



University  
of Glasgow

Pancreatic  
Cancer  
UK

# Therapeutic Development for Pancreatic Cancer: Precision-Panc

Pancreatic Cancer UK Meeting  
5 October 2022

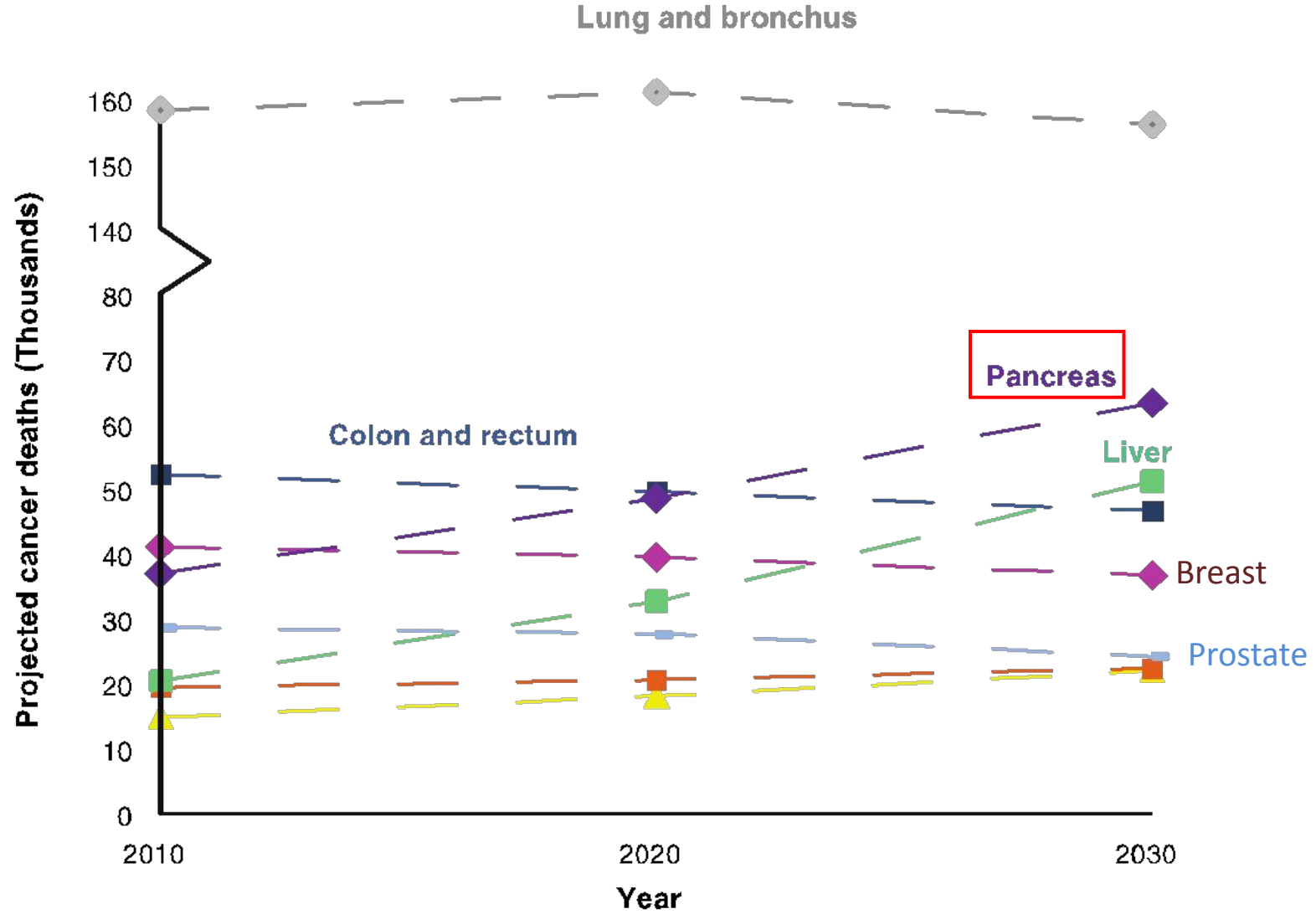
**Fieke E.M. Froeling**  
**Clinical Senior Lecturer & Consultant Medical Oncologist**



PRECISION  
PANC



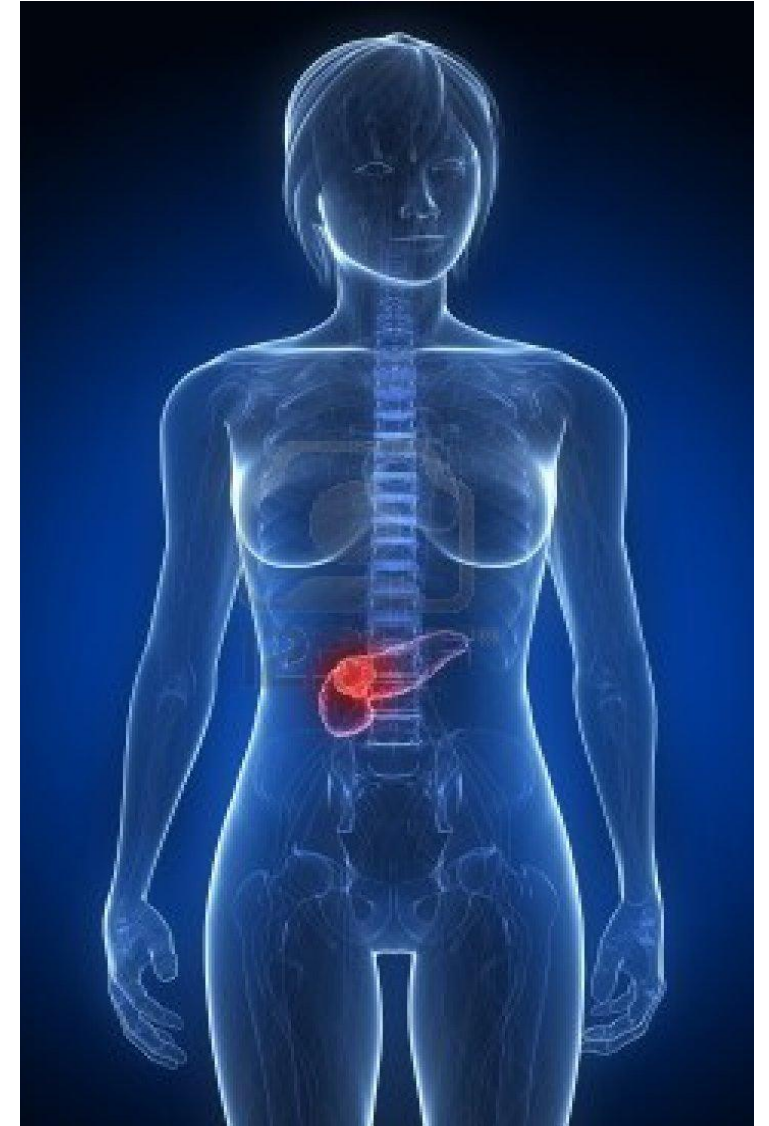
# Pancreatic Cancer: 2<sup>nd</sup> Highest Cause of Cancer Mortality Soon



