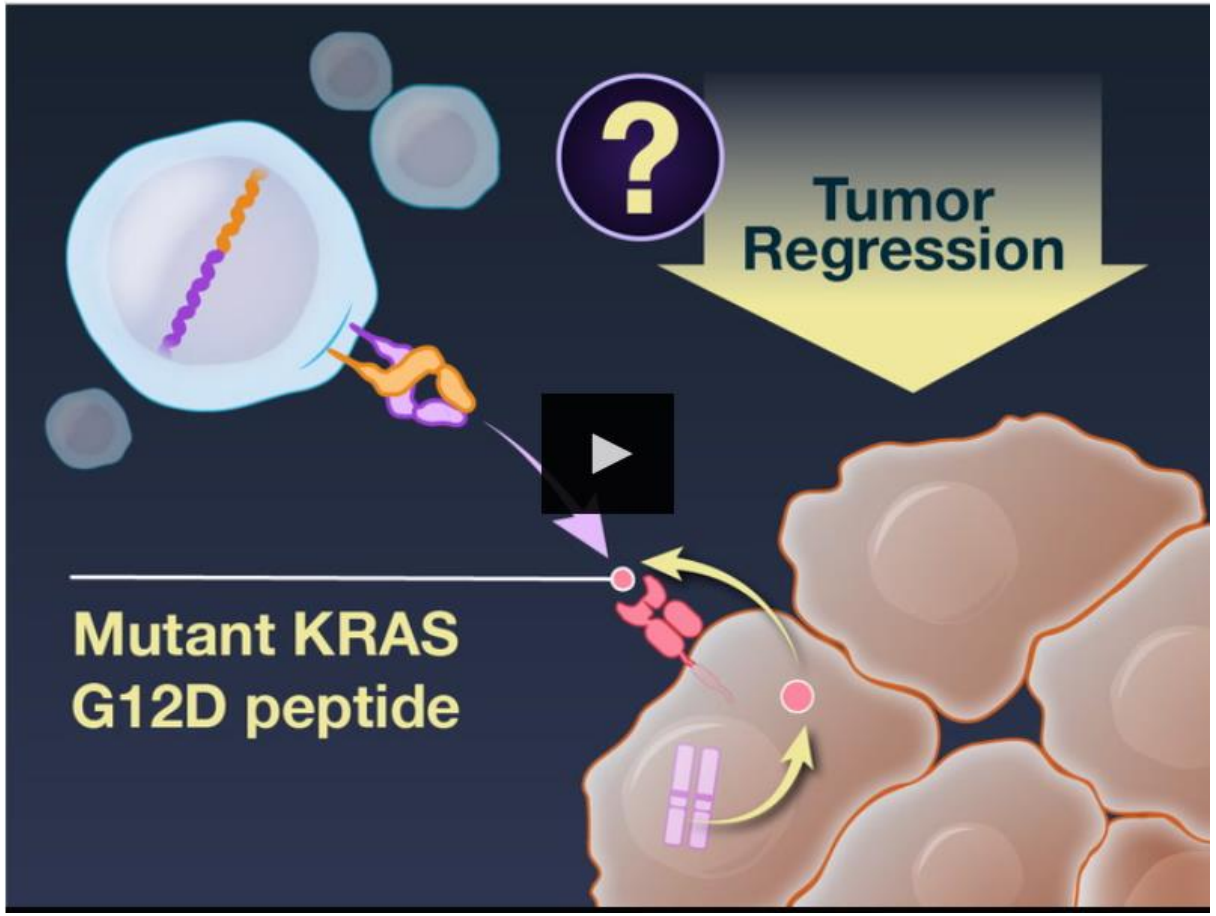
Journal of Medicinal Chemistry



(Wang et al. 2022)

Adoptive Cell Transfer and Engineered TCR Therapy:

Unleashing the Power of T Cells: Targeting the KRAS G12D Hot-Spot Mutation in Pancreatic Cancer Therapy

