University of Glasgow

Genomic Medicine

Pancreatic Cancer UK Webinar Series

20 February 2024

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Pancreatic Cancer UK

What do you know about genomic medicine?

A. Heard about it but don’t know much about it

B. Have seen results or requested tests for some patients

C. Discuss genomics with patients regularly

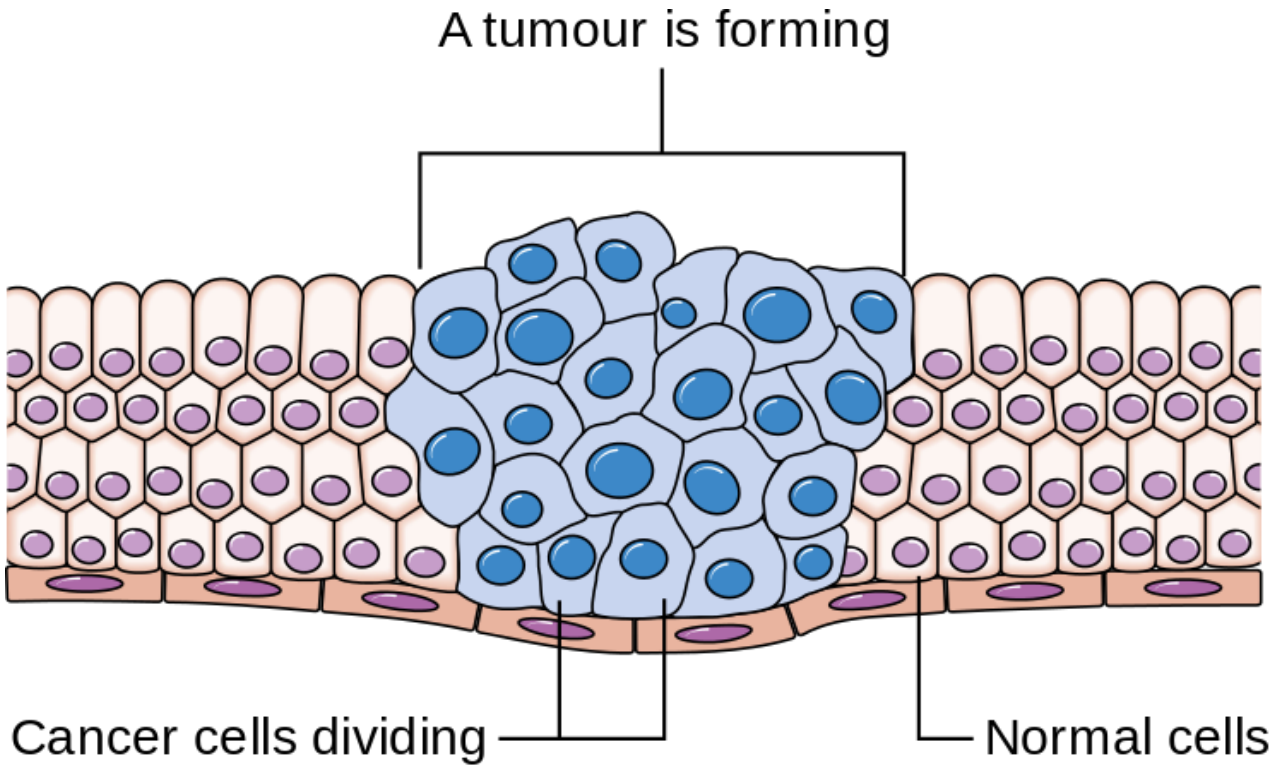
The role for genomics in pancreatic cancer

A. Sun Set: only applied in research setting and not proven helpful
B. Sun Rise: will be applied regularly for pancreatic cancer patients soon and change practice
C. Total darkness: we don't know
D. Other

What is cancer?

Genetic instructions normally tell cells when to stop dividing

But, the instructions can go wrong…



→ Can we identify, and therapeutically target, the genes that are driving the cancer?

Oncogenes
Tumour suppressor genes

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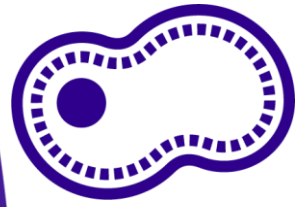
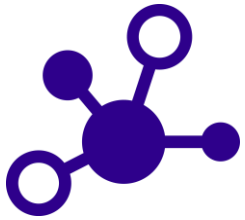
What causes errors in our DNA?

Ageing (mistakes build up over time)



Normal cell activities

Lifestyle factors such as smoking, diet and UV light



Certain viruses

Genes passed down in families

Changes in tumour DNA “somatic”

Changes in patient’s normal DNA, ”germline”

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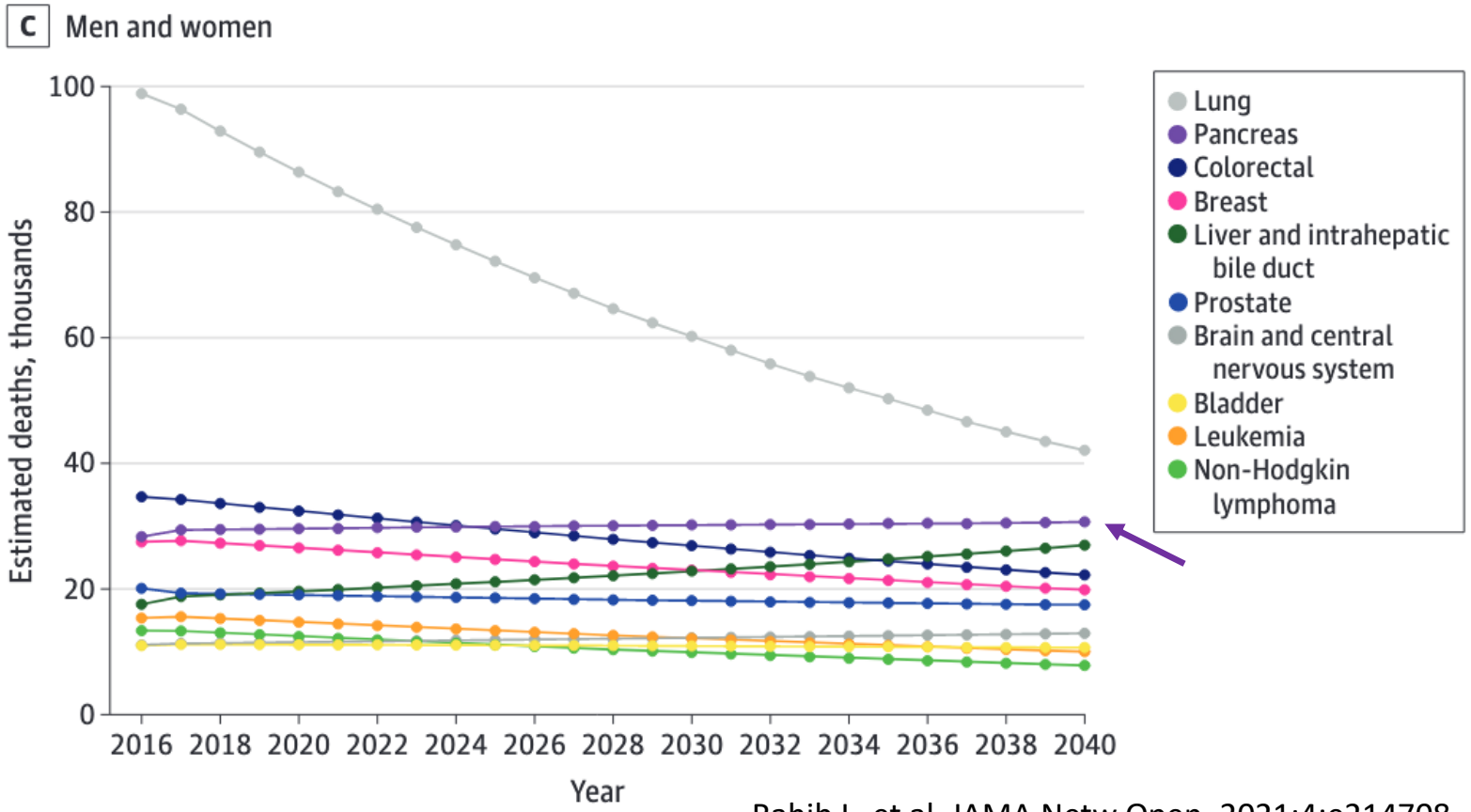
Pancreatic cancer statistics

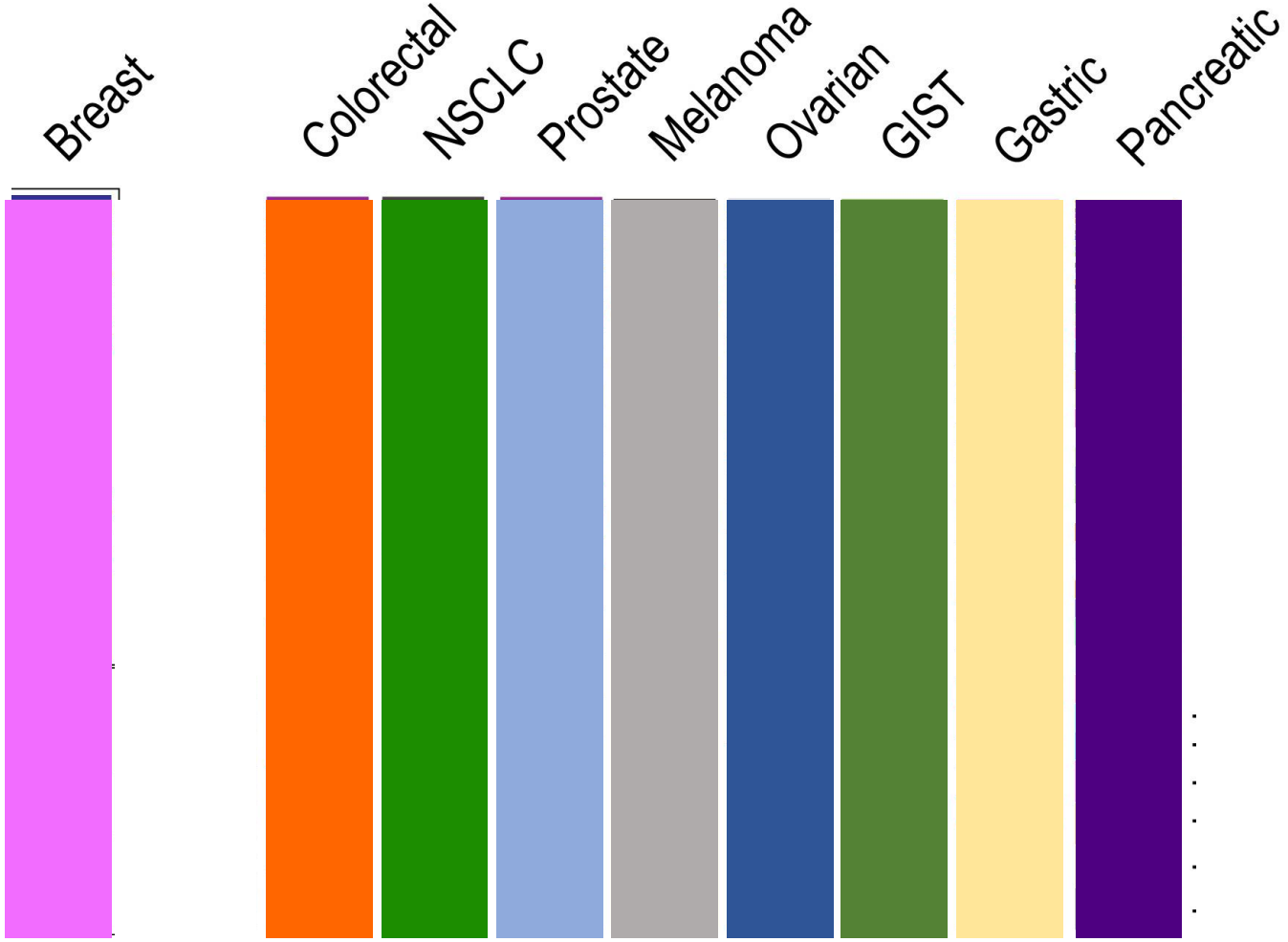
- 7% alive at 5 years
- Average survival ~6 months
- 90% die within a year
- Surgery only cure (~30 -35% 5-yr)
- Mortality not significantly changed for 50 years
- Majority metastatic – needs systemic treatment