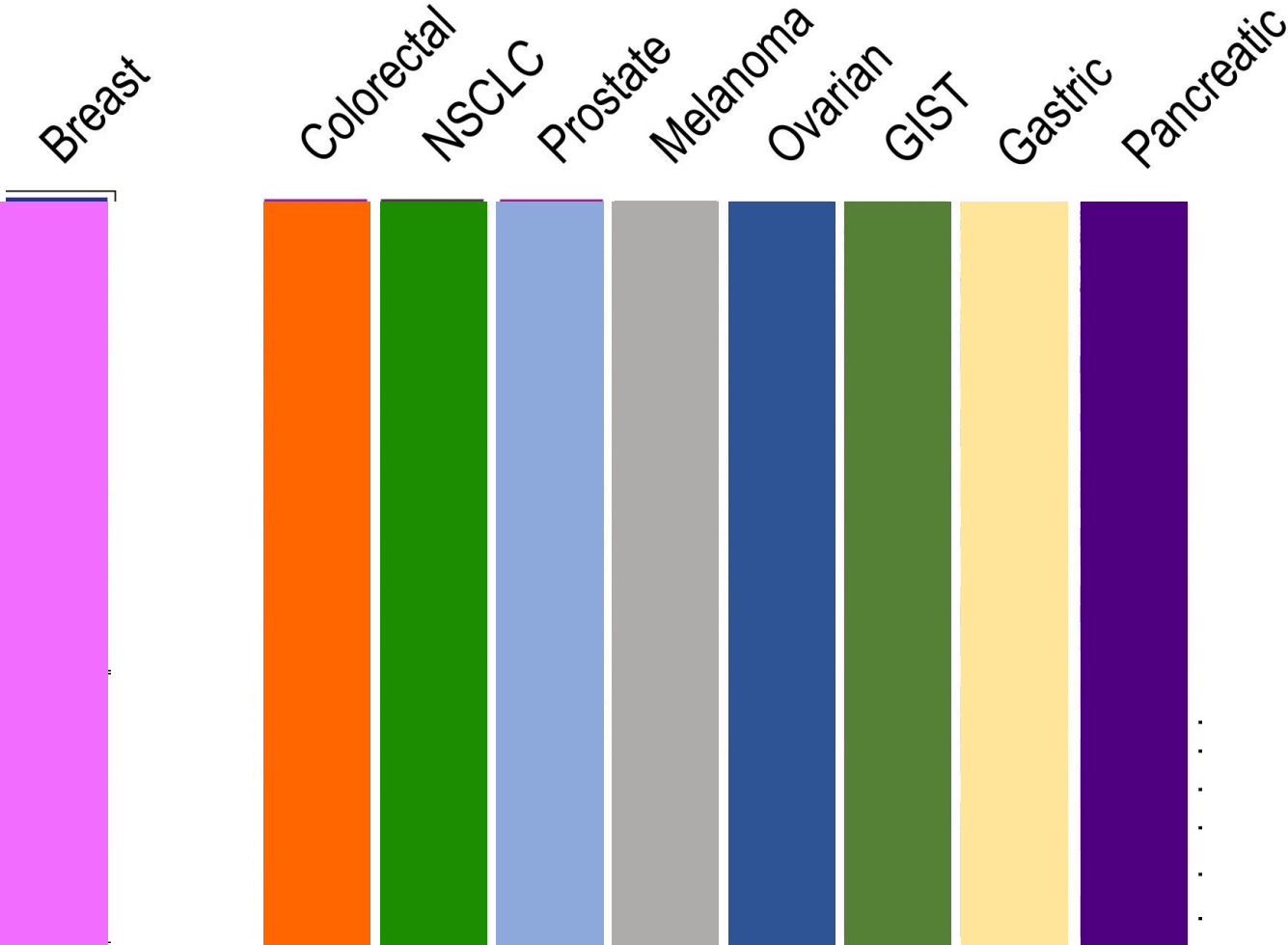
- ◆ Breast
- ▲ Bladder
- Liver and intrahepatic bile duct
- Prostate
- Colon and rectum
- Leukemia
- ◆ Pancreas
- ◆ Lung and bronchus

# Pancreatic Cancer

- 3<sup>rd</sup> cause of cancer death (2<sup>nd</sup> within a decade)
- 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 chemotherapy and targeted therapy.  
However **therapeutic development has been challenging**
- Treatments do work – **significant responses in undefined subgroups**



# Cancer is complex & Heterogeneous





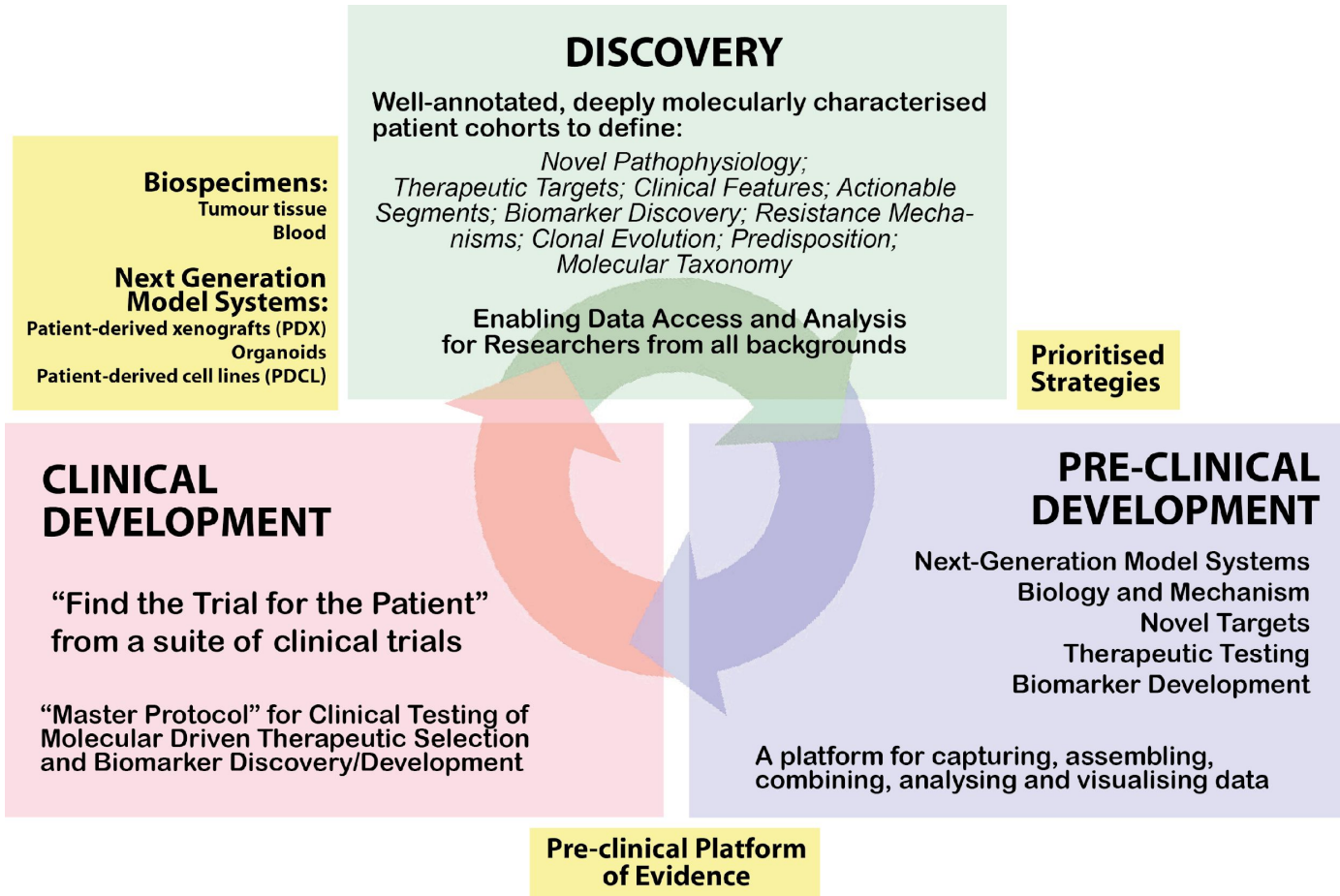
*Transforming  
research and treatment  
approaches  
for Pancreatic Cancer*