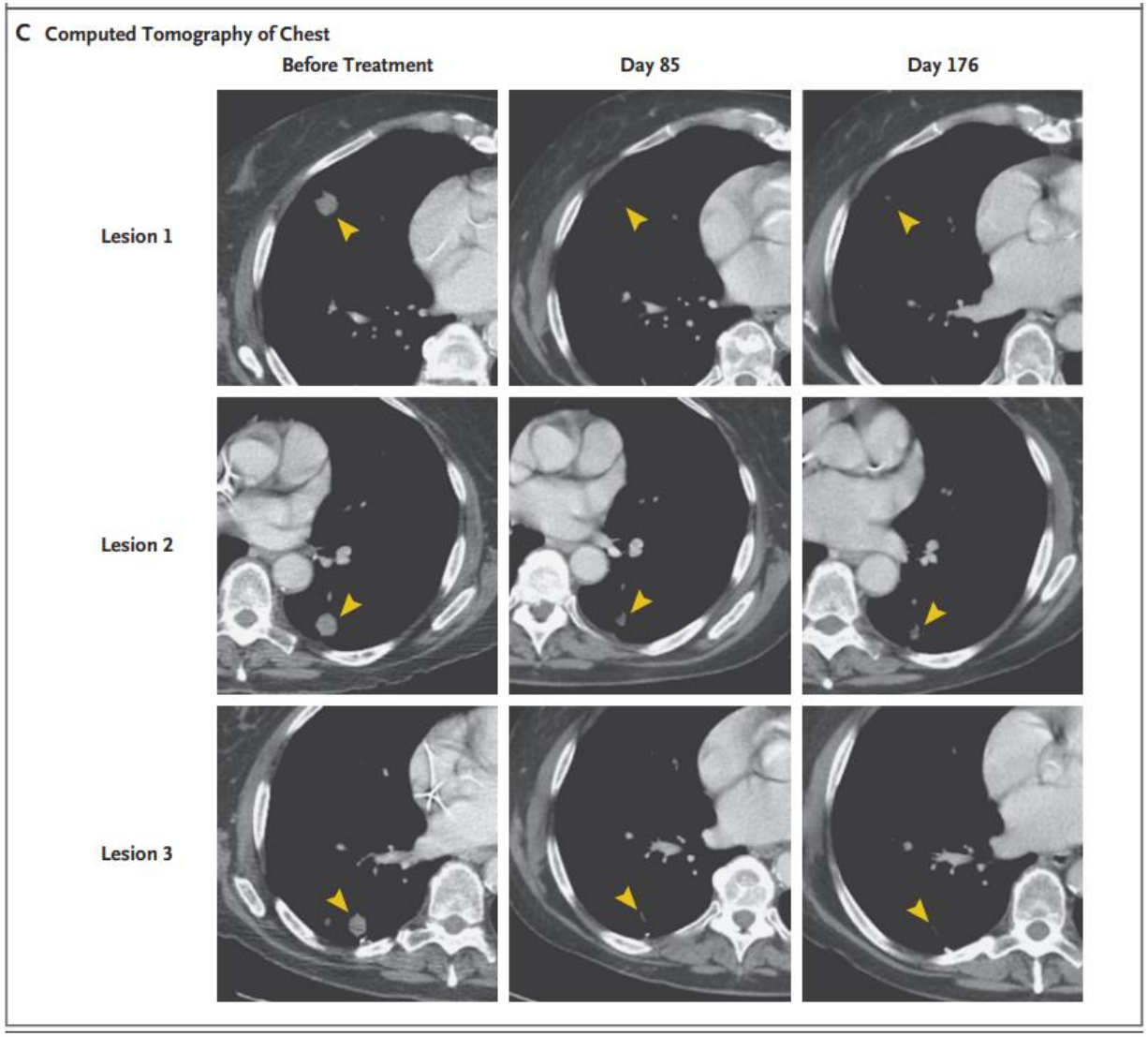


Administering Peripheral Blood Lymphocytes Transduced With a Murine T-Cell Receptor Recognizing the G12D Variant of Mutated RAS in HLA-A*11:01 Patients

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Administering Peripheral Blood Lymphocytes Transduced With a Murine T-Cell Receptor Recognizing the G12D Variant of Mutated RAS in HLA-A*11:01 Patients	• Gastrointestinal Cancer • Pancreatic Cancer • Gastric Cancer • (and 2 more...)	• Drug: Cyclophosphamide • Drug: Fludarabine • Drug: Aldesleukin • Biological: anti-KRAS **G12D** mTCR PBL	• National Institutes of Health Clinical Center Bethesda, Maryland, United States

Results with TCR Gene Therapy

(Leidner et al. 2022)