Rahib L, et al. JAMA Netw Open. 2021;4:e214708

- **Treatments do work – significant responses in undefined subgroups**

Cancer is complex & Heterogeneous



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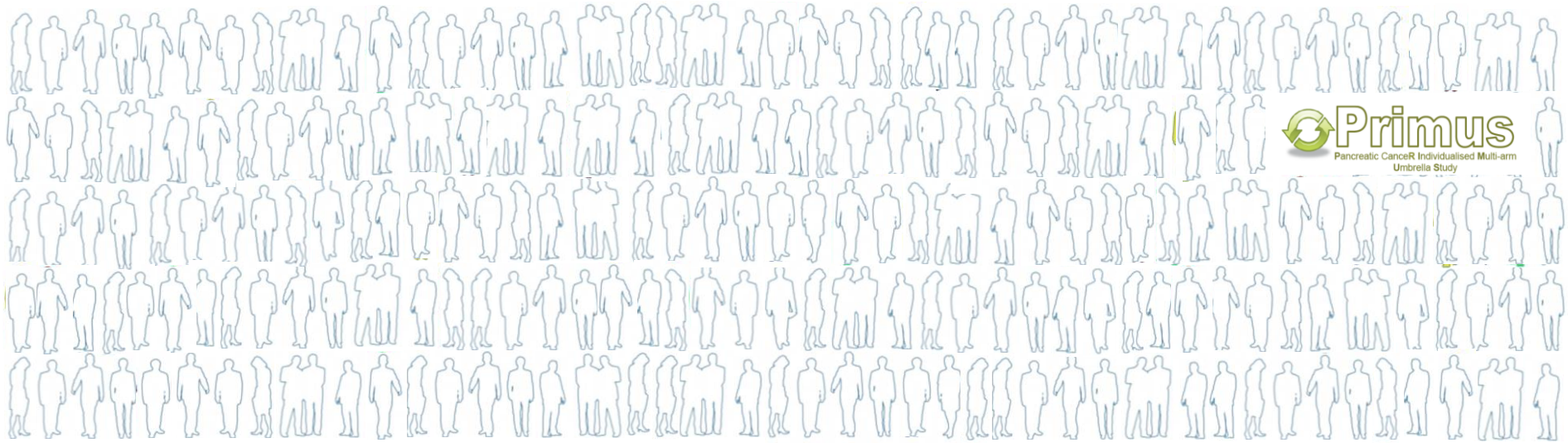
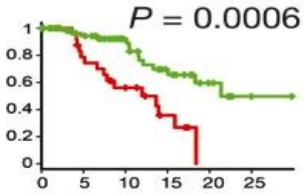
Delivery of Molecularly Phenotyped Trial Participants

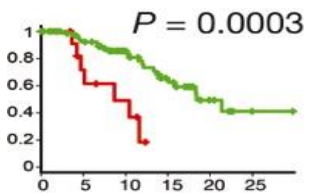


Next generation sequencing to identify genetic changes

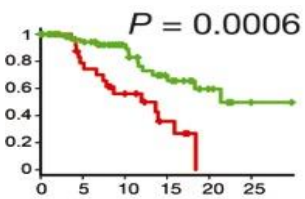
Trial of Drug A



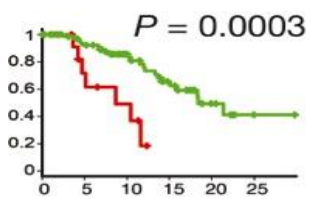
Trial of Drug B



Trial of Drug C



Trial of Drug D



Novel Targets and Drugs

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Challenges in management of pancreatic cancer

1. What is the optimal systemic treatment?

2. Rapid deterioration in performance status

→ Molecular biology:

- No strong, validated biomarkers apart from small subgroups of patients

Jones et al, Science 2008 ; Campbell et al, Nature 2010 ; Biankin et al, Nature 2012 ; Waddell et al, Nature 2015 ; Raphael et al, Cancer Cell 2017

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Improving outcomes through a dynamic research & development platform for Precision Medicine

A self-learning set up

Biospecimens:
Tumour tissue
Blood

Next Generation Model Systems:
Patient-derived xenografts (PDX)
Organoids
Patient-derived cell lines (PDCL)

DISCOVERY

Well-annotated, deeply molecularly characterised patient cohorts to define:

Novel Pathophysiology; Therapeutic Targets; Clinical Features; Actionable Segments; Biomarker Discovery; Resistance Mechanisms; Clonal Evolution; Predisposition; Molecular Taxonomy

Enabling Data Access and Analysis for Researchers from all backgrounds

Prioritised Strategies

CLINICAL DEVELOPMENT

"Find the Trial for the Patient" from a suite of clinical trials

"Master Protocol" for Clinical Testing of Molecular Driven Therapeutic Selection and Biomarker Discovery/Development

PRE-CLINICAL DEVELOPMENT

Next-Generation Model Systems
Biology and Mechanism
Novel Targets
Therapeutic Testing
Biomarker Development

A platform for capturing, assembling, combining, analysing and visualising data

Pre-clinical Platform of Evidence

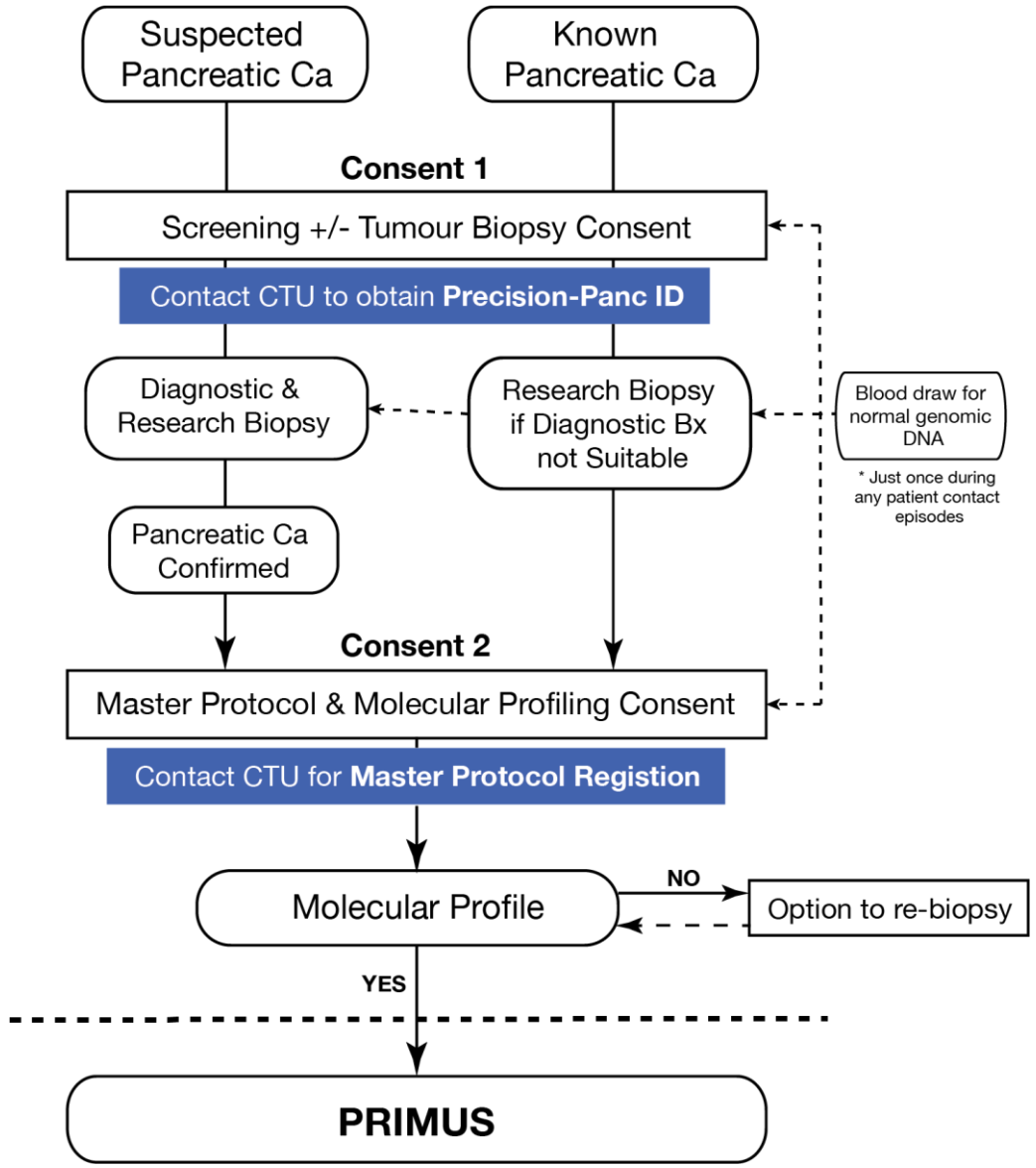
First patient recruited November 2017

ARGO Accelerating Research in Genomic Oncology
International Cancer Genome Consortium

Precision-Panc Master Protocol: a portal…

Clinical CI: Bristi Basu
Translational CI: David Chang

Tissue pathway



Patient pathway remapping:

- Surgeons
- Oncologists
- Endoscopists
- Radiologists
- Pathologists
- Trial coordinators
- Tissue biorepository
- Genome biologists
- Bioinformaticians
- Technologists
- And more…

To incorporate parallel tissue pathway…

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Timelines of the development of a UK network for therapeutic development

Optimized sequencing pipeline for low-input DNA

Switch to diagnostic surplus

Clinical Cancer Genome

Move to NHS Molecular Diagnostics Lab for ISO accredited NGS assay

National MTB

Precision-Panc Master Protocol

2017 2018 2019 2020 2021 2022 2023 2024

PRIMUS-001

PRIMUS-003

PRIMUS-002

PRIMUS-005

PRIMUS-007

PRIMUS-004

PRIMUS-006

PRIMUS-008

PRIMUS-009

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Genomics Innovation Alliance

ecmc

NCRI National Cancer Research Institute

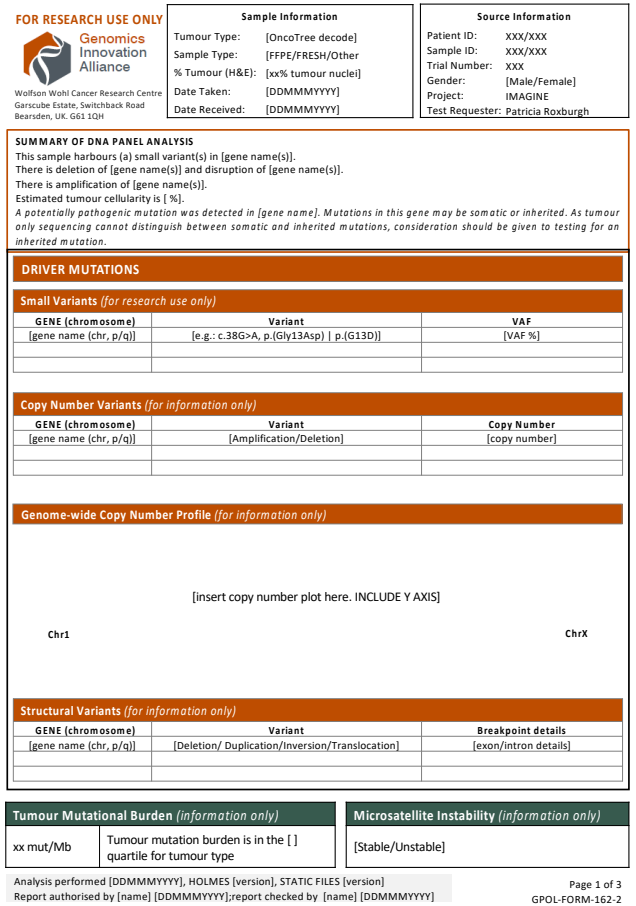
Partners in cancer research

Molecular Profiling for Precision-Panc (NHS accreditation)

Harmonised molecular profiling platform **designed specifically for pancreatic cancer**

Clinical Sequencing (real time)

1) GIA Clinical Cancer Genome **(92%)**
2) Integration with histopathology



FOR RESEARCH USE ONLY

Genomics Innovation Alliance

Wolfson Wohl Cancer Research Centre
Garscube Estate, Switchback Road
Bearsden, UK. G61 1QH

Sample Information	
Tumour Type:	[OncoTree decode]
Sample Type:	[FFPE/FRESH/Other
% Tumour (H&E):	[xx% tumour nuclei]
Date Taken:	[DDMMMYYYY]
Date Received:	[DDMMMYYYY]

Source Information	
Patient ID:	XXX/XXX
Sample ID:	XXX/XXX
Trial Number:	XXX
Gender:	[Male/Female]
Project:	IMAGINE
Test Requester:	Patricia Roxburgh

SUMMARY OF DNA PANEL ANALYSIS

This sample harbours (a) small variant(s) in [gene name(s)].
There is deletion of [gene name(s)] and disruption of [gene name(s)].
There is amplification of [gene name(s)].
Estimated tumour cellularity is [%].
A potentially pathogenic mutation was detected in [gene name]. Mutations in this gene may be somatic or inherited. As tumour only sequencing cannot distinguish between somatic and inherited mutations, consideration should be given to testing for an inherited mutation.