**CANCER  
RESEARCH  
UK**

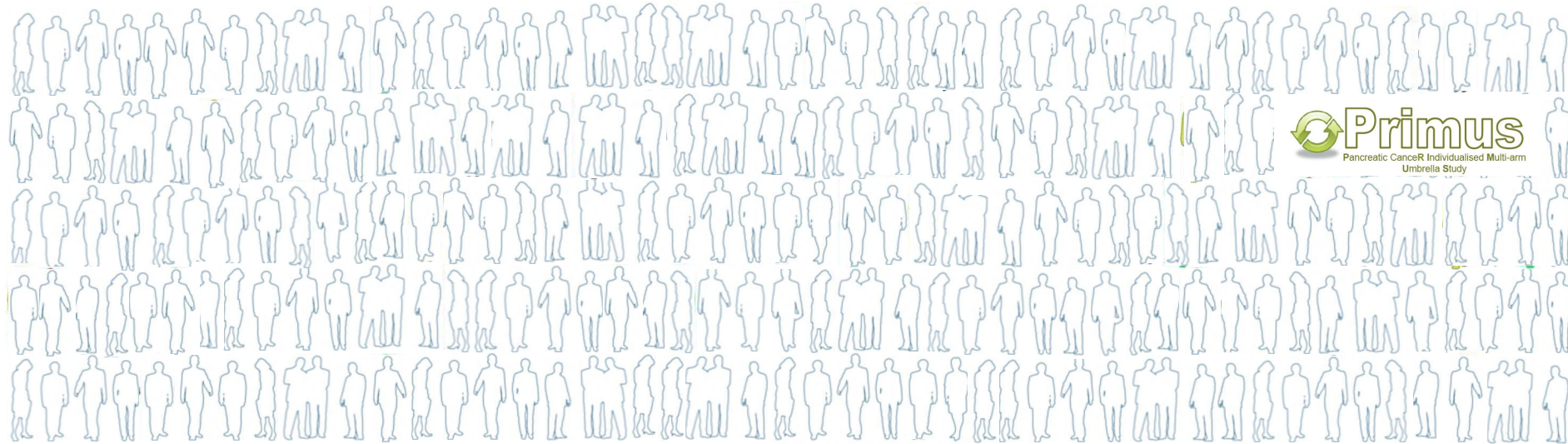
**PRECISION  
PANC**

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



**PIs:** Andrew Biankin  
David Chang  
Owen Sansom  
Jeff Evans  
Juan Valle

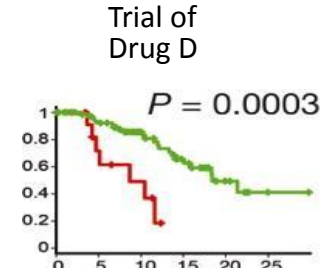
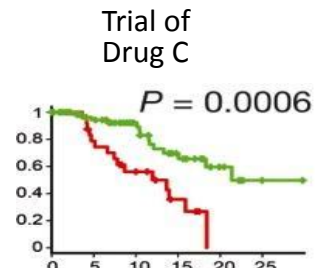
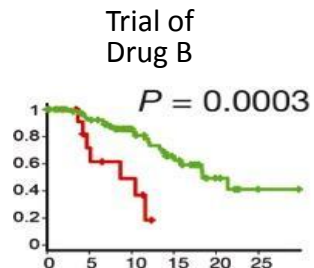
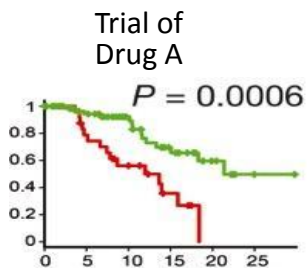
# PRECISION-Panc Delivery of Molecularly Phenotyped Trial Participants



Identifying 100 trial patients with biomarker requires >1000 tests – challenge for Drug Development