The NEW ENGLAND JOURNAL of MEDICINE

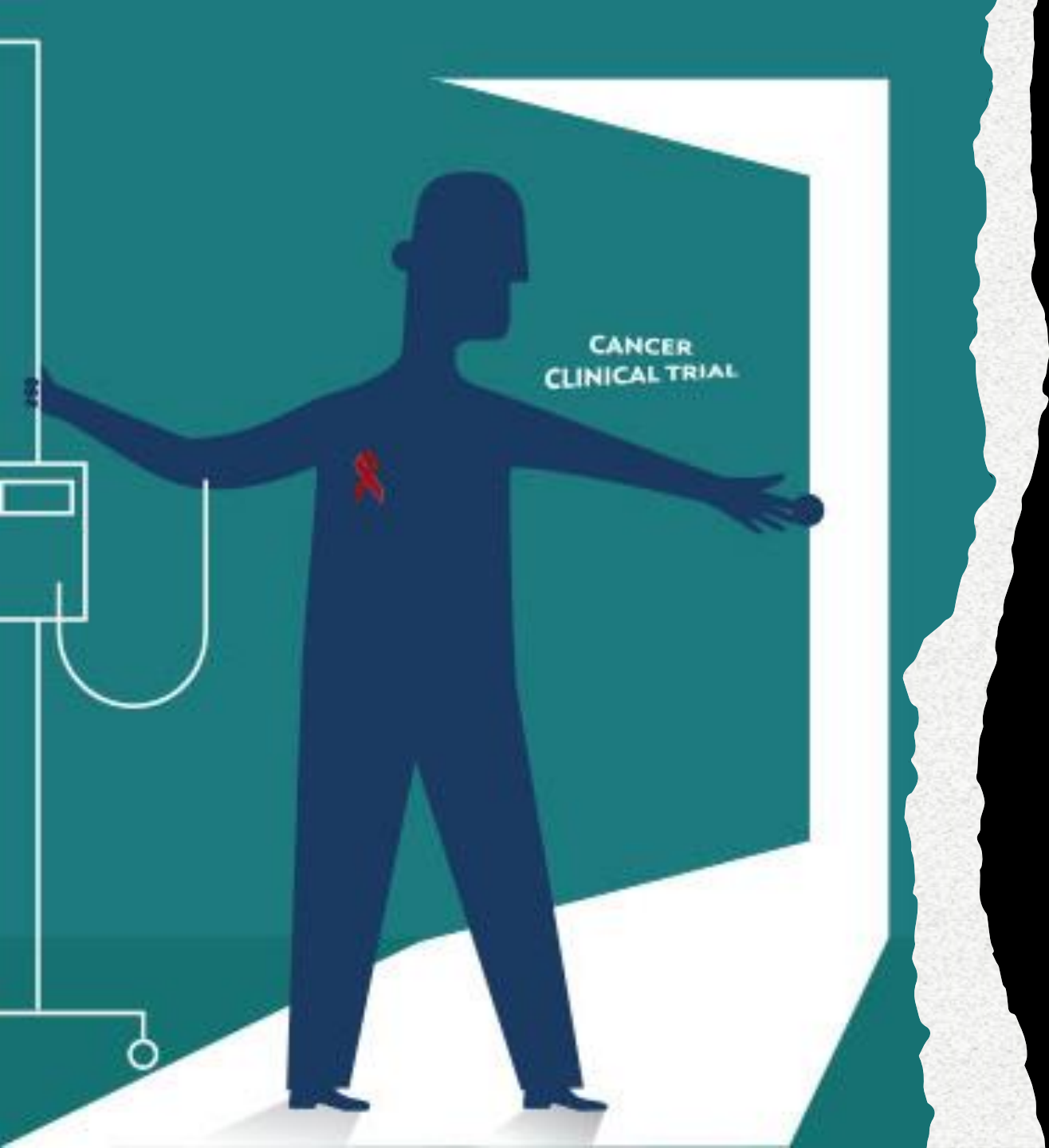
BRIEF REPORT

Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer

Rom Leidner, M.D., Nelson Sanjuan Silva, B.S., Huayu Huang, M.S., David Sprott, B.S., Chunhong Zheng, Ph.D., Yi-Ping Shih, Ph.D., Amy Leung, B.S., Roxanne Payne, M.N., Kim Sutcliffe, B.S.N., Julie Cramer, M.A., Steven A. Rosenberg, M.D., Ph.D., Bernard A. Fox, Ph.D., Walter J. Urba, M.D., Ph.D., and Eric Tran, Ph.D.

SUMMARY

A patient with progressive metastatic pancreatic cancer was treated with a single infusion of 16.2×10^9 autologous T cells that had been genetically engineered to clonally express two allogeneic HLA-C*08:02–restricted T-cell receptors (TCRs) targeting mutant KRAS G12D expressed by the tumors. The patient had regression of visceral metastases (overall partial response of 72% according to the Response Evaluation Criteria in Solid Tumors, version 1.1); the response was ongoing at 6 months. The engineered T cells constituted more than 2% of all the circulating peripheral-blood T cells 6 months after the cell transfer. In this patient, TCR gene therapy targeting the KRAS G12D driver mutation mediated the objective regression of metastatic pancreatic cancer. (Funded by the Providence Portland Medical Foundation.)



Thank You