DRIVER MUTATIONS

Small Variants *(for research use only)*

GENE (chromosome)	Variant	VAF
[gene name (chr, p/q)]	[e.g.: c.38G>A, p.(Gly13Asp) | p.(G13D)]	[VAF %]

Copy Number Variants *(for information only)*

GENE (chromosome)	Variant	Copy Number
[gene name (chr, p/q)]	[Amplification/Deletion]	[copy number]

Genome-wide Copy Number Profile *(for information only)*

[insert copy number plot here. INCLUDE Y AXIS]

Chr1 ChrX

Structural Variants *(for information only)*

GENE (chromosome)	Variant	Breakpoint details
[gene name (chr, p/q)]	[Deletion/ Duplication/Inversion/Translocation]	[exon/intron details]

Tumour Mutational Burden *(information only)*	
xx mut/Mb	Tumour mutation burden is in the [ ] quartile for tumour type

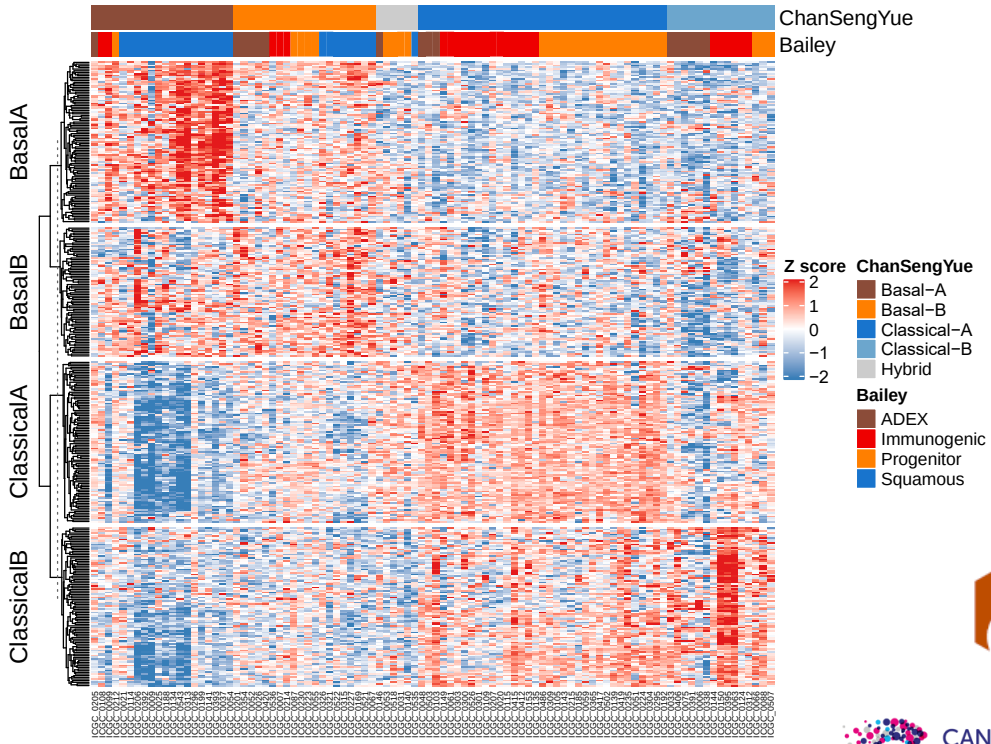
Microsatellite Instability *(information only)*
[Stable/Unstable]

Analysis performed [DDMMMYYYY], HOLMES [version], STATIC FILES [version]
Report authorised by [name] [DDMMMYYYY];report checked by [name] [DDMMMYYYY]

Page 1 of 3
GPOL-FORM-162-2

Research Sequencing (batched)

1) Transcriptome Sequencing **(95%)**
2) Liquid biopsy (cfDNA and methylation)
3) Others (single cell, spatial, proteome, WGS)



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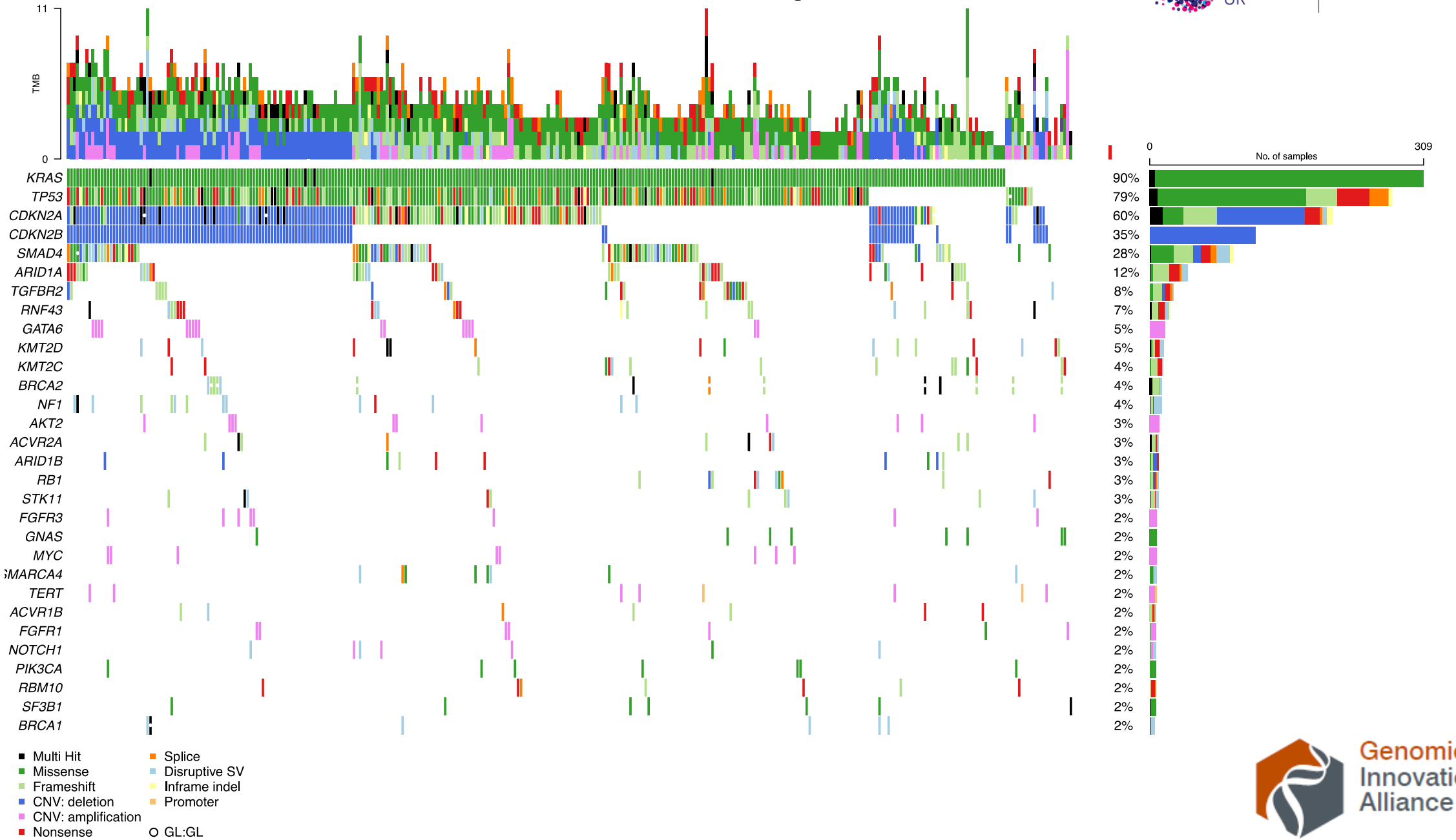
UK Precision-Panc: first 340 patients



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How could this help patients?

- Molecular reports shared with treating clinicians
- With NHS Molecular Genetics Lab working towards real-time, clinical grade reporting

How do I interpret this?

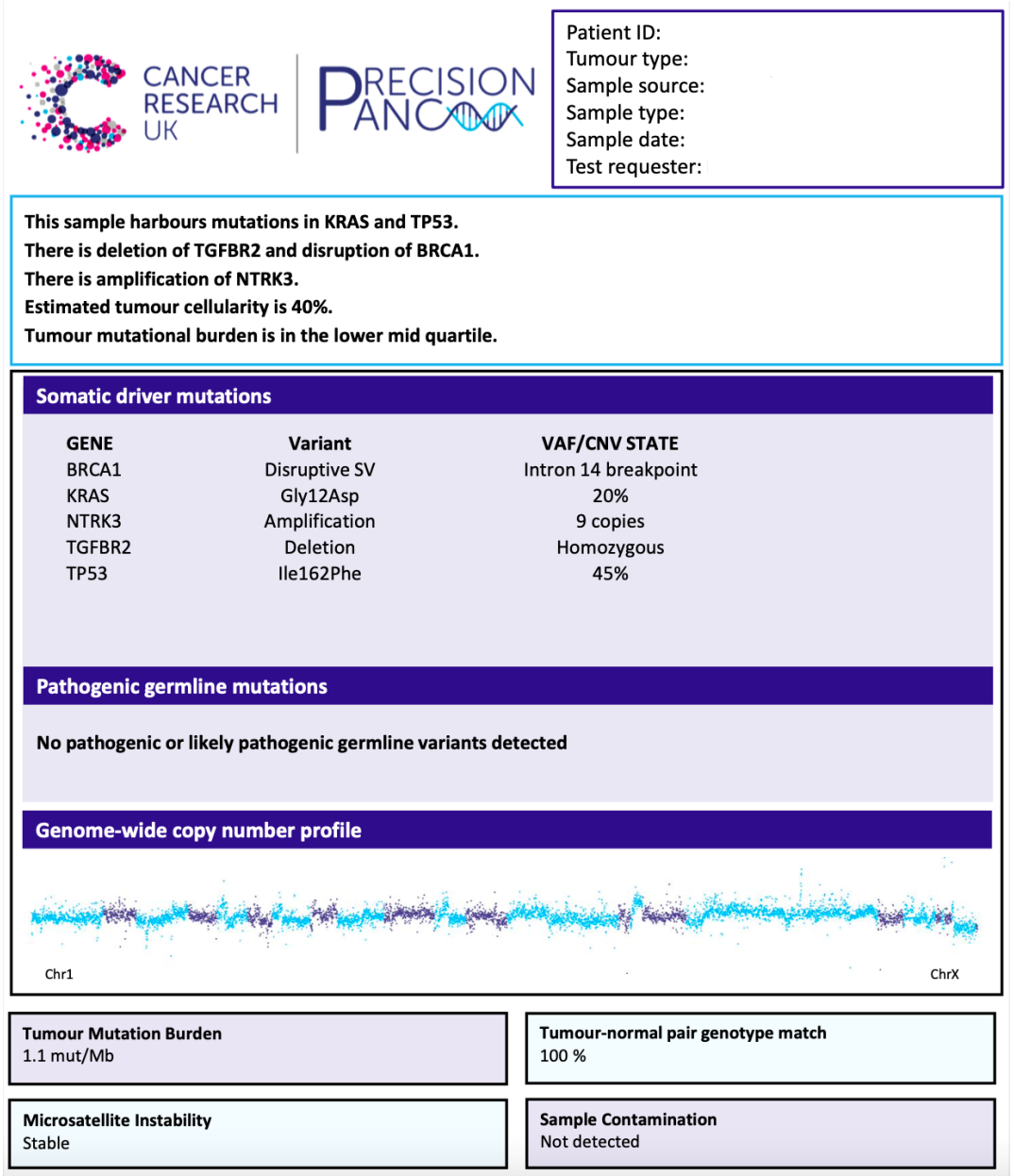
What is the clinical relevance?

Are there clinical trials?

How is data shared?

→ National Molecular Tumour Board

- **Educational platform for all involved**
- Enable trial enrolment
- Future collaborative research ideas
- Collect data and improve patient care



fieke.froeling@glasgow.ac.uk judith.dixon@glasgow.ac.uk

66 year old male

- Presenting symptoms: abdominal pain

- PMHx: nil
- Type II DM: no
- Smoking: ex-smoker
- Family Hx: no family history of note

- Baseline CT: 31/05/22 bilobar liver metastases
- Liver biopsy: pancreatic ductal adenocarcinoma
- Ca19.9: 12 August 1684

- Treatment: Gem/Nab-Paclitaxel within PRIMUS 001; Sept – Dec 2022

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This sample harbours mutations in BRAF and TP53.
The BRAF mutation is a rare (but recognised) driver variant; it is unclear if it acts as a class II or class III mutation.
Estimated tumour cellularity is 16%.
Tumour mutational burden is in the bottom quartile.