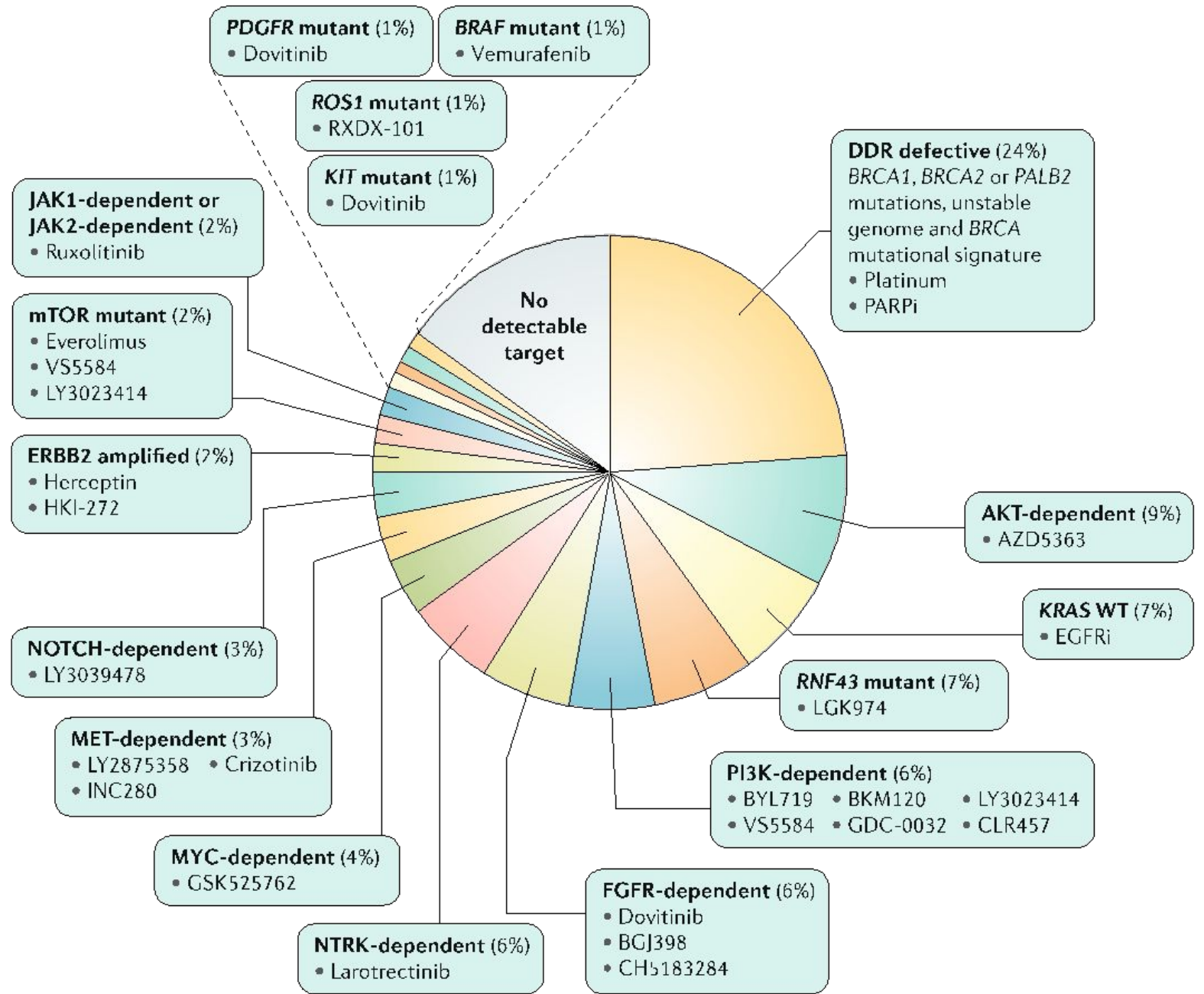
PRECISION-Panc Molecular Phenotypes all candidate targets



Novel  
Targets  
and  
Drugs

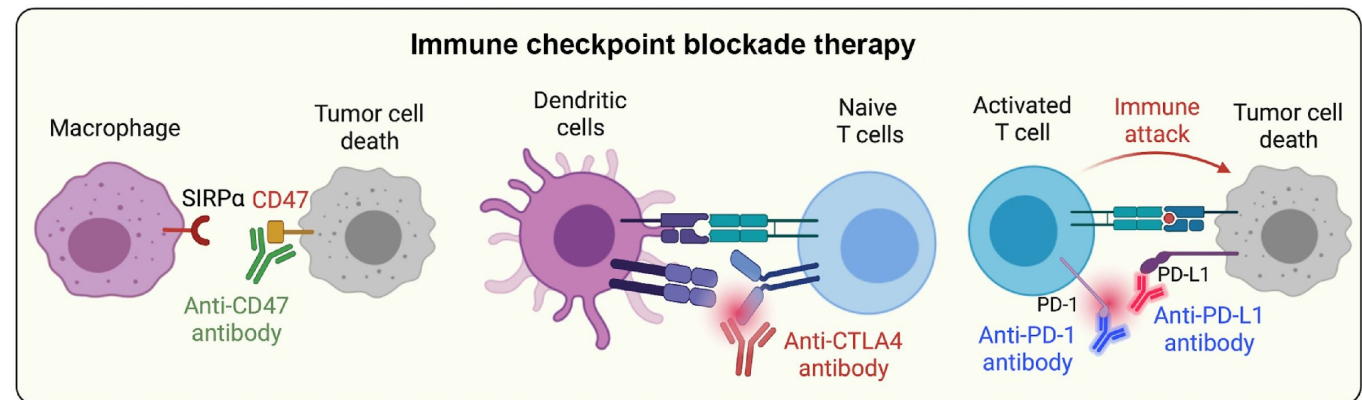
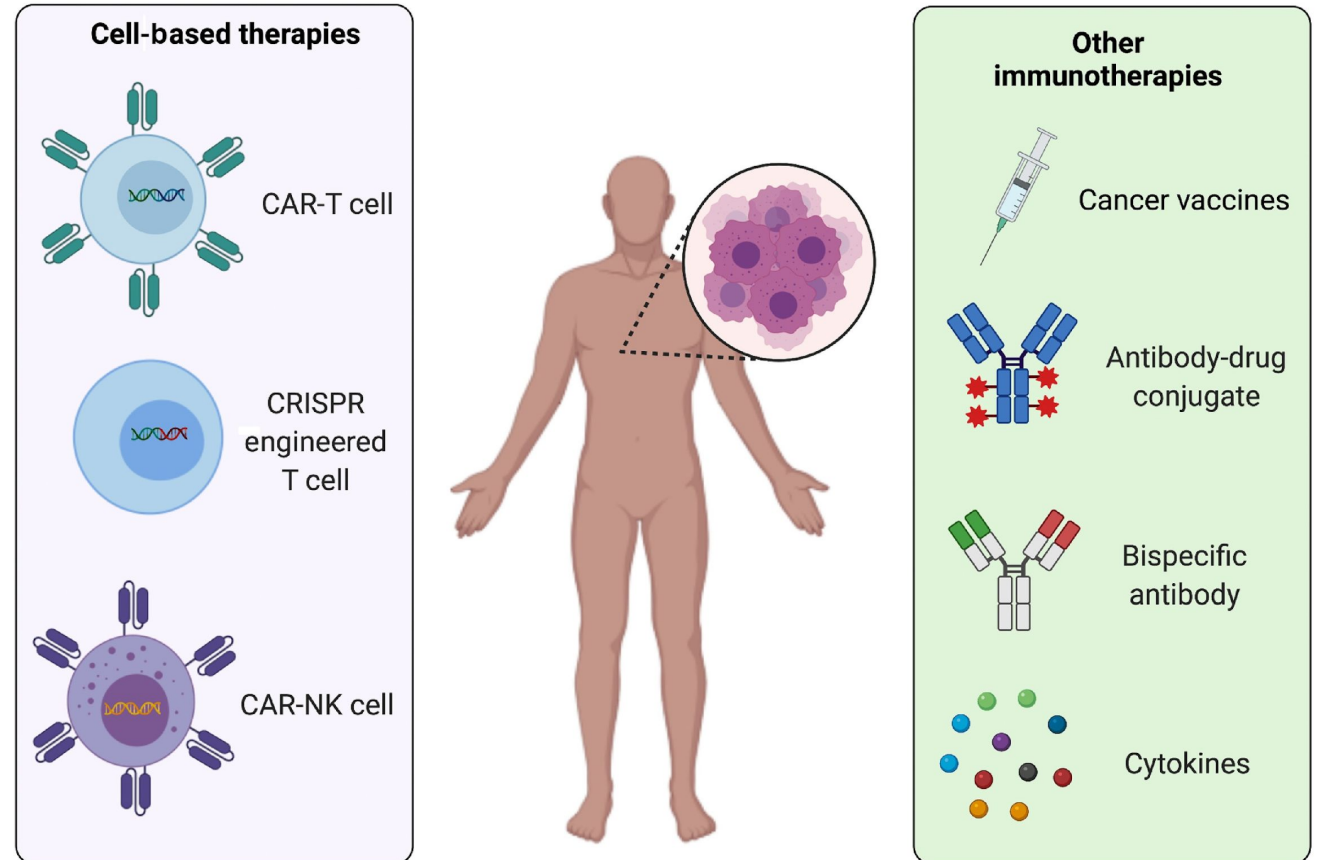


