Precision-Panc: The Next Generation Therapeutic Development Platform for Pancreatic Cancer

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University of Glasgow
Glasgow Royal Infirmary

NIHR Statistics Group Meeting
27th Feb 2019 Birmingham UK
Pancreatic Cancer

• 3rd cause of cancer death (2nd within a decade)
• 5% alive at 5 years
• Average survival ~6 months
• 90% die within a year
• Surgery only cure (~20%)
• Mortality not significantly changed for 50 years
• Chemotherapy modestly effective – but some significant responses in undefined subgroups
• Majority metastatic – chemotherapy and targeted therapy. However therapeutic development has been challenging
“Precision Medicine”
— Matching the Right Treatment to the Right Patient

• Cancer subtype responds to treatment ‘X’

Cancer Diagnosis

TEST

“Key Ingredients”
• Patients
• Drugs
• Selection biomarker
• Molecular assay

1 2 3 4

25% response 18% response 12% response 6% response

AVOID
Toxicity, delay, cost
Challenges of Therapeutic Developments in PDAC

- **Not enough patients**
  - relatively rare cancer, but high mortality
  - Rapid deterioration of PS
  - Need collaboration/consortium approach

- **No drugs made specifically for PDAC**
  - (Apart from PEGPH20)
  - Need to “repurpose” or “rescue”
  - Need to make PDAC “attractive” investment for pharma

- **No strong well validated biomarkers**
  - Needs better understanding of molecular pathology
  - Needs stronger pre-clinical evidence (clear line of sight)
  - Needs novel clinical trial design to seek signals

- **No molecular assay** made specifically for PDAC
  - (Apart from HA)
  - Need custom build
Transforming research and treatment approaches for Pancreatic Cancer

PRECISION-Panc

Improving outcomes through a dynamic research & development platform for Precision Medicine
Precision-Panc UK (Global)

Dynamic therapeutic development platform taking advantage of a continuous loop of discovery, learning, refinement, and implementation.
Precision-Panc Master Protocol

Consent 1
Screening +/- Tumour Biopsy Consent

Contact CTU to obtain Precision-Panc ID

Diagnostic & Research Biopsy
Pancreatic Ca Confirmed

Consent 2
Master Protocol & Molecular Profiling Consent

Contact CTU for Master Protocol Registration

Molecular Profile
Option to re-biopsy

PRIMUS

Clinical CI: Juan Valle
Translational CI: David Chang
The Master Protocol: what does it do

- Confirmed or Suspected PC patients
- Master Protocol
- Screening
- Biopsy
- Molecular Profiling
- Follow up

Different setting
- Advanced, 1st line, 2nd line
- Neoadjuvant
- Adjuvant

Different PS
- Different selection biomarker

Biomarker discovery
- Biomarker validation/development

The Master Protocol: what does it do

- PRIMUS XXX
- PRIMUS YYY
- PRIMUS ZZZ

SOC

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

- Adjuvant
- Biomarker validation/development
Molecular Profiling

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

**Clinical Sequencing (real time)**
1) GPOL Clinical Cancer Genome
2) Integration with histopathology

**Research Sequencing (batched)**
1) WGS (when possible)
2) Transcriptome Sequencing
3) Liquid biopsy (Manchester)
Targeted capture sequencing is the platform of choice for a *clinically-focussed assay*.

<table>
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<th>Variant type</th>
<th>Amp</th>
<th>TCS</th>
<th>WGS</th>
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<table>
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<th>Genomic assay requirement</th>
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<tr>
<td>Detect clinically significant events</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Real-world compatible (FFPE, low input DNA/tumour cellularity)</td>
<td>Yes</td>
<td>No</td>
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<td>Cost efficient (data production, analysis and archiving)</td>
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<td>No</td>
<td>±</td>
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<td>Clinically meaningful turnaround time (sample to report)</td>
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Amp: amplicon-based sequencing  
TCS: targeted capture sequencing  
WGS: whole genome sequencing  
WES: whole exome sequencing
Clinical Cancer Genome

- Bespoke design for PDAC
- Agilent baits
- Illumina sequencing
- ~ 300 - 500X coverage

2. TCS delivers high quality data on all classes of clinically-relevant alteration

- Targetable mutations
- Copy number variants
- Gene fusions
- Microsatellite instability
- Mutation burden
- TSG inactivation
- HR deficiency
- Resistance variants

3. Assay content informed by expert data analysis & curation

- Iterative redesign

New genomic datasets are analysed by GPOL experts to inform regular updating and redesign.