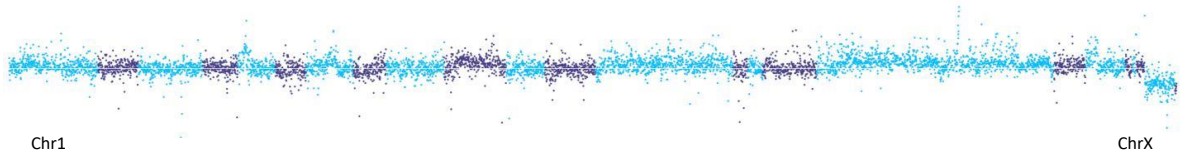
Somatic driver mutations

GENE	Variant	VAF/CNV STATE
BRAF	Asn486_Pro490del	8%
TP53	Cys242Arg	9%

Pathogenic germline mutations

No pathogenic or likely pathogenic germline variants detected

Genome-wide copy number profile



Tumour Mutation Burden
<0.6 mut/Mb

Tumour-normal pair genotype match
100%

Microsatellite Instability
Stable

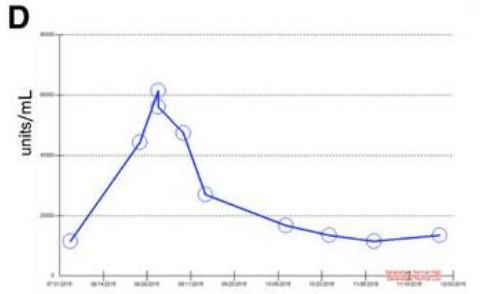
Sample Contamination
Not detected

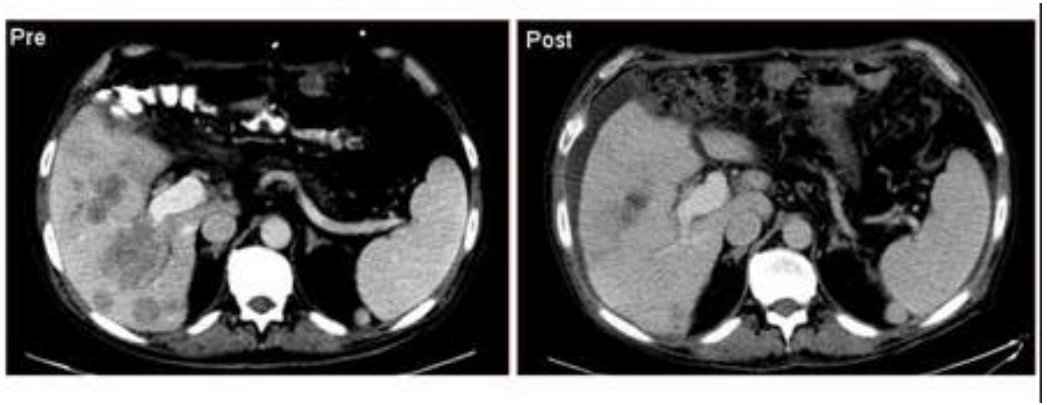
BRAF Asn486_Pro490del (N486_P490del)

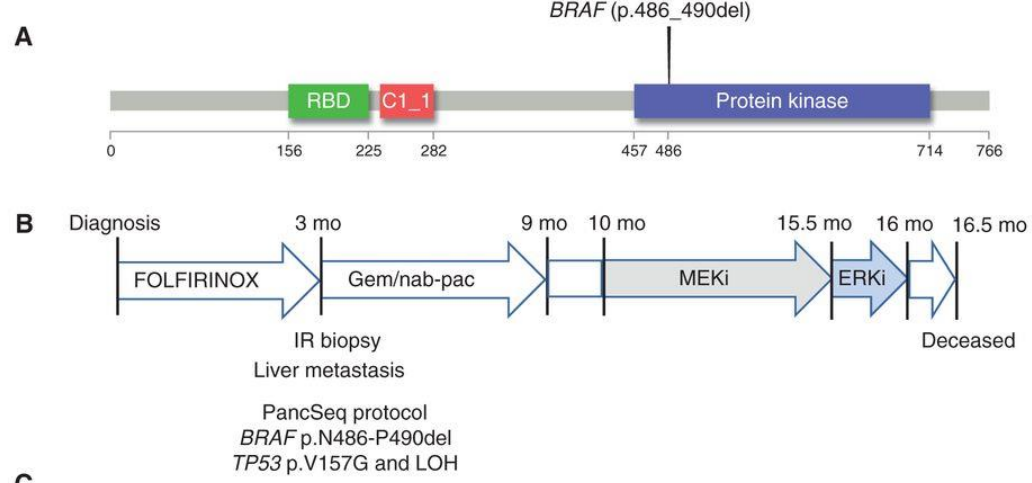
- In frame deletion of 5 amino acids near BRAF kinase domain → gain of Braf protein function → MAPK signalling

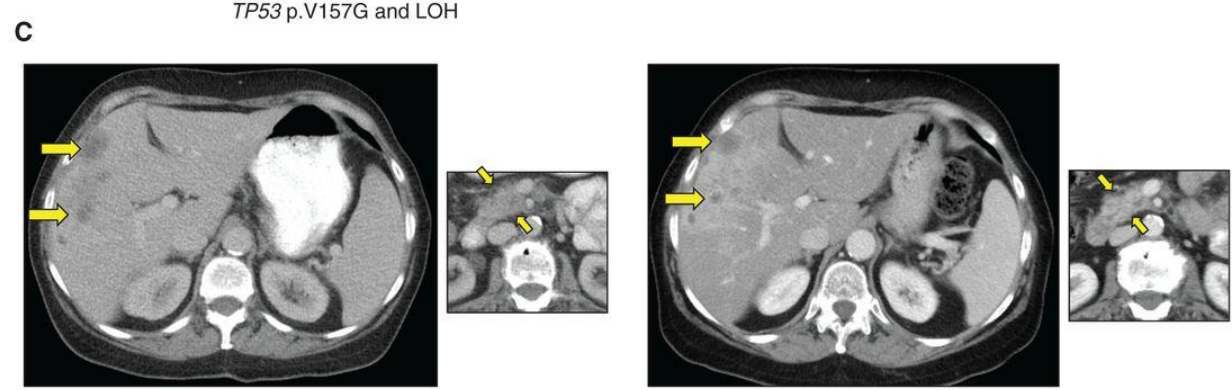
Identification of targetable BRAF ΔN486_P490 variant by whole-genome sequencing leading to dabrafenib-induced remission of a *BRAF*-mutant pancreatic adenocarcinoma

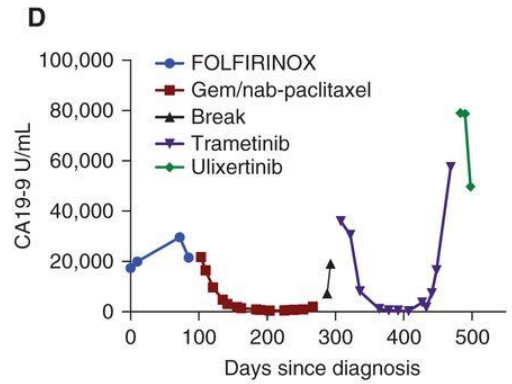
Kazimierz O. Wrzeszczynski[1], Sadia Rahman[1], Mayu O. Frank[2], Kanika Arora[1], Minita Shah[1], Heather Geiger[1], Vanessa Felice[1], Dina Manaa[1], Esra Dikoglu[1], Depinder Khaira[1], A. Rao Chimpiri[3], Vanessa V. Michelini[4], Vaidehi Jobanputra[1,5], Robert B. Darnell[1,2,6], Scott Powers[7] and Minsig Choi[8]

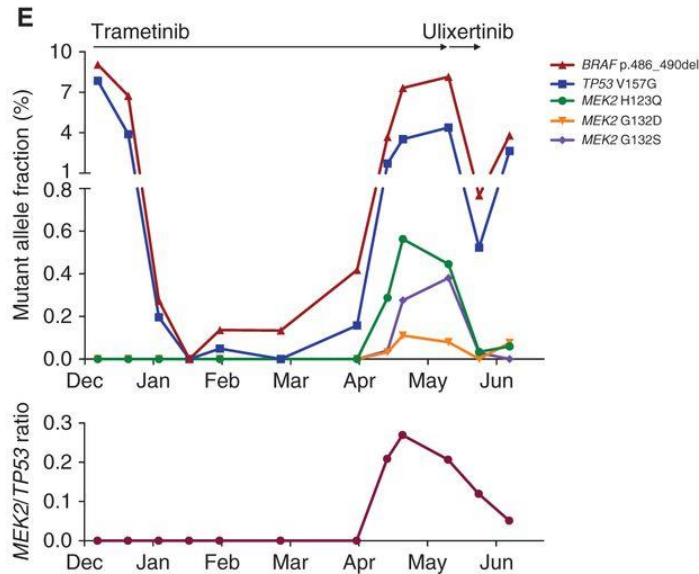




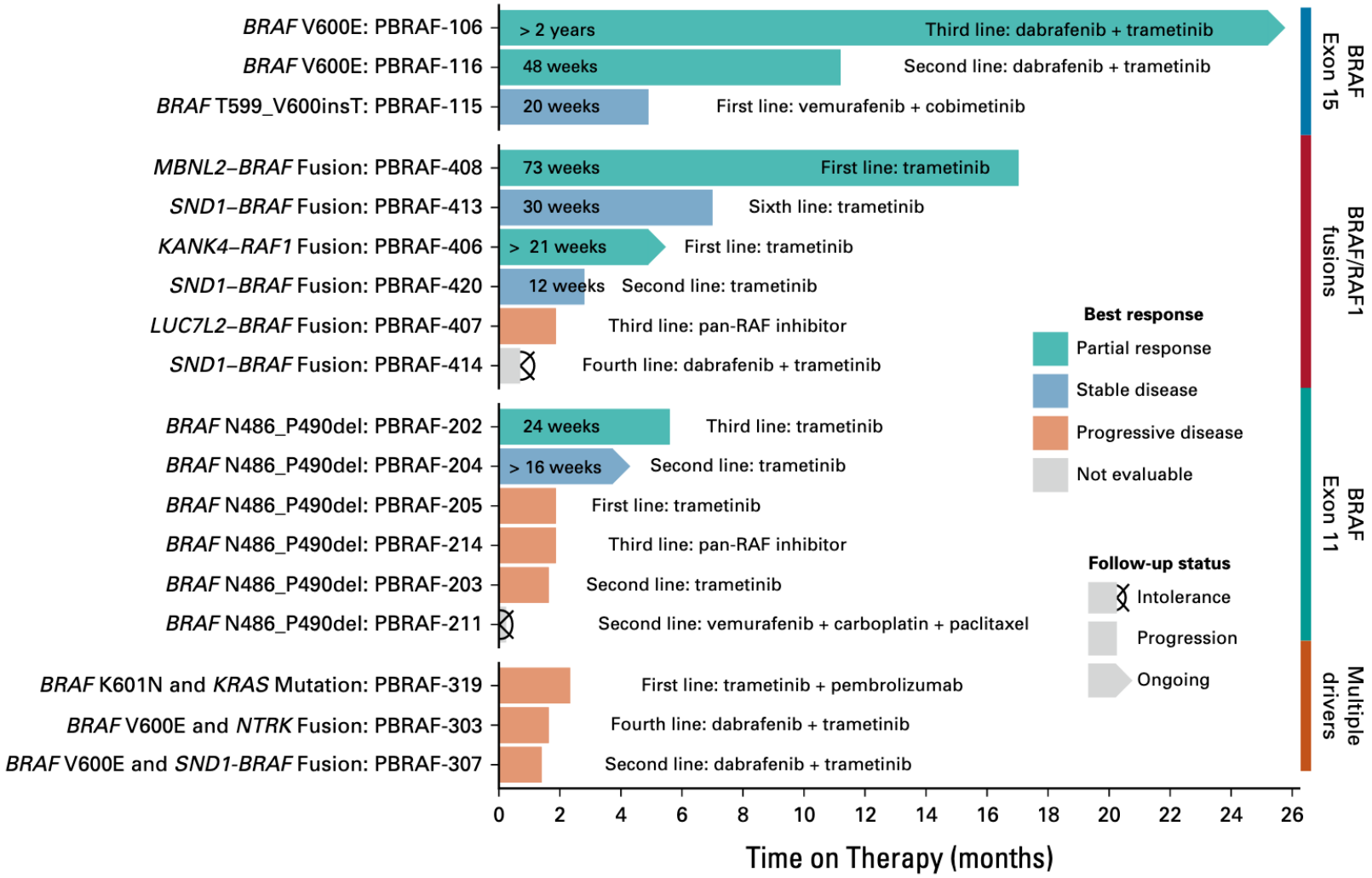








Aguirre et al, Cancer Discov 2018



Hendifar et al, JCO Precision Oncol 2021

2nd line treatment options

- TAPISTRY platform study, cohort J: Belvarafenib for BRAF class III mutant-positive tumours

→ Patient referred for participation in TAPISTRY trial; BRAF cohort closed
→ Consented to TARGET national:
BRAF N486_P490 del confirmed

- Funding and approval secured for off-label treatment with dabrafenib + trametinib, started April 2023

FOUNDATIONONE®LIQUID CDx

PATIENT: TNE4010072T1GLW, TNE4010072T1GLW
TUMOR TYPE: Pancreas cancer (NOS)
REPORT DATE: 13 March 2023
COUNTRY CODE: GB
ORDERED TEST #: ORD-1579491-01

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT
DISEASE Pancreas cancer (NOS)
NAME TNE4010072T1GLW, TNE4010072T1GLW
DATE OF BIRTH 01 January 1956
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN
ORDERING PHYSICIAN Evans, Thomas
MEDICAL FACILITY Beatson W of Scotland Cancer Ctr TARGET
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 325472
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN ID 03-2023-00082505 01/01/1956
SPECIMEN TYPE Blood
DATE OF COLLECTION 01 March 2023
SPECIMEN RECEIVED 06 March 2023

Genomic Signatures

Blood Tumor Mutational Burden - 4 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Gene Alterations

For a complete list of the genes assayed, please refer to the Appendix.

BRAF N486_P490del
TP53 C242R

Report Highlights

- Evidence-matched clinical trial options based on this patient's genomic findings: (p. 7)

GENOMIC SIGNATURES	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 4 Muts/Mb	No therapies or clinical trials. See Genomic Signatures section
Microsatellite status - MSI-High Not Detected	MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).
Tumor Fraction - Elevated Tumor Fraction Not Detected	Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Genomic Signatures section).

GENE ALTERATIONS		VAF%
BRAF -	N486_P490del	0.32%
5 Trials see p. 7		

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
None	None

61 year old female

- **Presenting symptoms:** Incidental finding of pancreatic tail mass and liver metastases on MRI spine
- **PMHx:** Seropositive rheumatoid arthritis 2021 on methotrexate
- **Type II DM:** no
- **Smoking:** no
- **Family Hx:** no history of cancer
- **Baseline CT:** Local infiltrative lesion within the tail of the pancreas involving the splenic hilum, encasing splenic vessels with left adrenal metastatic deposit. Multiple hepatic deposits. Adjacent prominent nodes. Complex pelvic mass as described MRI.
- **Biopsy:** Liver biopsy – metastatic adenocarcinoma
- **Ca19.9:** 67
- **Treatment:** Gemcitabine/Abraxane

FOR RESEARCH USE ONLY

Genomics Innovation Alliance
Wolfson Wohl Cancer Research Centre
Garscube Estate, Switchback Road
Bearsden, UK. G61 1QH
scs-contactgia@glasgow.ac.uk

Sample Information	
Tumour Type:	Pancreas
Preservation Type:	FFPE
% Tumour (H&E):	15%
Date Taken:	25 July 2023
Date Received:	21 September 2023

Source Information	
Patient ID:	
Sample ID:	
Trial Number:	
Gender:	
Project:	
Test Requester:	

Normal Sample Information

Sample Type:	N/A	Sample ID:	N/A
Date Taken:	N/A	Date Received:	N/A

SUMMARY OF CANCER PLUS DNA PANEL ANALYSIS [Tumour-Only]
This sample harbours small variants in EGFR and TET2.
There is amplification of MET.
There is a potential SLC4A4::ROS1 fusion.
Estimated tumour cellularity is 58%.

DRIVER MUTATIONS

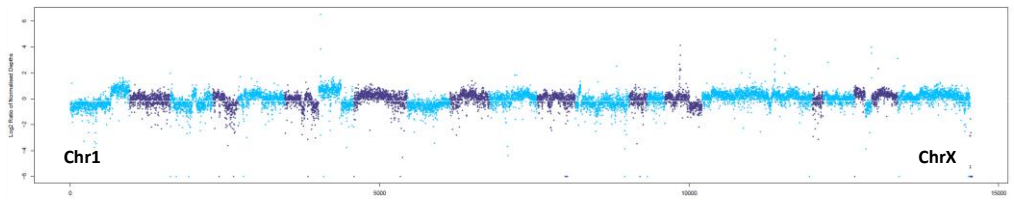
Small Variants *(for research use only)*

GENE (chromosome)	Variant	VAF
EGFR (7p)	c.293G>A | p.(Arg98Gln) | p.(R98Q)	29%
TET2 (4q)	c.3116C>A | p.(Ser1039X) | p.(S1039*)	51%

Copy Number Variants *(for information only)*

GENE (chromosome)	Variant	Copy Number
MET (7q)	Amplification	7 copies

Genome-wide Copy Number Profile *(for information only)*



Structural Variants *(for information only)*

GENE (chromosome)	Variant	Breakpoint details
ROS1 (6q)	translocation	SLC4A4 intron 24, ROS1 intron 33

Germline variants *(for information only)*

GENE (chromosome)	Variant, transcript	VAF
N/A	N/A	N/A

Tumour Mutational Burden *(information only)*

3.6 mut/Mb	Tumour mutation burden is in the top quartile for tumour type

Microsatellite Instability *(information only)*

Stable

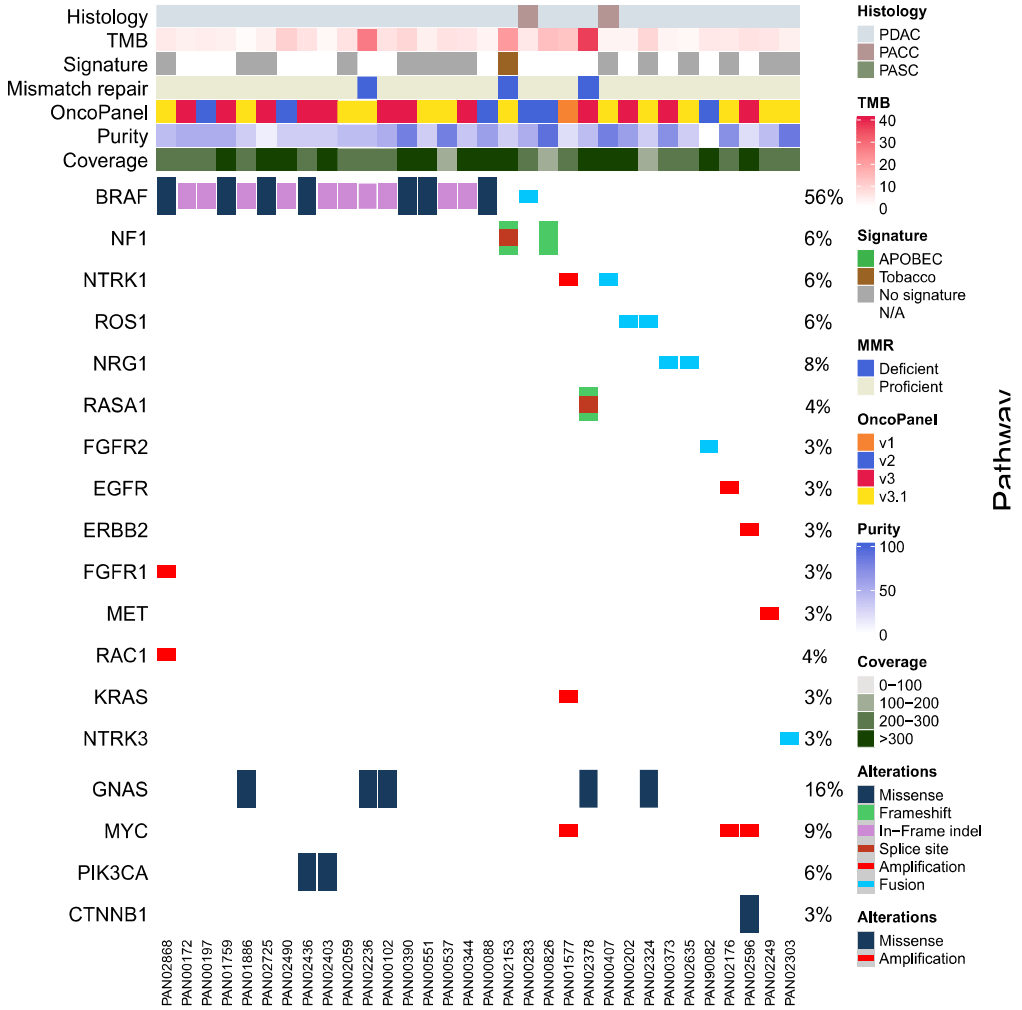
Remains rare but can be transformative for patient care

- Caris RNAseq database: of 175,350 tumours, ROS1 fusions indentified in 259 (0.15%)
- Enriched in KRAS WT pancreatic cancer: RTK fusion 6-11% of KRAS WT cancers

Table 1 List of cancer types in studied cohort

Cancer Type	N
Non-small cell lung cancer (NSCLC)	204
High Grade Glioma	18
Breast Carcinoma	7
Pancreatic Adenocarcinoma	4
Ovarian	4
Cancer of Unknown Primary	3
Cholangiocarcinoma	3
Colorectal Adenocarcinoma	3
Gastric Adenocarcinoma	3
Sarcoma	3
Esophageal and Esophagogastric Junction Carcinoma	2
Bladder cancer—urothelial	1
Melanoma	1
Neuroendocrine tumors	1
Small Intestinal Malignancies	1
Thyroid Carcinoma	1
Total	**259**

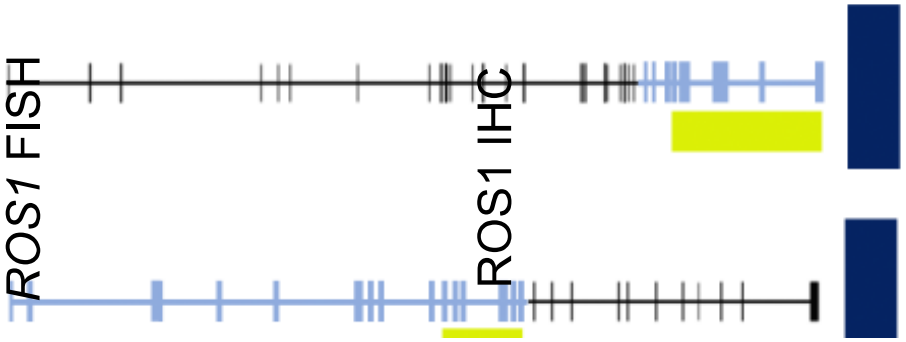
Nagasaka et al, BMC Cancer 2023



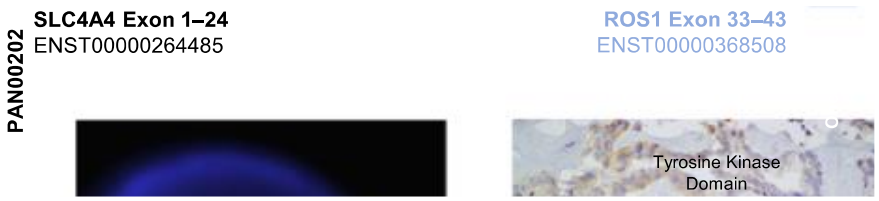
Singh et al, CCR 2023

Case reports of durable responses in ROS1+ pancreatic cancer

83 yo man, mPDAC
OncoPanel: KRAS WT, CDKN2A loss, ROS1 rearrangement

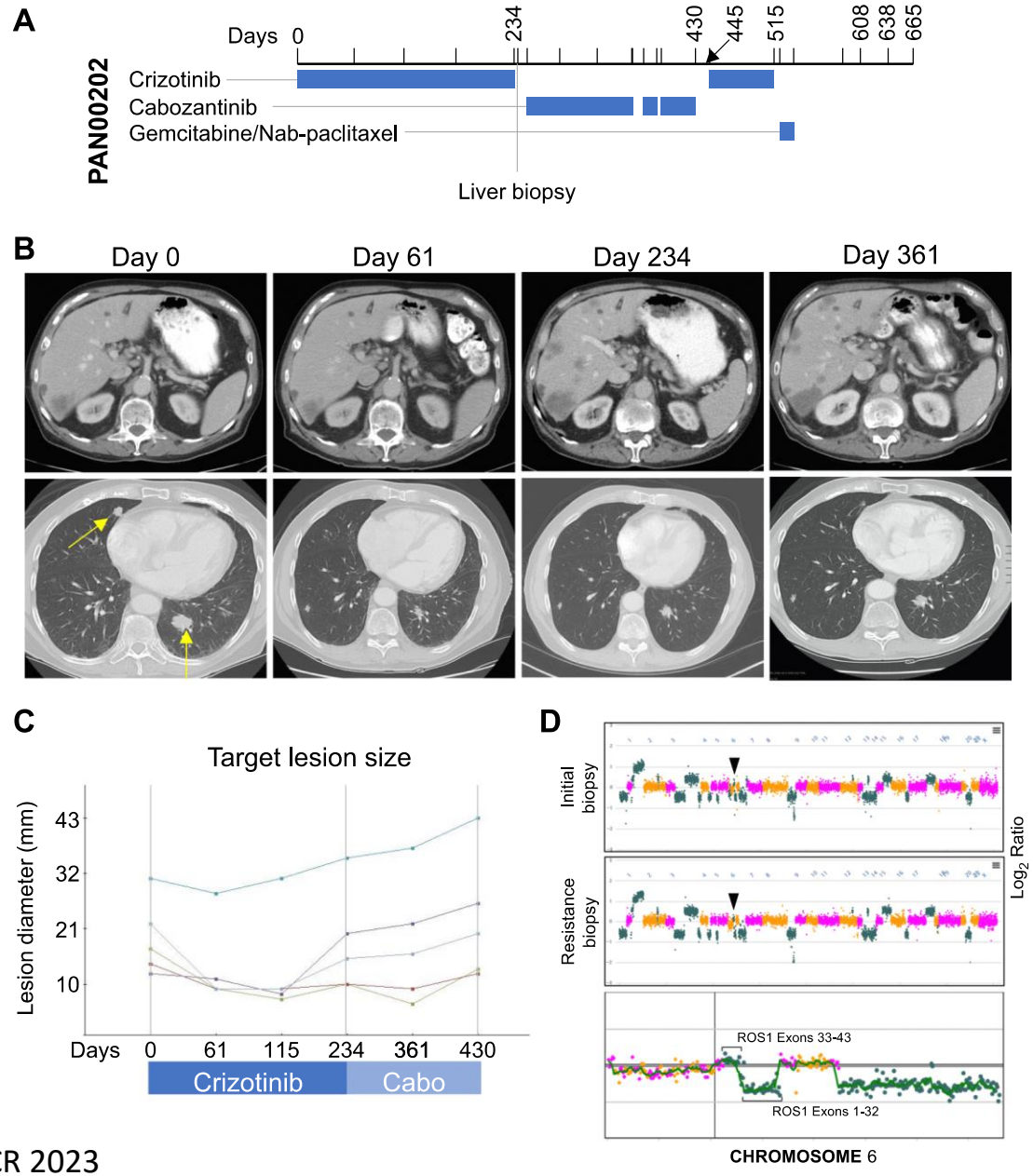


- CT @ 2 months: PR -31.2%
- CT @ 8 months: PD → repeat biopsy progressing liver metastasis: IHC and RNA based fusion assay in-frame fusion involving exons 1–24 of SLC4A4



- Cabozantinib: stable disease 6 months

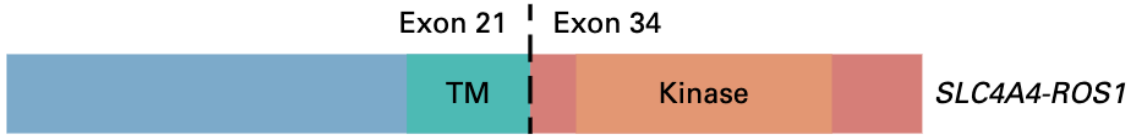
→ Clinical benefit TKIs 14 months; OS 22 months

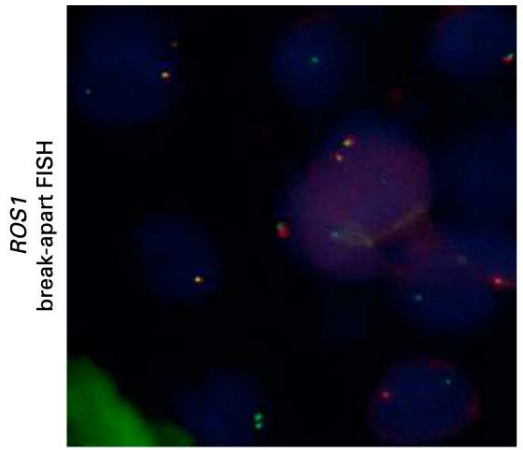


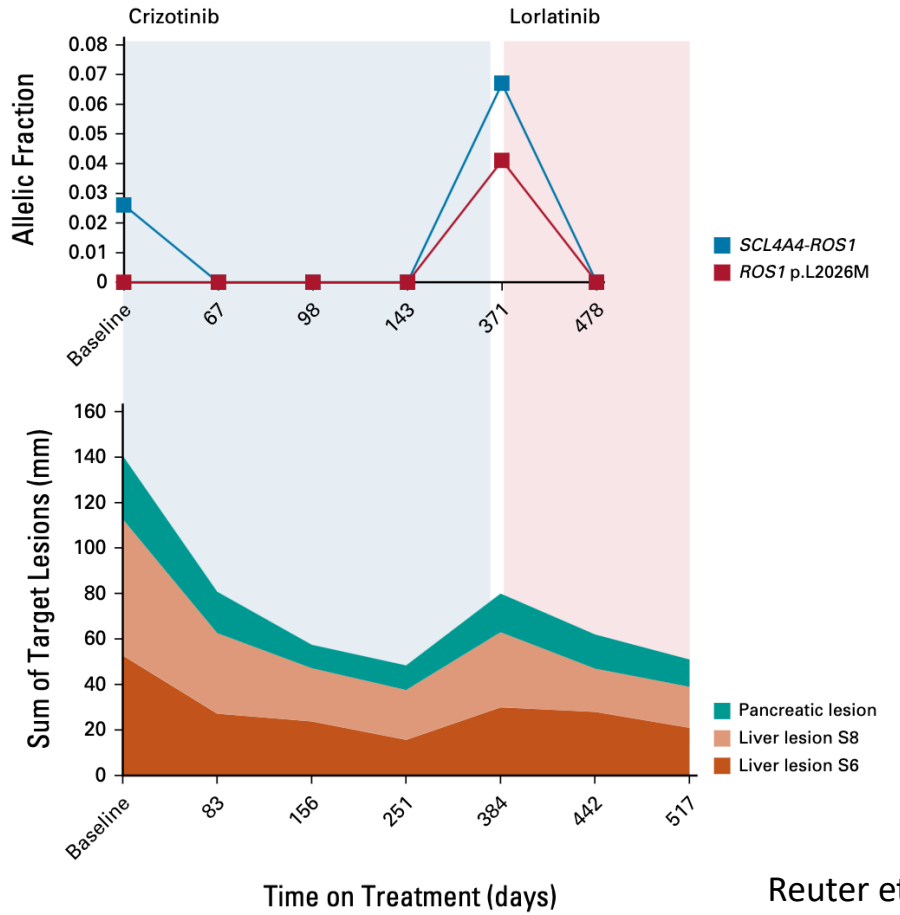
Singh et al, CCR 2023

55 yo women, mPDAC (liver, LN)

- multiple lines of chemo; DNA+RNA seq baseline tumour sample
- KRAS WT, **in-frame fusion of SLC4A4 (exons 1-21) to ROS1 (exons 34-43)**, FGFR4 p.G388R, AURKA p.F31I, SLX4 p.I1421F, INPP4A p.V253M







PS=3 ; off-label crizotinib started with longitudinal assessment of ctDNA

- clinical response within 1 week
- CT @ 2 months: PR -43%
- CT @ 12 months: PD → repeat liver biopsy:
  SCL4A4-ROS1 fusion in tumour + ctDNA
  resistance-mediating p.L2026M gatekeeper mutation in ctDNA

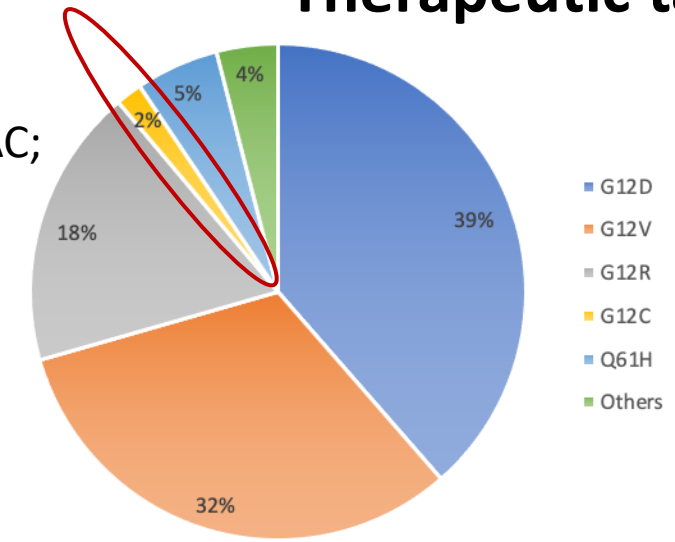
→ change to lorlatinib, CT @ 6 weeks: SD -16%, CT @ 3 months -32%, ongoing disease control at 12 months

Reuter et al, JCO Precis Onco. 2023

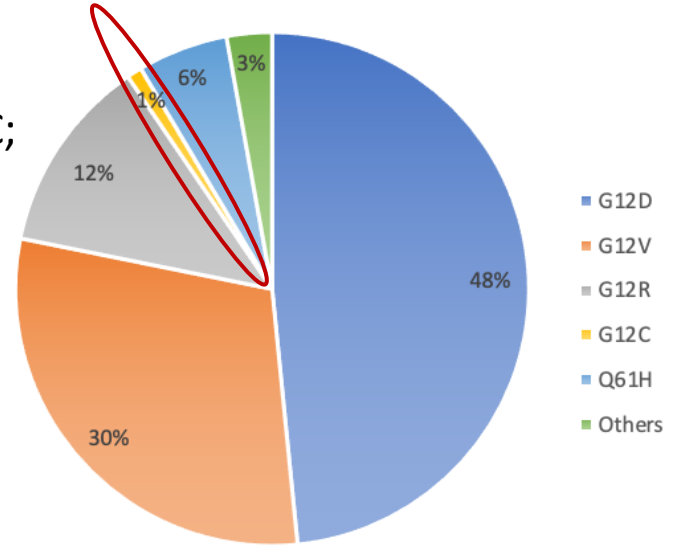
Most pancreatic cancers have KRAS mutations

Therapeutic targeting of oncogenic KRAS

ICGC (resectable PDAC; n=350)



Precision-Panc (metastatic PDAC; n=316)



Mutant-specific KRAS inhibitors

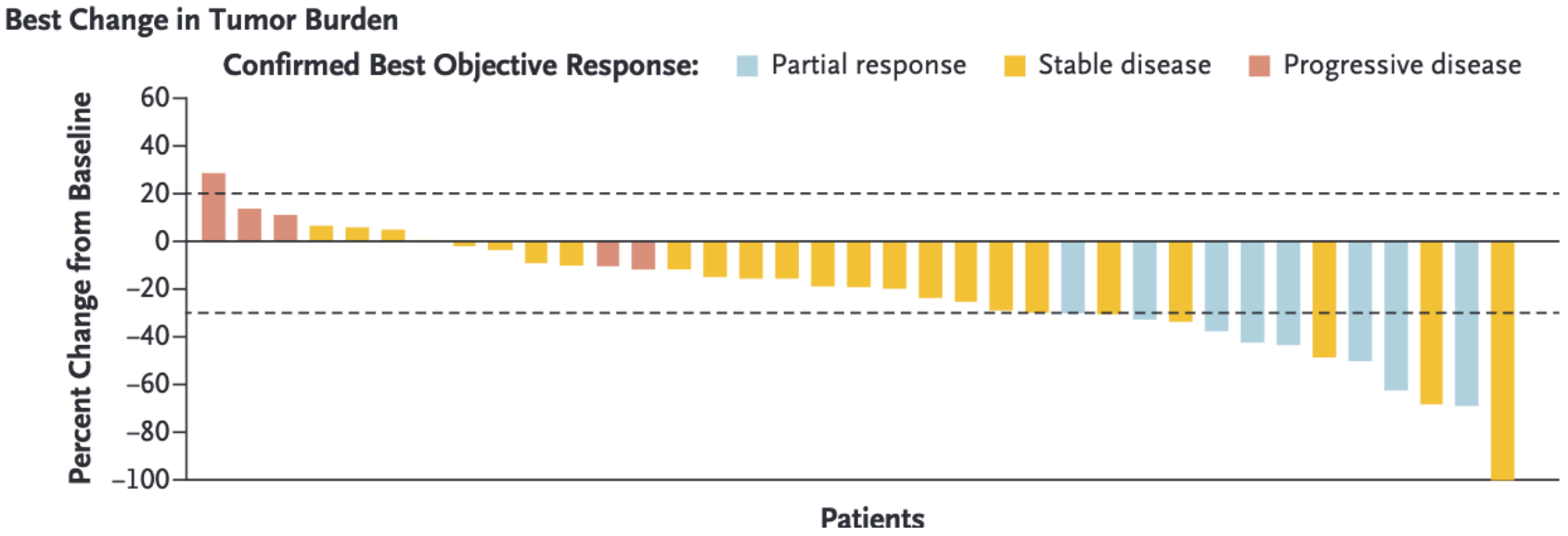
Programs (company)	IND	Target	Phase
Sotorasib/AMG 510 (Amgen)		$KRAS^{G12C}$	Approved
Adagrasib/MRTX849 (Mirati)			
D-1553 (InventisBio)			
JDQ443 (Novartis)			
RG6330/GDC-6036 (Roche)			Clinical
LY3537982 (Eli Lilly)			
BI 1823911 (Boehringer Ingelheim)			
JAB-21822 (Jacobio)			
GFH925 (GenFleet)			
GH35 (Genhouse Bio)			
MRTX1133 (Mirati)		$KRAS^{G12D}$	Preclinical
KRASG12D1-3 (Boehringer Ingelheim)			
RAS(ON) G12D (Revolution Medicines)			
RAS(ON) G13C (Revolution Medicines)		$KRAS^{G13C}$	

Pan-(K)RAS inhibitors

Programs (company)	IND	Target	Phase
RSC-1255 (RasCal Therapeutics)		Pan-RAS	Clinical
BI-pan-KRAS1-4 inhibitors (Boehringer Ingelheim)		Pan-KRAS: $KRAS^{G12D/V}$, KRAS wild-type	
BI-pan-KRASdegrader1 (Boehringer Ingelheim)		Pan-KRAS: $KRAS^{G12C/D/V/A}$, $KRAS^{G13C}$, $KRAS^{A146T/P}$, $KRAS^{Q61E/P}$, KRAS wild-type	Preclinical
RMC-6236 (Revolution Medicines)		Pan-RAS: $KRAS^{G12D/V}$, $KRAS^{G13D}$, $KRAS^{Q61K}$, RAS wild-type	

Hofmann et al. Cancer Discovery 2022

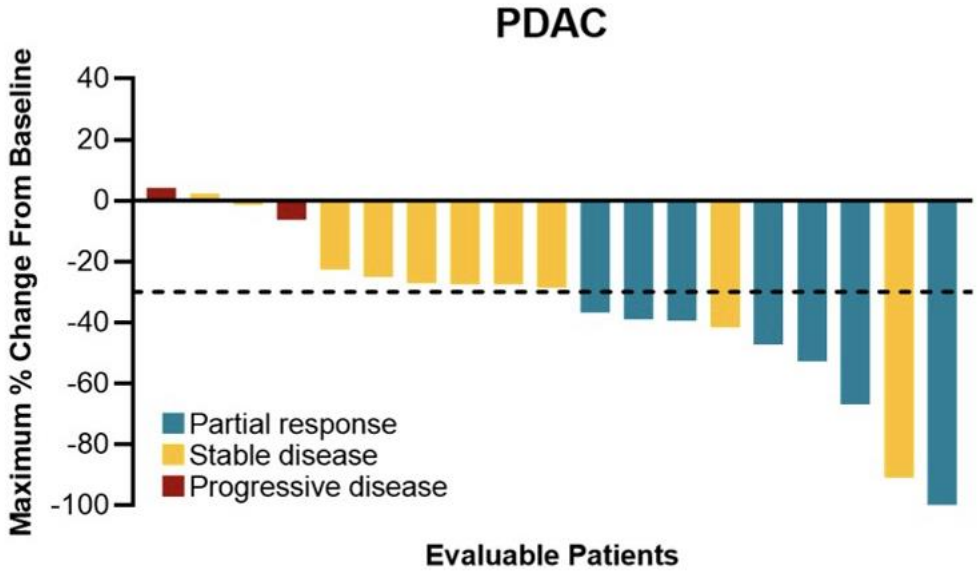
CodeBreaK 100 Phase I/II trial of Sotorasib (AMG510)