# Pancreatic Cancer “Actionable Genome”



# What about immunotherapy?

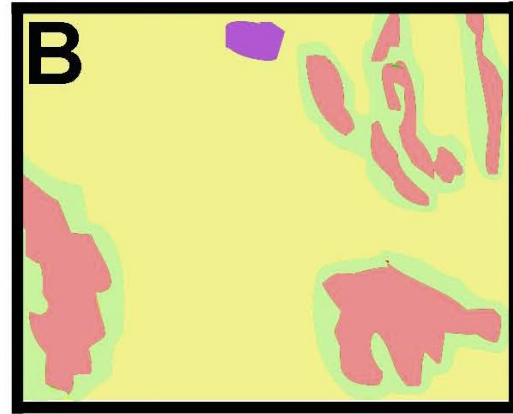
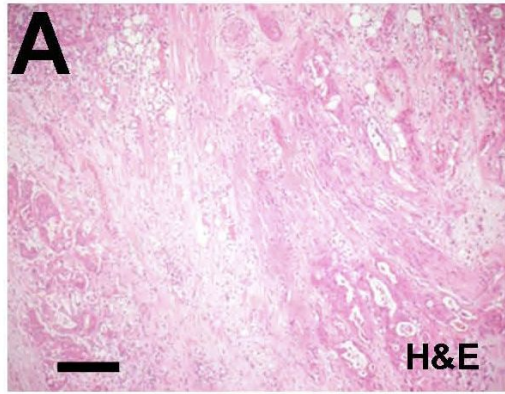
## Approaches for cancer immunotherapy



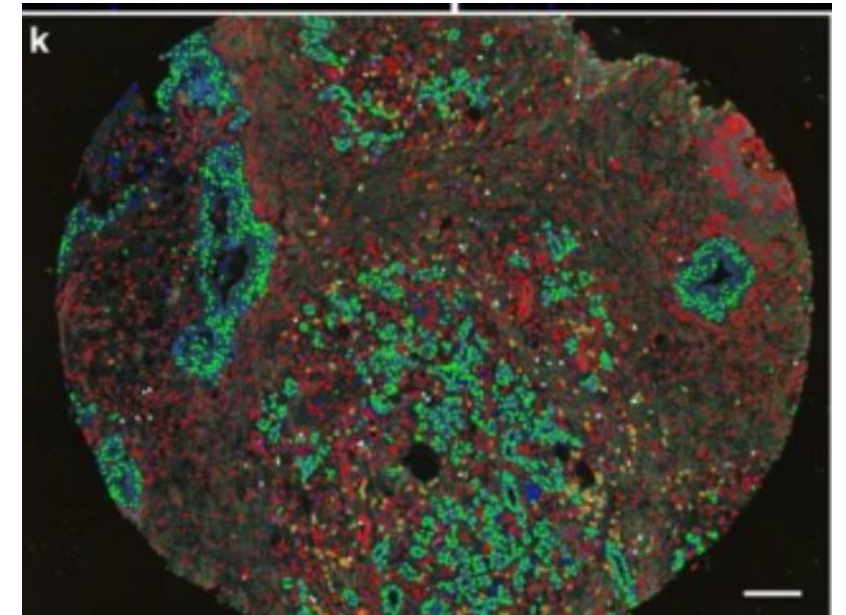
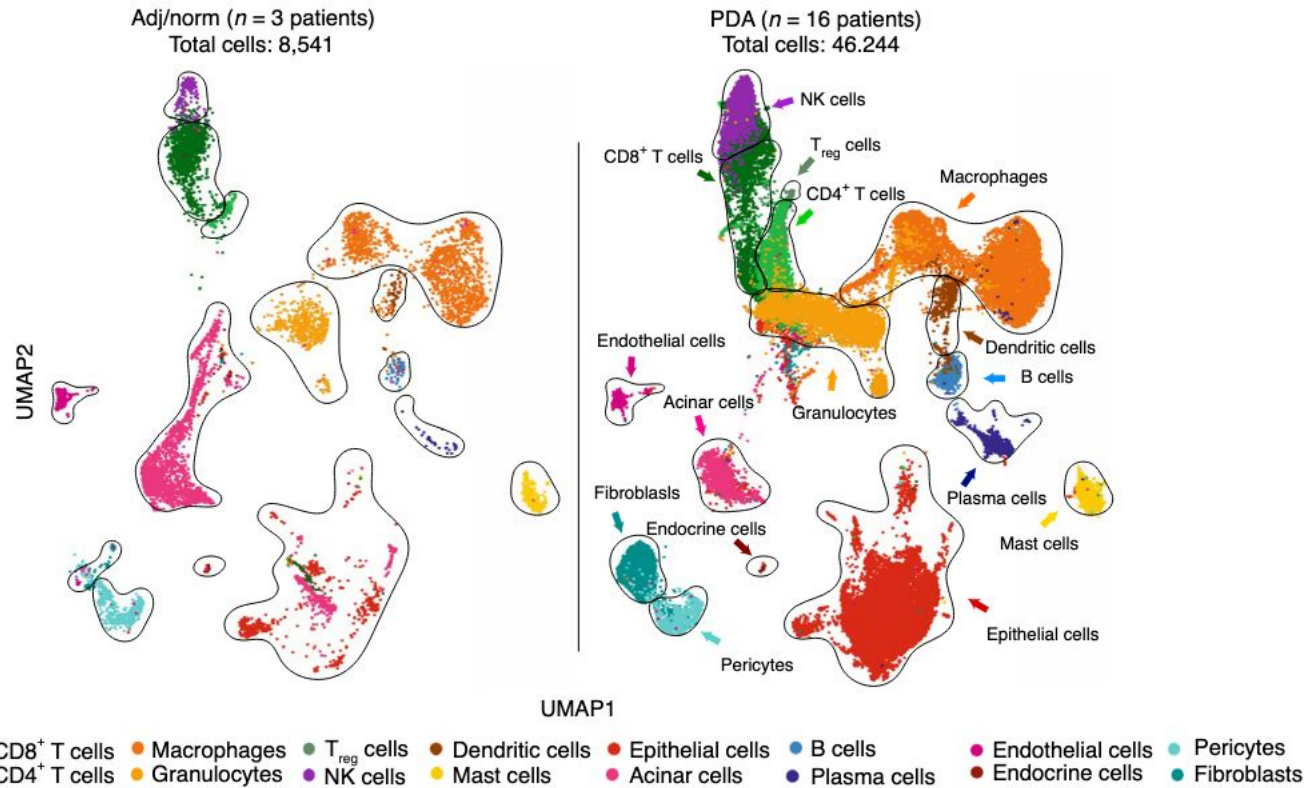
Gupta et al, *Trends in Cancer* 2022