Susie Cooke, Philip Beer
Patient ID:  
Tumour type: Pancreatic adenocarcinoma  
Sample source: 04 FEB 2018  
Sample type: Pancreatic resection (macrodissected)  
Test requester:  

Tumour cellularity was estimated at 60% by pathology and 36% by sequencing. This sample harbours pathogenic mutations in ARAS and TP53, has loss of CDKN2A/2B and SMAD4, amplifications of CDKN1 and AKT2 and a pattern of structural variants consistent with homologous recombination deficiency (HRD). This spectrum of mutations is consistent with Pancreatic Ductal Adenocarcinoma (PDAC). HRD is associated with response to platinum-based chemotherapy or PARP inhibition.

Somatic driver alterations  

<table>
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<th>Alteration</th>
<th>Potential therapies, trials or biomarkers</th>
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<tr>
<td>ARAS</td>
<td>G12V, VAF 18%, 4x high coverage</td>
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<tr>
<td>TP53</td>
<td>Frameshift, VAF 19%, 5x high coverage</td>
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<tr>
<td>SMAD4</td>
<td>Homozygous deletion</td>
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<tr>
<td>CDKN2A/2B</td>
<td>Homozygous deletion</td>
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<tr>
<td>CDKN1</td>
<td>Amplification 3+ copies</td>
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<tr>
<td>AKT2</td>
<td>Amplification 9+ copies</td>
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**Potential clinical trials**
- MEK inhibitor, ERK inhibitor
- CDK4/6 inhibitor
- AKT inhibitor/MTOR inhibitor

Homologous Recombination Deficiency Present?
- Not detected

Microsatellite Instability
- Not detected

Tumour Mutation burden: ≤1.2 mutations per Mb

HMA Typing
- In development

Tumour-Normal pair genotype match
- 100%

Sample Contamination
- None

Passenger mutations and Variants of Unknown Significance: NIL

**Gene panel identified:**
- 16 genes which are known to harbour inherited high prevalence cancer susceptibility alleles.
- Each approximate coverage has been given for the patient's potential epithelial neoplasms in these genes will also be assessed for homologous recombination variants in the table below.

If you have any questions or require any further assistance with the interpretation of any of the results contained within this report, please contact Oncology or Diagnostics at GPOL.

**Genes included in sequencing and types of alterations reported:**
- ACHREB, ACHREB2, AHER, AHERB, AHERC, AHERD, AHERE, AHERF, AHERG, AHERH, AHERI, AHERJ, AHERK, AHREL, AHERM, AHERN
- ACHREB, ACHREB2, AHER, AHERB, AHERC, AHERD, AHERE, AHERF, AHERG, AHERH, AHERI, AHERJ, AHERK, AHREL, AHERM, AHERN
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CANCER RESEARCH UK  PRECISION CANCER
Tissue: Why EUS-guided biopsy?

• There is always a primary to biopsy (any clinical stage)
• May select patients with low volume metastatic disease (better PS)
• Same setting as ERCP
• Can biopsy some of the liver and nodal lesions at the same time
• Additional research samples can be obtained at the same time
• If we can sequence this, should have no issues with perc biopsy
• Enables precision medicine approach
Study progress: low failure rate

(QC N = 0)

(failure)
Precision-Panc Clinical Trials

• **PRIMUS-001**: 1\(^{st}\) line metastatic (FOLFOX-A Vs AG)
  - Adaptive randomised Phase II/III, up to 460 patients, ongoing
  - DDR biomarker

• **PRIMUS-002**: neoadjuvant (FOLFOX-A & AG)
  - Phase II, up to 250 patients, starts March 2019
  - DDR biomarker