ORR: 8/38 pts (21%)
Disease control: 32/38 (84%)
mPFS 4.0 months
mOS 6.9 months

Strickler et al, NEJM 2023

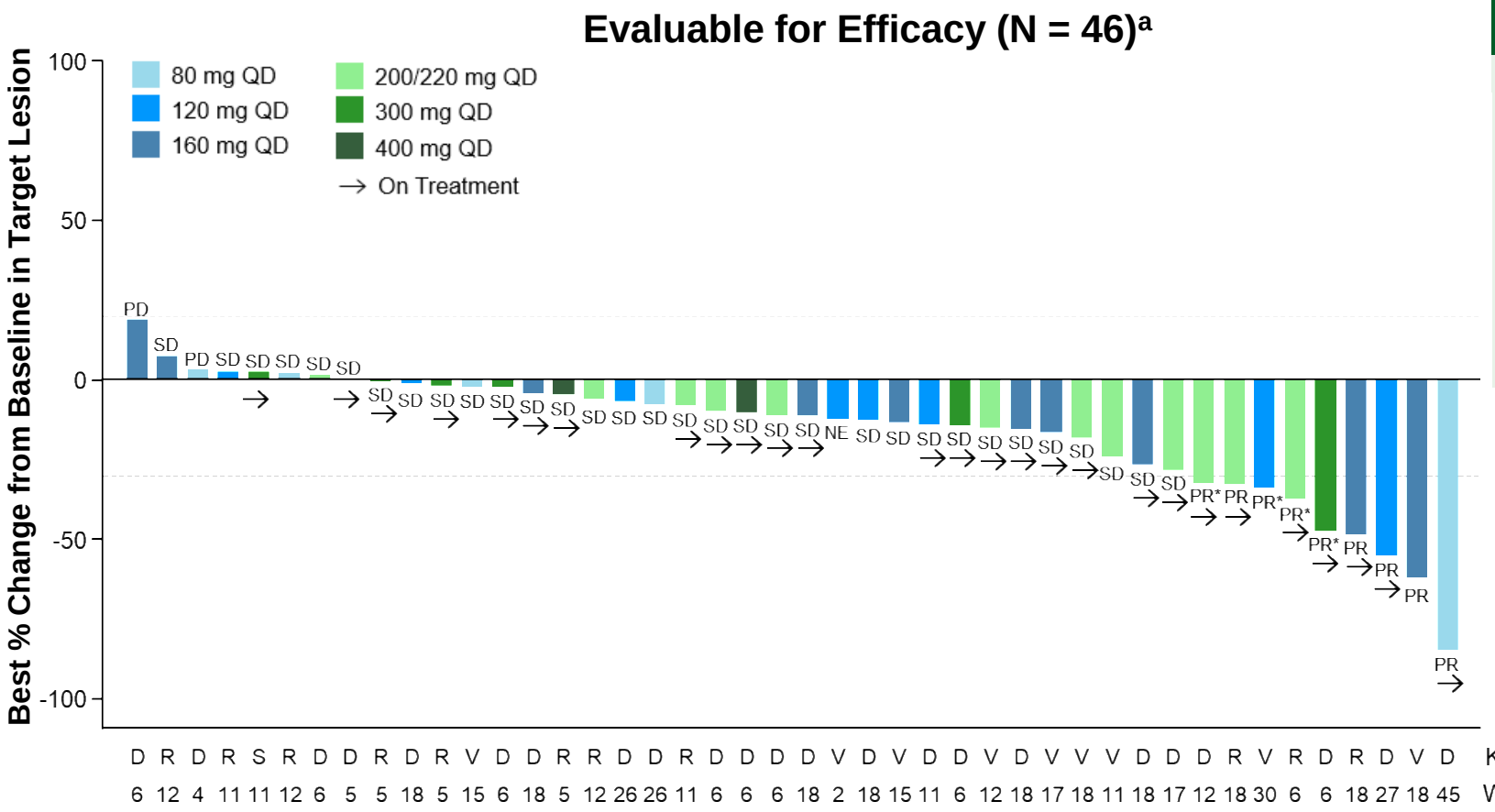
KRYSTAL-1: Phase I/II of Adagrasib (MRTX849)



ORR: 7/21 pts (33%)
Disease control: 17/21 (81%)
mPFS 5.4 months
mOS 8.0 months

Pant et al, ASCO 2023

KRAS^{G12X} PDAC: Best Response



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
PR	9 (20)
SD	31 (67)
PD	3 (7)
NE[b]	3 (7)
ORR, n (%)	9 (20)
Confirmed, n	5
DCR (CR+PR+SD), n (%)	40 (87)

*Unconfirmed PR per RECIST 1.1.

[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.

[b]Two patients died prior to first post-baseline scan; 1 patient had scan after 11 days of treatment and subsequently died due to PD.

Arbour et al, ESMO 2023

- Multiple KRAS inhibitors in early phase drug development

Pathogenic germline variants: inherited gene alterations

- Detected in blood
- Detected in 5.8% of cases, many do not have a family history of cancer

Gene	N (%)
BRCA2	9 (2.62)
CDKN2A	3 (0.87)
PALB2	3 (0.87)
ATM	2 (0.58)
BRCA1	1 (0.29)
MSH6	1 (0.29)
SMAD4	1 (0.29)
TP53	1 (0.29)
MUTYH	1 (0.29)
Total*	21 (5.81)

Consider referring to clinical genetics

Testing of affected individual (proband) where the individual +/- family history meets one of the following criteria. The proband has:

1. Pancreatic cancer age <50, OR
2. Pancreatic cancer age <70, AND

a. Breast cancer age <60, melanoma age <60, OR ovarian cancer, OR
b. One first / second degree relative with pancreatic cancer age <60, OR
c. Two first / second degree relatives with any of breast cancer age <60, melanoma age <60, OR ovarian cancer

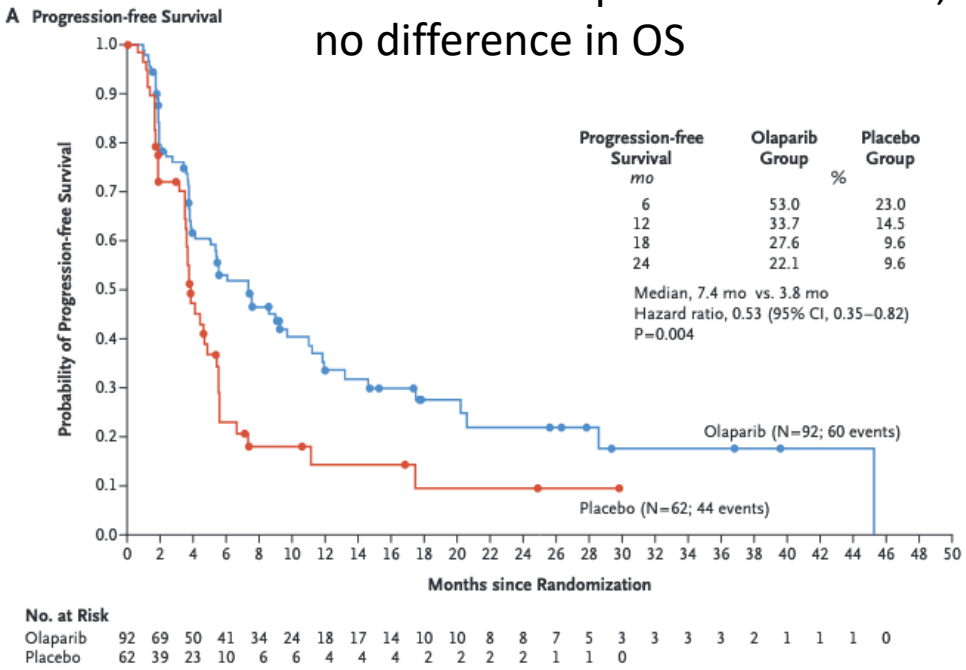
NOTE: If there is a family history of BRCA-related cancers (breast, ovarian, prostate, pancreatic) or history of melanoma and the patient does not meet the above criteria, please consider if they meet testing criteria for the hereditary breast, ovarian or melanoma panels.

Therapeutic targeting of DNA Damage Response

- Maintenance PARPi therapy in platinum sensitive disease

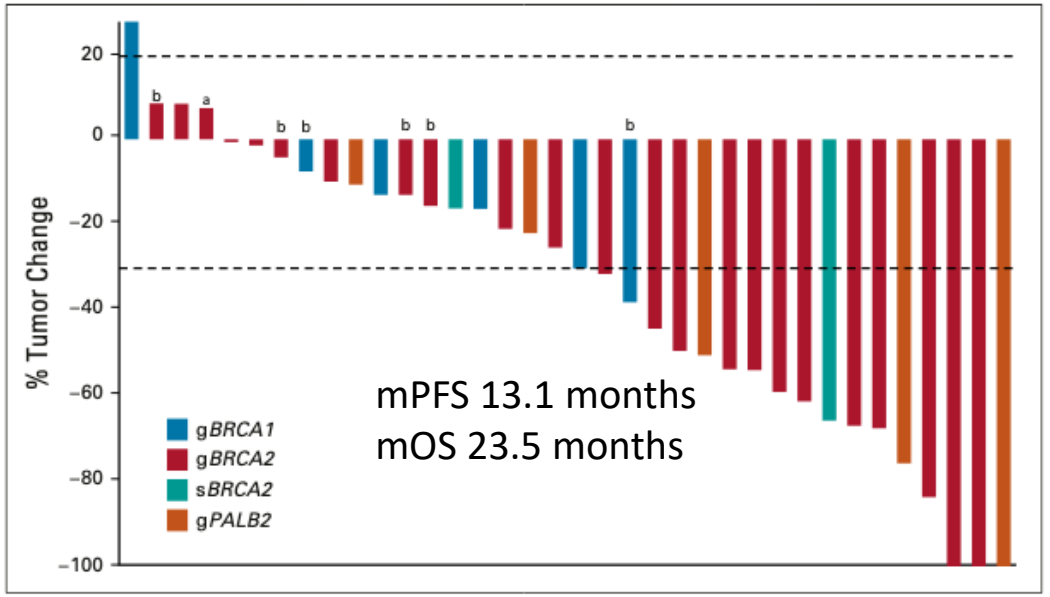
POLO trial: gBRCA1/2, maintenance Olaparib

3.6 months improvement in PFS;
no difference in OS



Golan et al, NEJM 2019
Kindler et al, JCO 2022

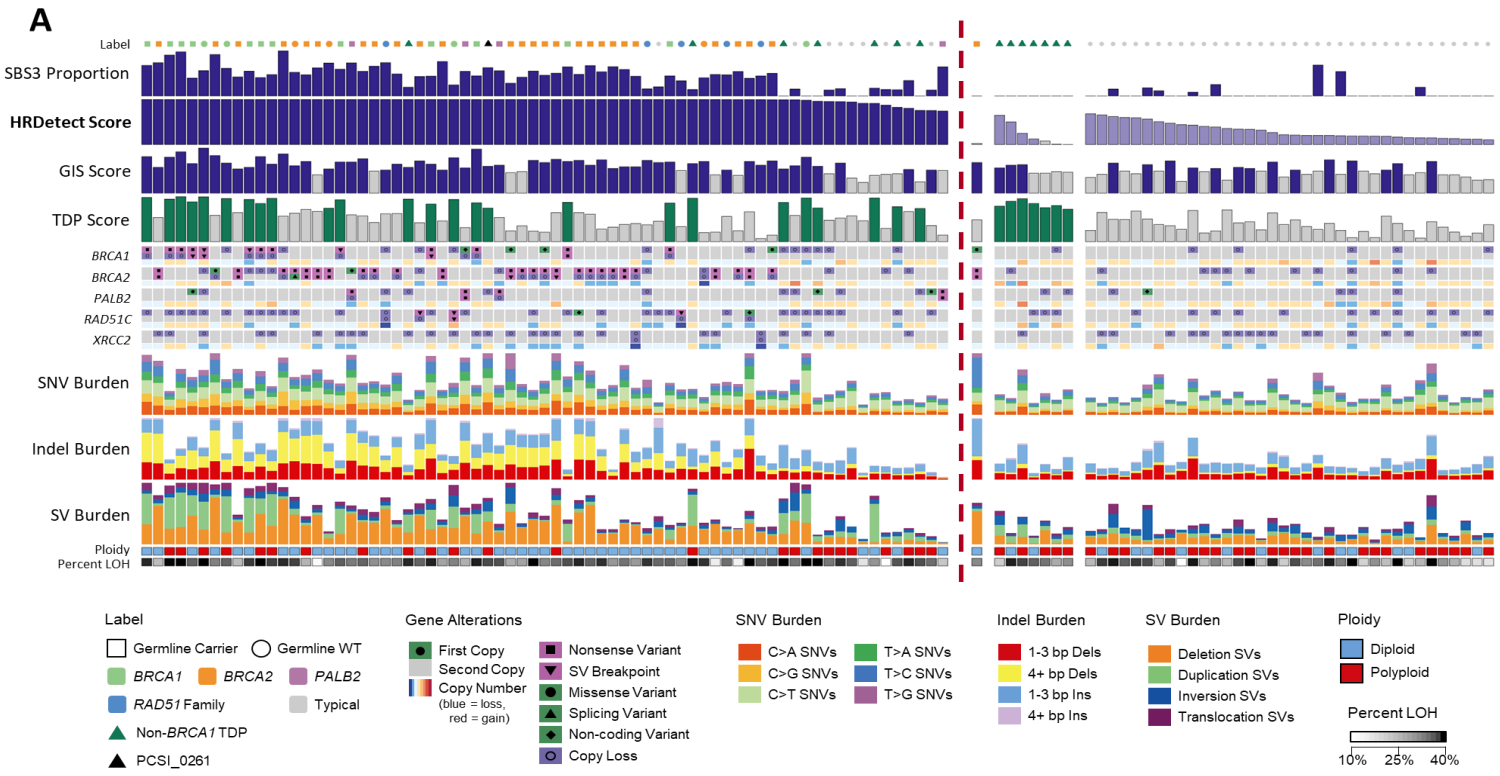
RUCAPANC: g/s BRCA1/2 or PALB2



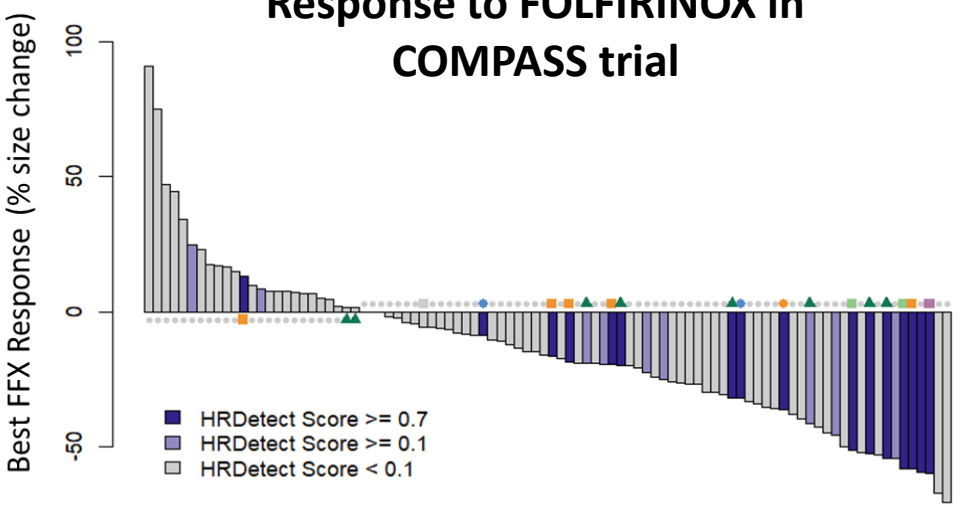
Reiss et al, JCO 2021

~10% of gBRCA1/BRCA2 do not harbour HRD: monoallelic

HRDetect identifies an additional 7% patients with HRD beyond gBRCA1/1 or PALB2



Golan, O'Kane et al, Gastroenterology 2021



Median OS
HRDetect^{hi}/platinum = 16.9 (14.6, 35.5)
HRDetect^{hi}/no platinum = 8.7 (5.85,--)
HRDetect^{lo}/platinum = 9.5 (8.5, 11.6)
HRDetect^{lo}/no platinum = 7.5 (5.4, 9.2)

Precision-Panc PRIMUS-001 trial:

- Does HRD predict response to FOLFOX-A?

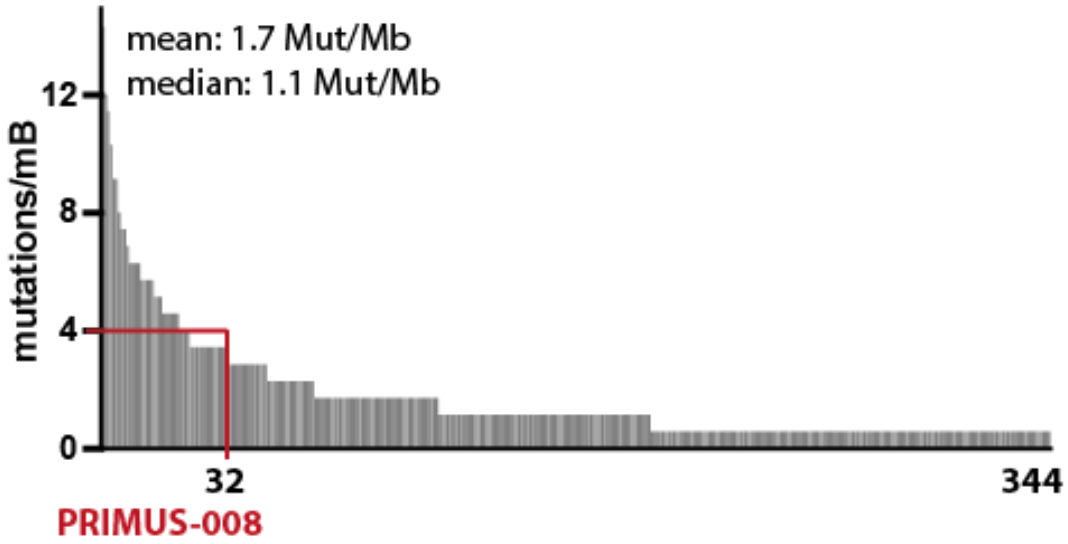
Microsatellite instability, mismatch repair deficiency and tumour mutational burden

- Errors in DNA base pairing are not corrected → microsatellite instability and many mutations.

- Testing for microsatellite instability or loss of mismatch repair proteins recommended for colon and endometrial cancer (Lynch syndrome).

TMB	Mean	1.7	
	SD	1.9	
	MEDIAN	1.1	
	Range	<0.57-114	
	>4 mut/Mb	32	9.3%
	>10 mut/Mb	4	1.2%

PRIMUS-008 (Pemola)



65 year old female

- Presenting symptoms: Abdominal pain
- PMHx: Nil
- Type II DM: No
- Smoking: No
- Family Hx: Mother, brother and cousin have all had bowel cancer

- Baseline CT: locally advanced pancreatic lesion with mediastinal and para-aortic lymph nodes, confirmed avid on FDG PET
- Biopsy: moderately differentiated pancreatic adenocarcinoma
- Ca19.9: 37

- Treatment: commenced Gem/Abraxane on PRIMUS 001

FOR RESEARCH USE ONLY

CANCER RESEARCH UK | PRECISION PANCREAS

This microsatellite unstable sample harbours multiple driver mutations. Key alterations include activating mutations of ERBB2, GNAS and PIK3CA, and loss of function mutations of ARID1A and RNF43. Of note, the tumour is KRAS wild-type.

Estimated tumour cellularity is 40%.

Tumour mutational burden is in the top quartile.

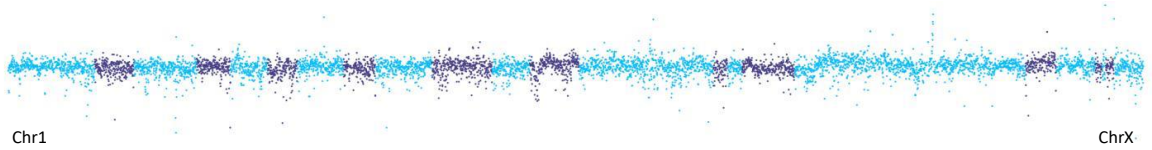
Somatic driver mutations

GENE	Variant	VAF/CNV STATE	GENE	Variant	VAF/CNV STATE
ARID1A	Q758fs	14%	MAP2K4	Arg281X	19%
ARID1A	Arg2158X	14%	PIK3CA	Pro471Leu	23%
ARID2	P1087fs	14%	PIK3CA	His1047Arg	6%
ARID2	K1791fs	27%	PTCH1	Arg1345His	9%
B2M	S16fs	11%	RNF43	G659fs	35%
CDKN1B	G97fs	16%	ROBO2	P1094fs	15%
ERBB2	Arg678Gln	16%	SMARCA4	Thr910Met	6%
GNAS	Arg201Cys	19%	SMARCA4	Gly1162Ser	11%
KMT2D	P2354fs	8%	TGFBR2	P129fs	18%

Pathogenic germline mutations

No pathogenic or likely pathogenic germline variants detected

Genome-wide copy number profile



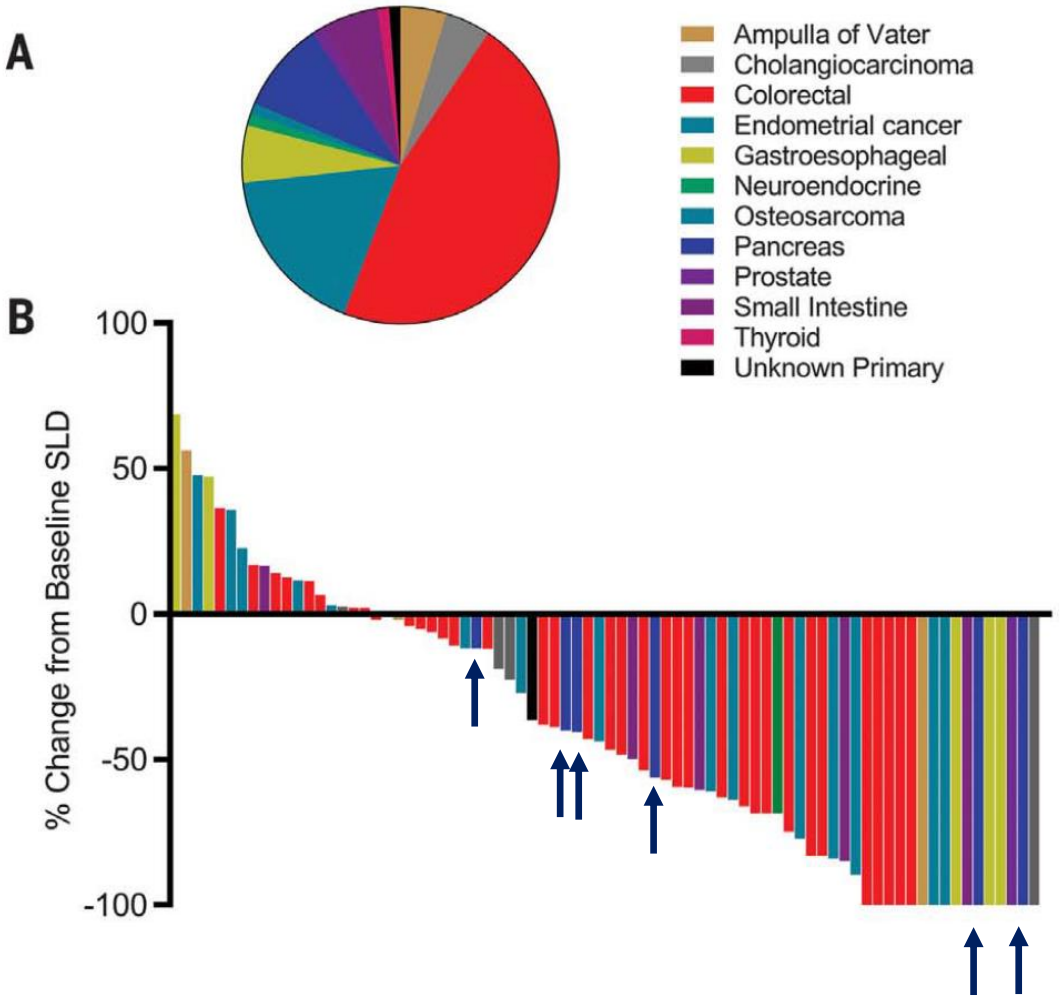
Tumour Mutation Burden
16.6 mut/Mb

Tumour-normal pair genotype match
100%

Microsatellite Instability
UNSTABLE

Sample Contamination
Not detected

Pembrolizumab for refractory non-CRC MSI-H patients (n=86); 8 patients with MSI-H PDAC



Type of Response-no (%)	Pancreas n=8
Complete Response	2 (25)
Partial Response	3 (37)
Stable Disease	1 (12)
Progressive Disease	0 (0)
Not Evaluable[1]	2 (25)
Objective Response Rate (%)	62
Disease Control Rate (%)[2]	75

2 year PFS 53% (95% CI 42-68%)
Median PFS and OS not reached

Le et al, Science 2017

Le et al, NEJM 2017

Genomic Medicine for pancreatic cancer February 2024 and beyond

HRD	MSI / MMRd	KRAS WT	KRAS	Many Others
- Platinum-based chemotherapy - PARPi	- Immunotherapy	- Gene fusions - BRAF - Others	- G12C - Others in development	

- Many exciting agents in development
  - vaccines, antibody drug conjugates, bispecific antibodies
  - treatm,ent within clinical trial if possible

GENOME UK
The future of healthcare

→ **Can we get molecular profile within the NHS?**
  - work in progress in all devolved nations
  - ongoing advocacy and data collection needed for both testing and drug access
  - referral to clinical genetics if <50 years or <70 years and other specified cancer

The role for genomics in pancreatic cancer

A. Sun Set: only applied in research setting and not proven helpful
B. Sun Rise: will be applied regularly for pancreatic cancer patients soon and change practice
C. Total darkness: we don't know
D. Other

Genomics Innovation Alliance

CANCER RESEARCH UK | PRECISION PANCREAS