# Pancreatic cancer: heterogeneous, immune evasive, tumour microenvironment



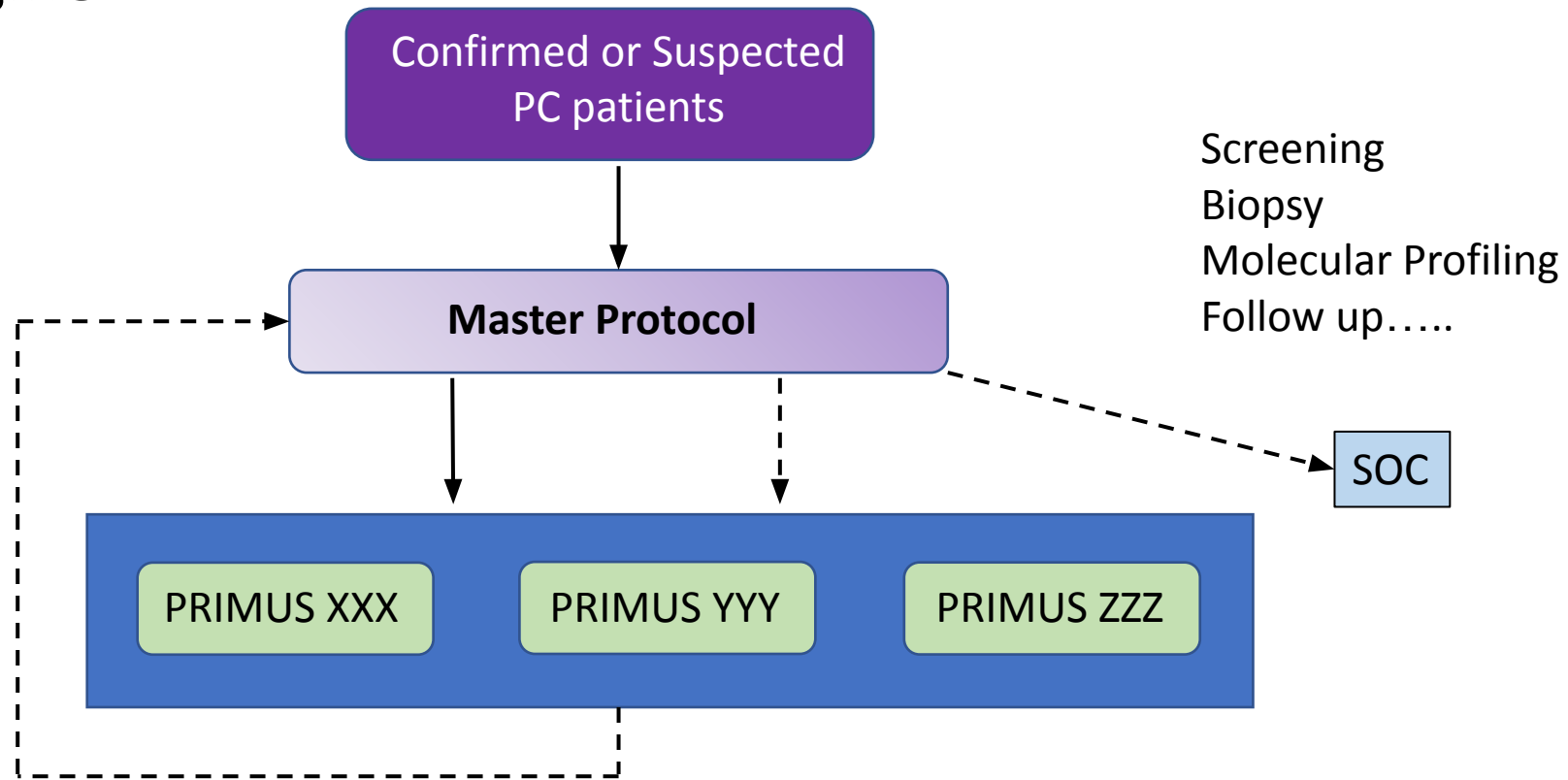
- Pan-stroma
- Juxta-tumoural stroma
- Cancer
- Peri-neural invasion