• **PRIMUS-003**: 2\(^{nd}\) line metastatic (CXCR2 + PDL-1)
  - Phase Ib, 20 patients, complete
  - Immune & Tumor microenvironment

• **PRIMUS-004**: 2\(^{nd}\) line metastatic umbrella
  - Currently 1 appendix (2 cohorts), 90 patients, start Q2 2019
  - PARPi + ATRi combination overcome acquired platinum resistance

• More under plan (neoadjuvant & adj/maintenance umbrella)
  - Preclinical Therapeutic Testing Board
  - NCRI CSG Subgroup / Master Protocol Strategy Board
Synthetic Lethality as Therapeutic Strategy in Cancer

McLornan et al NEJM 2014
PRIMUS-001: A randomised adaptive Phase II/III study of FOLFOX-A versus AG in metastatic PC, with integrated DDR biomarker evaluation.
PRIMUS-002

An umbrella phase II study examining two neo-adjuvant regimens (FOLFOX-A and AG) in resectable and borderline resectable Pancreatic Ductal AdenoCarcinoma (PDAC), focusing on biomarker and liquid biopsy development.

Oncology CI: Derek Grose
Surgical/Endoscopy CI: Colin McKay
Translational CI: David Chang

- DDR BM evaluation
- Clonal evolution
- Intra-tumoral heterogeneity
- Resistance mechanism
- Feasibility of liquid biopsy
PRIMUS-004: 2nd line Metastatic Umbrella

Patients with metastatic pancreatic cancer, progressed on or intolerant to first-line chemotherapy
Registered in Precision-Panc Master Protocol and DNA available for biomarker analysis
Multi-centre, multi-arm, non-comparative phase II

pre-specified target biomarker subgroup

Appendix 1
post platinum-based chemotherapy
HRRm status
Olaparib+AZD6738

Appendix 2
Appendix 3
Appendix ...

Additional appendices to be added

All appendices Bayesian predictive probability design, assessing response after 10/ 20/ 30/ 40 patients:
- >87% power to detect response rates of >25%, but allows early stopping if response rates are low (<10%).
- Primary endpoint: ORR
- Secondary endpoints: PFS, OS, safety
- Exploratory endpoint: correlation of ORR, PFS and OS to molecular profile and hypothesised biomarkers

Translational CI: David Chang
Clinical CI: Fieke Froeling
PRIMUS-004 (Appendix 1)

1st Line Chemotherapy Metastatic PC

Metastatic PC

Primary Biomarker Stratification

1. HRRm Status
2. Best Response to Platinum

PRIMUS-001 (FOLFOX-A)

Platinum Regimen (Non-PRIMUS)

2nd Line Chemotherapy Metastatic PC

Response to Platinum

CR
PR
SD
at least 50% CR/PR in each cohort

HRRm +ve
Olaparib + AZD6738

HRRm -ve
Olaparib + AZD6738

Oncology Lead: Mairead McNamara
Translational Lead: Stephan Dreyer
Randomised to PRIMUS-001 (30)
10 Beatson WoSCC
  5 Christie
  4 Addenbrookes
  4 Bristol
  3 Aberdeen
  3 UCLH
  1 Royal Marsden
  4 being considered

Screened (98)
40 GRI
14 Aberdeen
12 Addenbrookes
10 Christie
  8 UCLH
  8 Bristol
  5 Royal Marsden
  1 Manchester Royal

Registered (69)
26 GRI
10 Addenbrookes
  9 Christie
  8 Aberdeen
  7 UCLH
  7 Bristol
  2 Royal Marsden

Considered for PRIMUS-001 (69)

Reasons not registered (26)
Unavoidable
• 7 patients did not have PDAC
• 2 patients had non-diagnostic biopsy
• 2 patients declined registration (reasons not recorded at site)
• 1 patient declined PRIMUS study therefore not registered

Potentially Avoidable
• 5 patients not fit
• 4 did not have measurable disease
• 4 patients died prior to randomisation

Reasons not rand (35)
Unavoidable
• 10 declined trial (reasons next slide)
• 2 ineligible
  ▪ 1 previous oxaliplatin
  ▪ 1 serious concurrent illness

Potentially Avoidable
• 14 patients not fit
• 5 patients did not have measurable metastatic disease
• 4 died prior to randomisation
Reasons for Declining PRIMUS-001 *(N = 10)*

- 2 x wanted to start chemotherapy immediately
- 2 x wanted Standard of Care treatment
- 2 x due to travel
- 2 x declined all treatment
- 1 x chose FOLFIRINOX due to gBRCA carrier
- 1 x chose single agent chemotherapy
Lessons Learnt...