Carstens et al, *Nature Comm* 2017

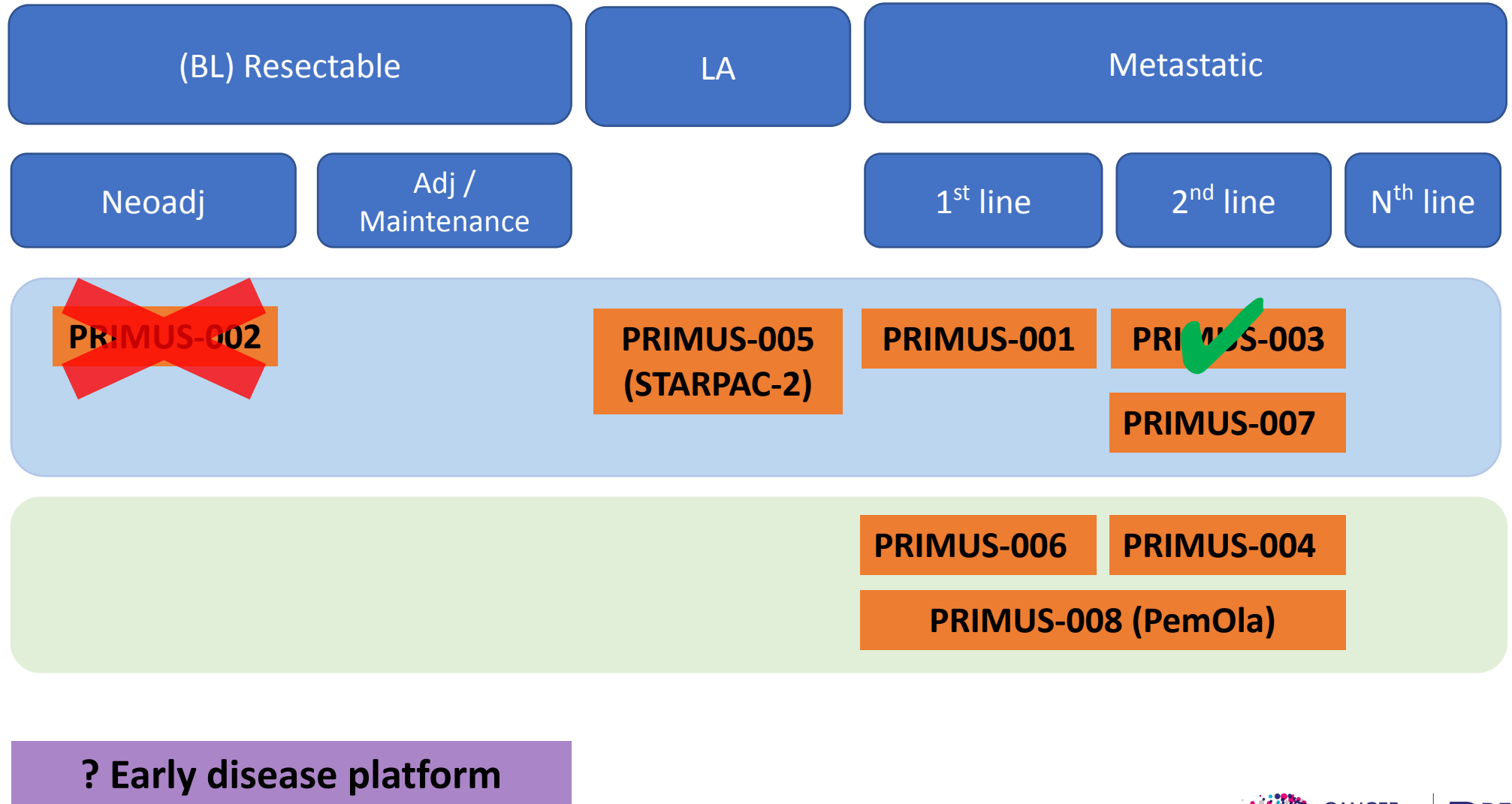
Steele et al, *Nature Cancer* 2020

# The Master Protocol: the central engine...



Lots of opportunities for complimentary, non-competing trials  
Therapeutic and biomarker development  
A platform for all to use  
Pharma & industry buy ins

# Precision-Panc PRIMUS Trials Overview / Opportunities



- **PRIMUS-001:** 1<sup>st</sup> line metastatic (FOLFOX-A Vs AG)
  - Adaptive randomised Phase II/III, up to 460 patients, **ongoing**
  - HRD biomarker
- **PRIMUS-002:** neoadjuvant (FOLFOX-A & AG)
  - Phase II, up to 250 patients, **stopped recruiting**
  - HRD biomarker
- **PRIMUS-003:** 2<sup>nd</sup> line metastatic (CXCR2 + PDL-1)
  - Phase Ib, 20 patients, **completed**
  - Immune & Tumor microenvironment
- **PRIMUS-004:** 2<sup>nd</sup> line metastatic umbrella
  - Appendix 1: Olaparib and AZD6738 - suspended
  - Appendix 2: SRA515 (BRD4) + Olaparib
  - up to 80 patients, **starts Q3 2022**

CIs: Graham & Chang



CIs: Grose & Chang

CI: Evans



CIs: Chang & Froeling



- **PRIMUS-005 / STARPAC-2:** LAPC (AG Vs AG + ATRA)

- Phase II, up to 180 patients
- **Opened April 2022**
- Candidate Biomarkers: FABP5, CRABP2, PTX3

CI: Kocher



- **PRIMUS-006:** 1<sup>st</sup> line metastatic (GEM + Pembro + IMM-101)

- Phase II signal seeking, 80 patients
- Endorsed by CRUK, contract negotiations ongoing
- PS 1(-); PS 2 patients no longer eligible

CIs: Chang & Evans



- **PRIMUS-007:** 2<sup>nd</sup> line metastatic (RXC004, porcupine inhibitor)

- RNF43 mutant tumours, **ongoing**
- Contract negotiations with GPOL ongoing

CI: Valle



CI: Corrie



- **PRIMUS-008 / PemOla:** metastatic (Pembro + Olaparib)