• Be as patients and clinicians friendly as possible
  ▪ Patient pathway
    o Embed research activities into SoC
    o Shorten & simplify
    o Attractive and available trial options (stages & PS)
    o Novel trial designs (adaptive with integrate biological Qs)
  ▪ Tissue pathway
    o Use “surplus”
    o Use exist structure/pathway if possible
    o Bring cyto/pathology & biorepository together
    o Clinically meaningful TAT
• Be pragmatic & realistic (clinical Vs research)
• Help each site set up (strength vs challenges)
• Identify “champions” from each specialty @ each site
• Start small, then grow...
• Ensure “key ingredients” of precision medicine are secured
Glasgow Precision Oncology Laboratory

Andrew Biankin
David Chang
Susie Cooke
Judith Dixon-Hughes
Anna Morris

Sarah Allison
Maja Bailey
Dario Beraldi
Holly Brunton
Giusy Caligiuri
Euan Cameron
Ricky Cunningham
Stephan Dreyer
Lisa Evers
Amanda Ewing
James Stuart

Eirini-Maria Lampraki
John Marshall
Brian McDade
Daniel McElroy
Liz Musgrove
Viola Paulis-Hock
Donna Ramsay
Rosie Upstill-Goddard
Derek Wright
Donna Ramsay
Paul Grimwood

Search: University of Glasgow
Glasgow Royal Infirmary

Colin McKay
Ross Carter
Euan Dickson
Nigel Jamieson
Fraser Duthie
Lyn Smith
Janet Graham

Queen Elizabeth University Hospital

Nicola Williams
Paul Westwood
Clinical Genetics lab
Christine Whilshire
GGC Biorepository

Derek Grose
David McIntosh
Abdulla Al-Adhami
Elspeth Cowen
Kimberley Booth
Endoscopy staff
Patients and families

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CRUK Glasgow Centre
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David Chang
Jeff Evans
Susie Cooke
Fraser Duthie
Judith Dixon
Anna Morris
Janet Graham
Derek Grose
Nigel Jamieson
Robert Jones
Colin McKay

Beatson Institute of Cancer Research
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Jen Morton
Catherine Winchester

Cambridge University
CRUK Cambridge Institute
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Bristi Basu
Pippa Corrie
Tessa Kasia

Glasgow CTU
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Jamie Stobo
Sarah Bradley

Manchester University
CRUK Manchester Research Institute
Juan Valle
Caroline Dive
Claus Jorgensen
Ged Brady
Mairead McNamara
Derek O'Reilly

University of Oxford
Cancer Research UK Oxford Centre
Eric O’Neill
Somnath Makerjee

The Institute of Cancer Research, London
Chris Lord

Precision-Panc centres around the UK
Thank you for your attention
DNA / RNA Yield sufficient for NGS
The discoverable space: novel cancer genes

Current knowledge of cancer genes is close to saturation

Undiscovered cancer genes:
- Biologically weak drives
- Too rare for prognostic models
- Unattractive therapeutic targets

Assay design: defining content

Commercial and LDT cancer panels show **poor concordance** in gene selection, likely due to lack of objective methodologies.

Panel genes overlap:
- **All 8 panels**: 159
- **7 of 8**: 45
- **6 of 8**: 57
- **5 of 8**: 60
- **4 of 8**: 74
- **3 of 8**: 223
- **2 of 8**: 122
- **1 of 8**: 344

*n=1,084 genes*

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2nd Highest Cause of Cancer Mortality Soon

Rahib et al Cancer Res 2014

![Graph showing projected cancer deaths by year and site. The graph indicates that prostate cancer will become the 2nd highest cause of cancer mortality soon.](image-url)