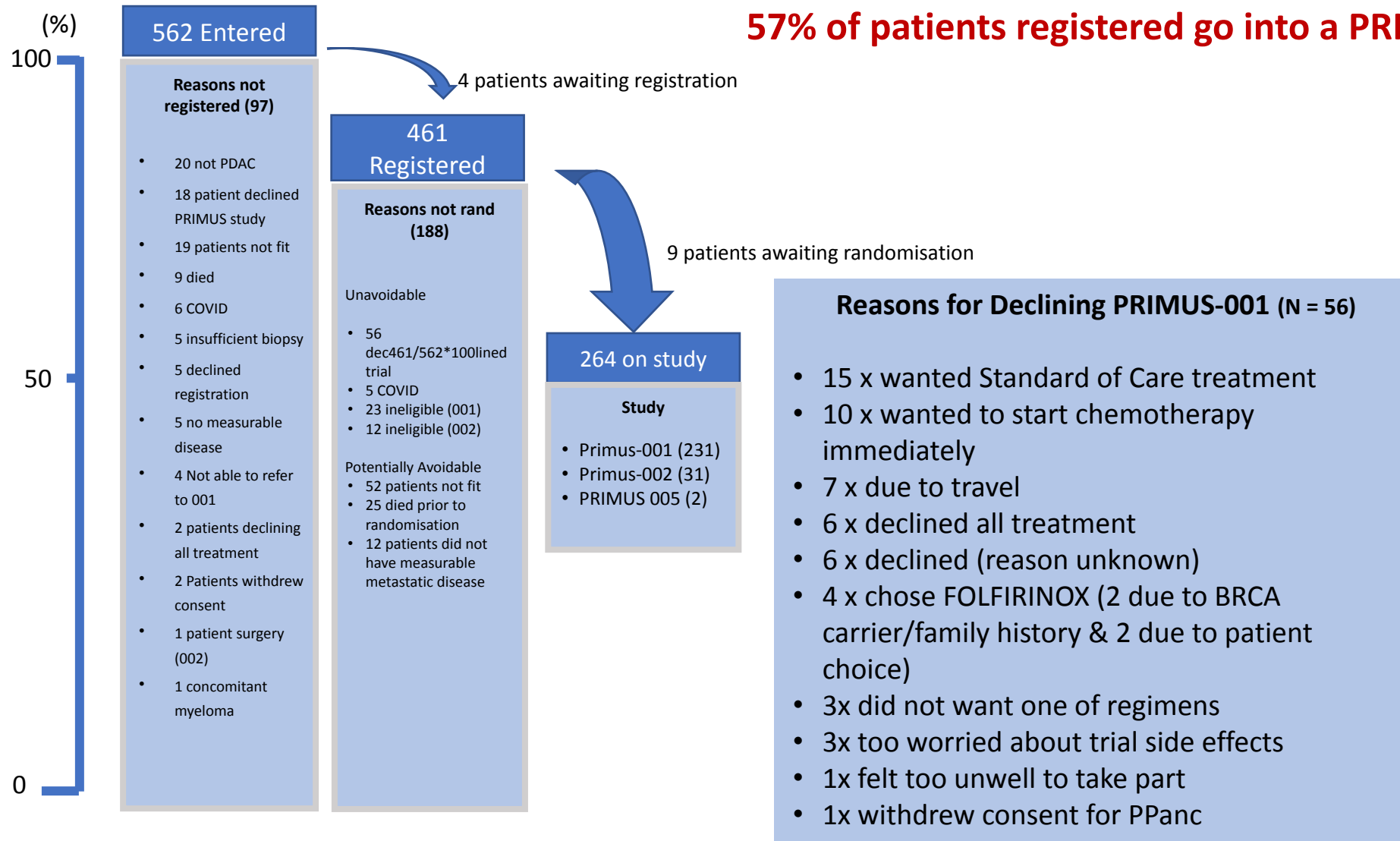
- Phase II signal seeking in TMB  $\geq$  4 mut/mb
- **Starts Q3 2022**



**Investigators from all around the UK**

# Precision-Panc Study Flow diagram 10 August 2022

**82% of patients screened go on to be registered**  
**57% of patients registered go into a PRIMUS study**



# Sequencing Reports

- Molecular reports released ad hoc
- Q4 2022 real time reporting

## 266 reports sent back to sites

- 55 patient letters sent back to site (where sequencing result not possible)
- 16 reports awaiting confirmation of updated consent

☐ Regular Molecular MDT every ~4-6 weeks

☐ Multiomic profiling meeting ~2x / year



Patient ID:  
Tumour type:  
Sample source:  
Sample type:  
Sample date:  
Test requester:

This sample harbours mutations in KRAS and TP53.  
There is deletion of TGFBR2 and disruption of BRCA1.  
There is amplification of NTRK3.  
Estimated tumour cellularity is 40%.  
Tumour mutational burden is in the lower mid quartile.

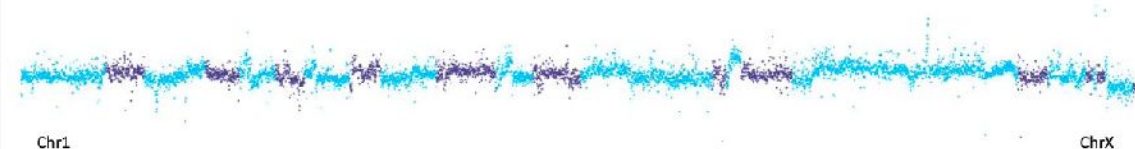
### Somatic driver mutations

GENE	Variant	VAF/CNV STATE
BRCA1	Disruptive SV	Intron 14 breakpoint
KRAS	Gly12Asp	20%
NTRK3	Amplification	9 copies
TGFBR2	Deletion	Homozygous
TP53	Ile162Phe	45%

### Pathogenic germline mutations

No pathogenic or likely pathogenic germline variants detected

### Genome-wide copy number profile



Tumour Mutation Burden  
1.1 mut/Mb

Tumour-normal pair genotype match  
100 %

Microsatellite Instability  
Stable

Sample Contamination  
Not detected



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## Molecular MDT

- Started February 2022
- Regular Molecular MDT every ~4-6 weeks
- Selection of cases:
  - Molecular alteration of interest
  - Patients who are alive
- Open platform for all to attend, participate and learn

**Next MDT: October 2022, date TBC**

fieke.froeling@glasgow.ac.uk

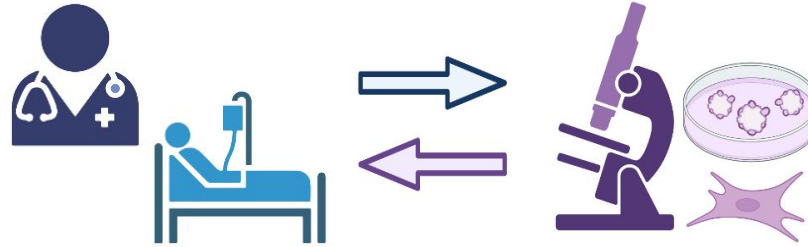




# Precision-Panc: national platform for therapeutic development of PC

## Before

- No molecular testing
- Research biopsies taken during additional invasive procedure
- No UK-wide biomarker-based clinical trial
- Links to basic and translational labs limited



## Now and the future

- Research biopsies taken at diagnostic procedure
- > 200 patients treated within biomarker-based clinical trials, with multiple translational endpoints
- Established UK-coordinated links to basic and translational labs
- Studies developed for molecular subgroups of patients
- Patient groups involved

according to centre





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**Patients  
&  
Families**

**University of Glasgow  
CRUK Glasgow Centre**

David Chang  
Jeff Evans  
Andrew Biankin  
Judith Dixon  
Sarah Bradley  
Ann Shaw  
Jamie Stobo  
Janet Graham  
Fraser Duthie  
Derek Grose  
Robert Jones  
Colin McKay

**Beatson Institute of Cancer Research**

Owen Sansom  
Jen Morton  
Catherine Winchester

**Cambridge University  
CRUK Cambridge Institute**

Duncan Jodrell  
Bristi Basu  
Pippa Corrie  
Tessa Kasia

**The Institute of Cancer Research, London**

Chris Lord

**Manchester University**

**CRUK Manchester Research Institute**

Juan Valle  
Caroline Dive  
Claus Jorgensen  
Ged Brady  
Mairead McNamara

**University of Oxford**

**Cancer Research UK Oxford Centre**

Eric O'Neill  
Somnath Makerjee

**Precision-Panc centres around the UK**

# Precision Oncology Therapeutic Development does not happen in a vacuum, the supporters on this slide are invaluable to the success of the project

Precision-Panc is supported by:

