Early Phase Combination Studies and Working with Industry

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Disclosures

- **Honoraria / Consultancies / Speaker:**

  Astra Zeneca

  Bayer

  Bristol Myers Squibb

  Celgene

  Clovis

  Genentech

  Glaxo Smith Kline

  Jennerex / Transgene

  Karus Therapeutics

  Otsuka

  Roche

Overview

- Combination Studies arising from:
  - ideas from our own laboratory or exploratory clinical studies
  - ideas from industry / academic collaborators' laboratory or exploratory studies
  - ideas from the published literature
- Can be commercial or academic studies
- Not necessarily a CTIMP – can be biomarker studies

Principles

- The idea / proposal should be:

  based on a sound rationale - the agents, the combo, the tumour type(s), the clinical setting

  have supporting pre-clinical evidence

  must be feasible and deliverable

  must be attractive to patients, collaborators, regulators, ***and the funders***

  have a development path / strategy

Principles

- **Early phase (combination) studies**

  optimal dose and schedule

  proof of concept / mechanism

  PK and PD….hitting the target, influencing the biology

  refine / enrich patient population

  allow stop : go decisions to reduce phase III attrition (and resources)

COMBINATIONS ALLIANCE

4
STUDIES IN SET UP

136 EXPRESSIONS OF INTEREST RECEIVED

27 NAC submissions

CLINICAL STUDIES ONGOING 10

10
PRECLINICAL STUDIES ONGOING

1
FOCUS

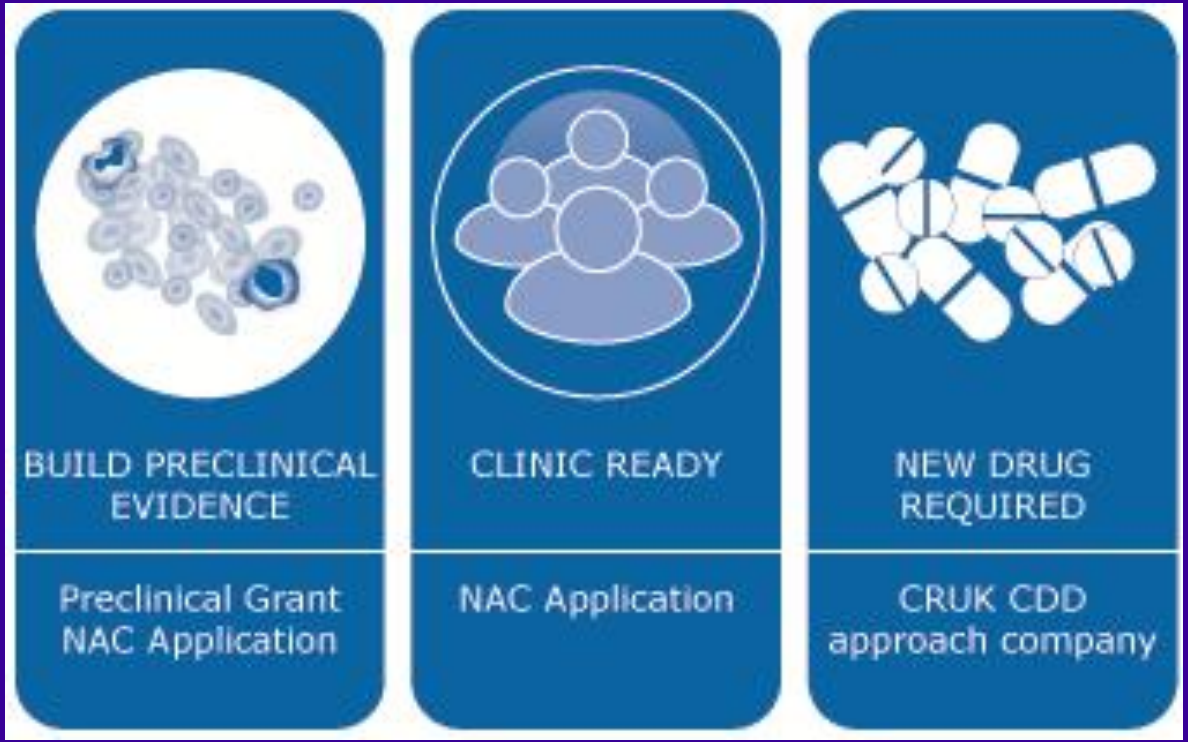
6 COMBINATIONS ALLIANCE PARTNERS

28
DRUGS OFFERED

195
NUMBER OF PATIENTS TREATED

1
NUMBER OF CLINICAL STUDIES CLOSED

COMBINATION ALLIANCE - CATEGORIES



COMBINATIONS ALLIANCE - PROCESS

Portfolio

- Company provides access to a drug or portfolio of oncology agents (under MOU)
- Expressions of interest (EOI) are requested from the academic community

Review

- Proposals are reviewed by the company, CDD team and JSC
- Seek approval from New Agents Committee (NAC)

Sponsor

- ECMC will sponsor the proposed clinical study under a CTAg
- Studies are driven by the ECMC Alliance Team and overseen by a JSC

Study

- Investigator led trial opens within 12 months
- Multiple centres within 1 protocol

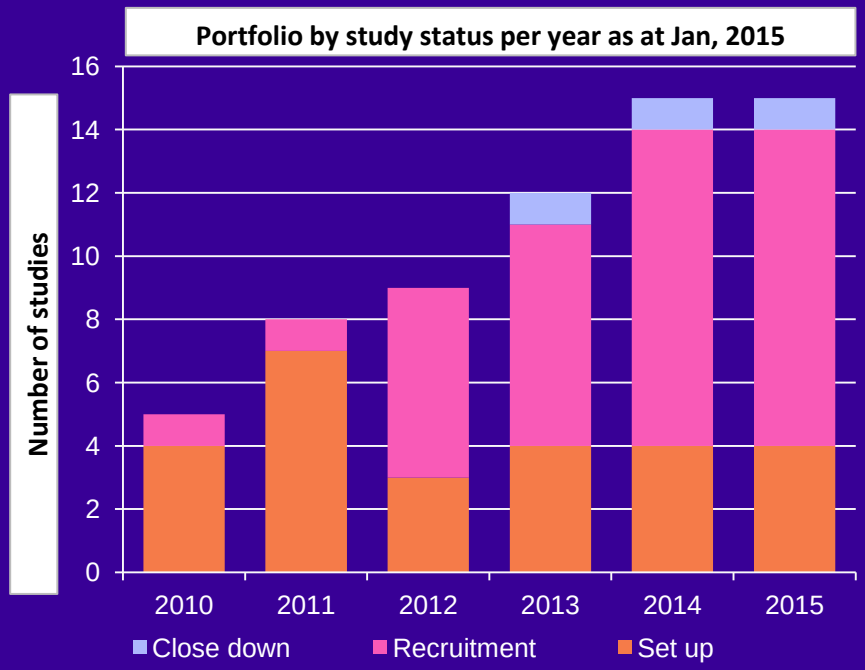
Study portfolio

Study	CI	Sponsor	Combination	Indication
ORCA2	Forster	UCL	PARP inhibitor + Cisplatin + RT	HNSCC
PIONEER	Evans	Glasgow	PARP inhibitor + Capecitabine + RT	Pancreatic
TORCMEK	Schmid+Middleton	Barts	MTOR inhibitor + MEK inhibitor	NSCLC
TBA	Glasspool	Glasgow	Hedgehog inhibitor + Paclitaxel	Ovarian
FACING	Evans	Glasgow	FGFR inhibitor + Cisplatin/Capecitabine	Oesophogastric
DEBIOC	Thomas	Oxford	mixed Erb Inhibitor + Oxiplatin/Capecitabine	Oesophogastric
RADICAL	Seckl	Imperial	FGFR inhibitor + Anastrozole + Letrozole	Breast
FIESTA	Chester	Leeds	FGFR inhibitor + Gemcitabine / Cisplatin	Bladder
VANSEL	Talbot	Oxford	MEK inhibitor + RET, EGFR, VEGF inhibitor	NSCLC
TAX-TORC	Banerji	ICR	mTOR inhibitor + Taxane	Ovarian / Fallopian
ComPAKT	Yap	ICR	AKT inhibitor + PARP inhibitor	Solid tumours
PATRIOT	Harrington	RMH/ICR	ATR inhibitor + RT	H&N/Abdo/pelvic/thorax
PANtHER	Hochhauser	UCL	EGFR inhibitor +FOLFIRI	CRC
VIBRANT	Thirlwell+Sarker	UCL	RET, EGFR, VEGF inhibitor + Iodine-131 MIBG	Pheos and PG
DREAM	Saunders	Manchester	MEK inhibitor + VEGFR inhibitor	CRC

ECMC Combinations Alliance

FUTURE OF COMBINATIONS ALLIANCE

- Expand Portfolio
  - Double the number of studies recruiting by 2016
  - Increase number partners
    - Currently 6
    - Portfolios to single project
    - Big Pharma to biotech
  - Drive more novel: novel combinations



Lessons Learned

- **Challenges**

  Emerging toxicity data

  Additional NHS resources

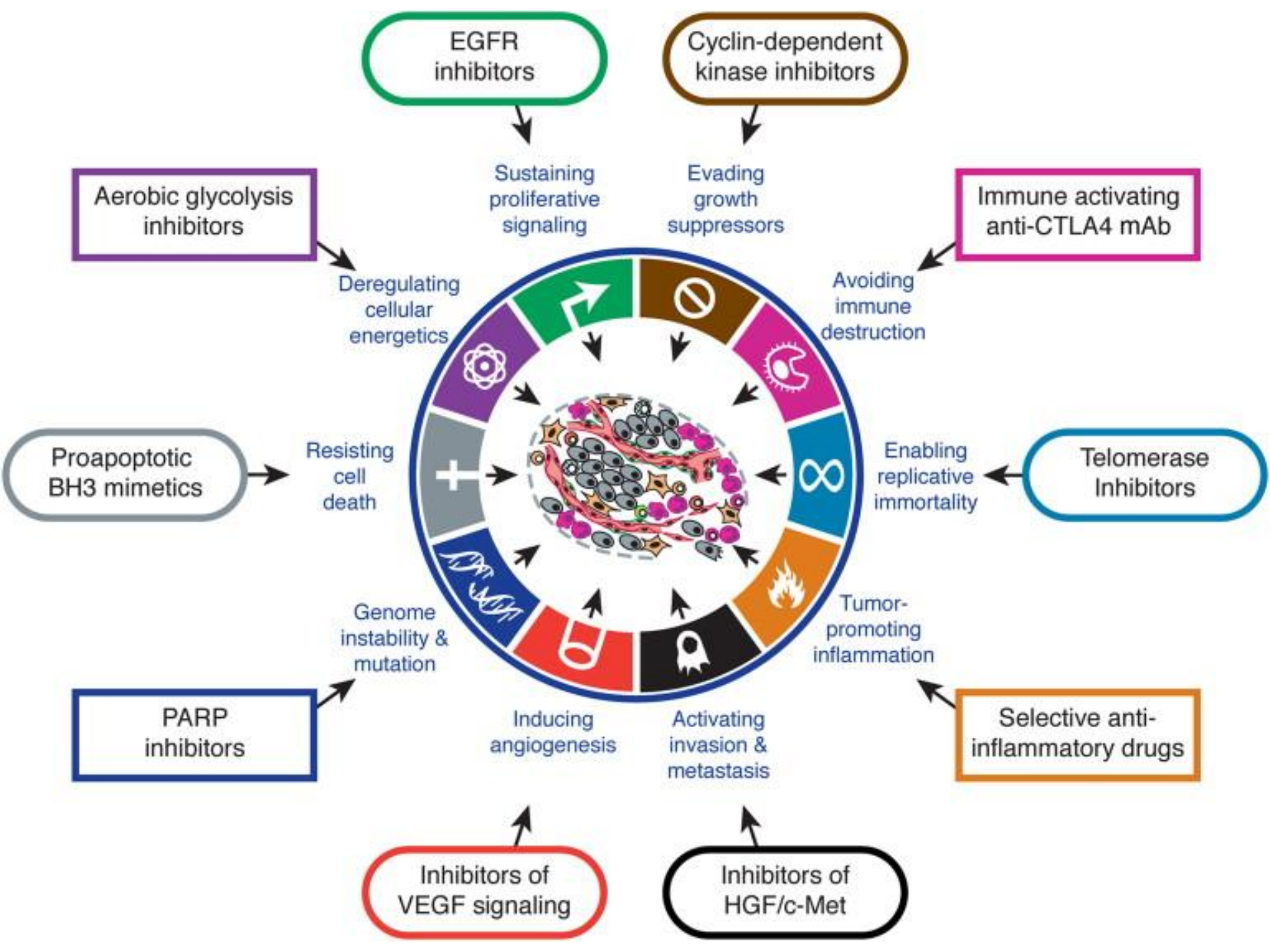
  Working with external vendors

- **Advantages**

  supportive sponsors

  work with a recognised CTU

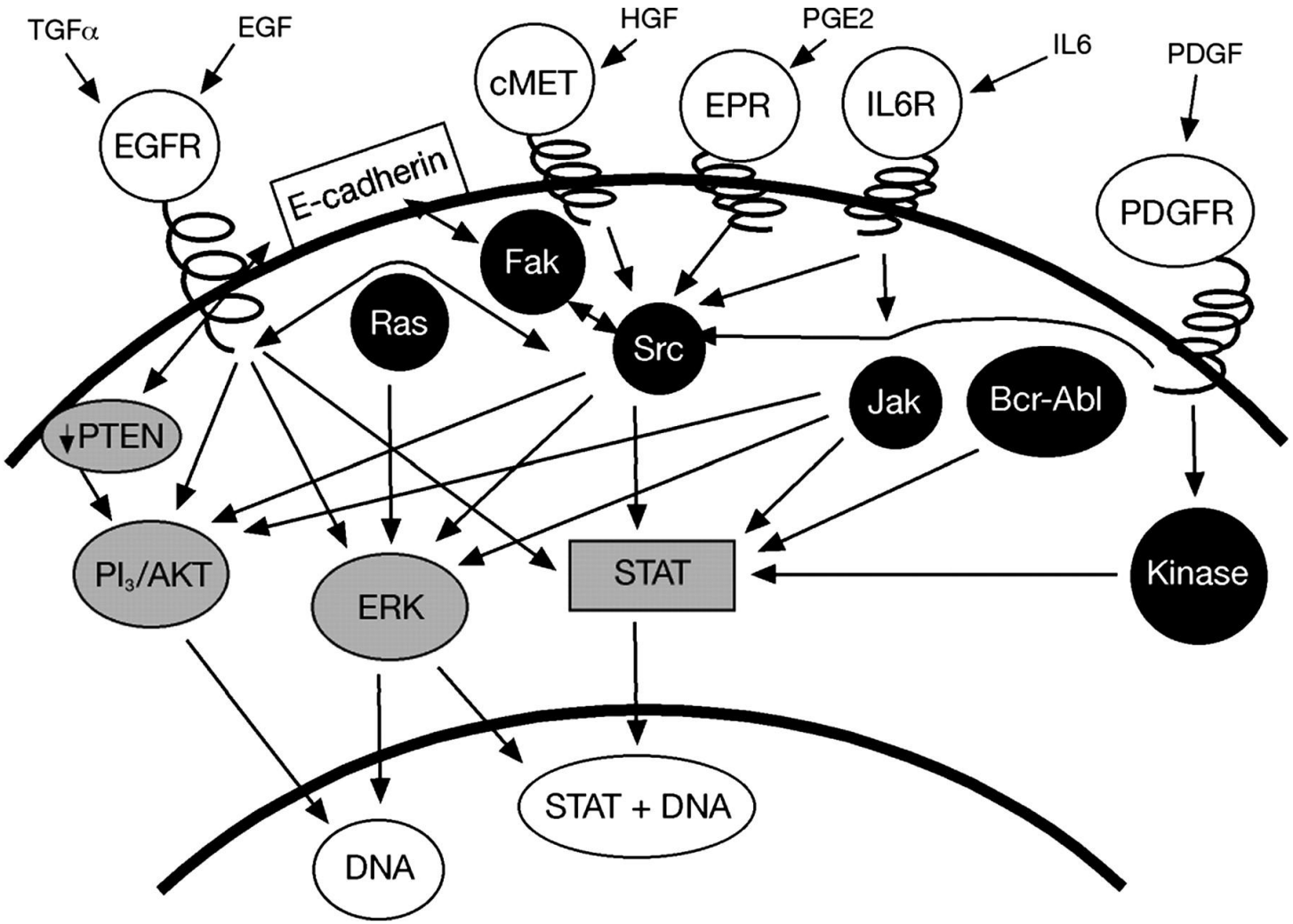
  relationships with funders, industry, ECMC network


EGFR inhibitors
Cyclin-dependent kinase inhibitors
Aerobic glycolysis inhibitors
Sustaining proliferative signaling
Evading growth suppressors
Immune activating anti-CTLA4 mAb
Deregulating cellular energetics
Avoiding immune destruction
Proapoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability & mutation
Tumor-promoting inflammation
PARP inhibitors
Inducing angiogenesis
Activating invasion & metastasis
Selective anti-inflammatory drugs
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met

Example 1

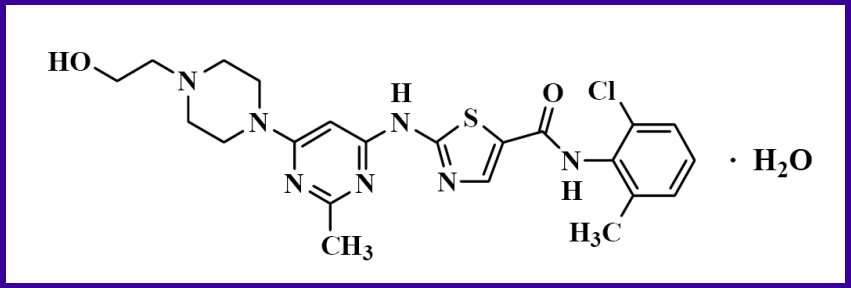
- 2006: publish biomarkers of Src Kinase inhibition by dasatinib
- 2009: publish Phase I trial of dasatinib (previous ASCO presentations)
- 2007: CR-UK funding: anti-invasive therapies in mouse model of PDAC
- 2010: publish in vitro / in vivo studies
- 2012: “Trials in Progress” poster, ASCO
- 2014: Randomised Phase II ESMO – World GI

Src-signalling pathways in the cell.

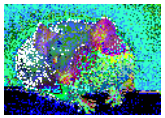


Dasatinib - Introduction

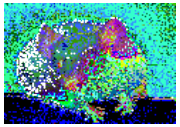
- Potent, orally active inhibitor of several oncogenic protein tyrosine kinases, including the SRC family kinases, and BCR-ABL
- In vitro and in vivo activity

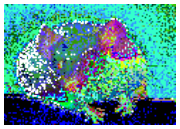


Tyrosine kinase	IC_{50} (nM)
FYN	0.2
c-SRC	0.55
YES	0.41
LCK	1.1
c-KIT	22
PDGF-Rβ	28
BCR-ABL	3.0
EPHA2	17

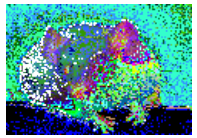


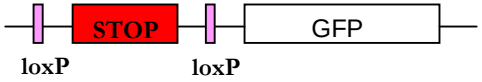
X

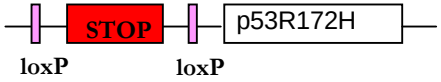


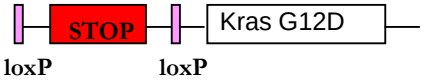


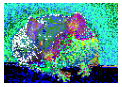
x







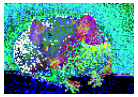


F1 

Pdx1 Cre^{+} LSL GFP$^{fl/+}$
1/4

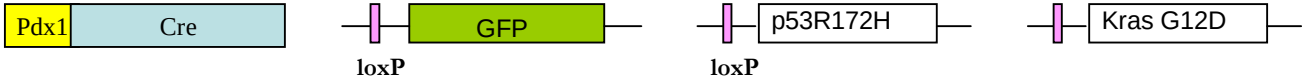
x

LSL P53$^{R172H/+}$ Kras$^{G12D/+}$
1/4

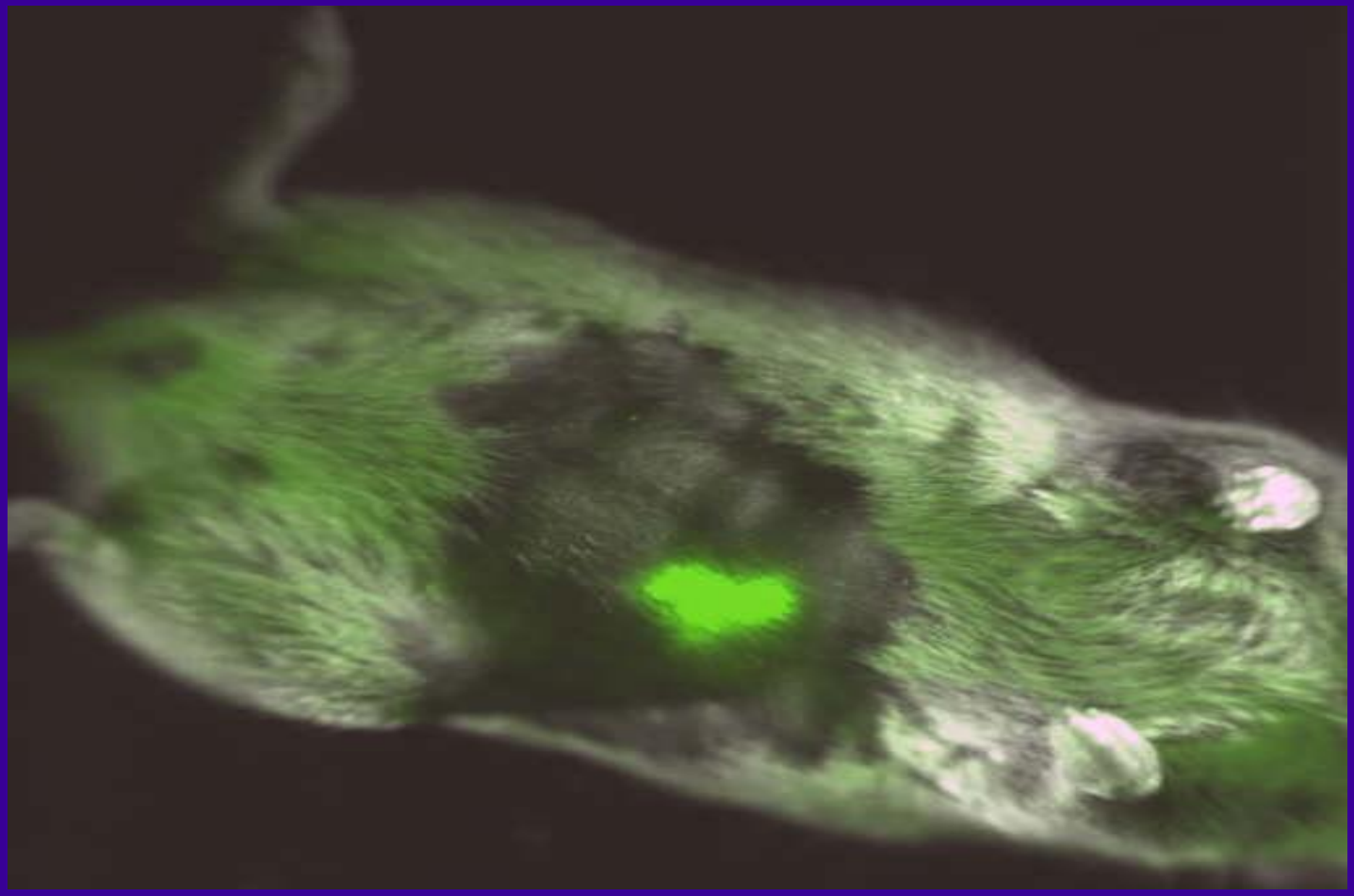


In Pancreas

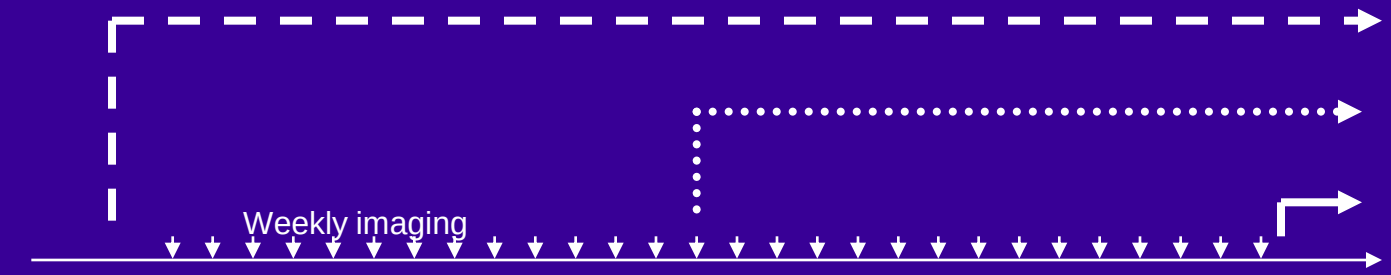
F2



$Pdr Cre^{+}$ GFP^{+} $Kras^{G12D/+}$ $Trp53^{R172H/+}$



Experiment Plan



Weaning Pan (1)

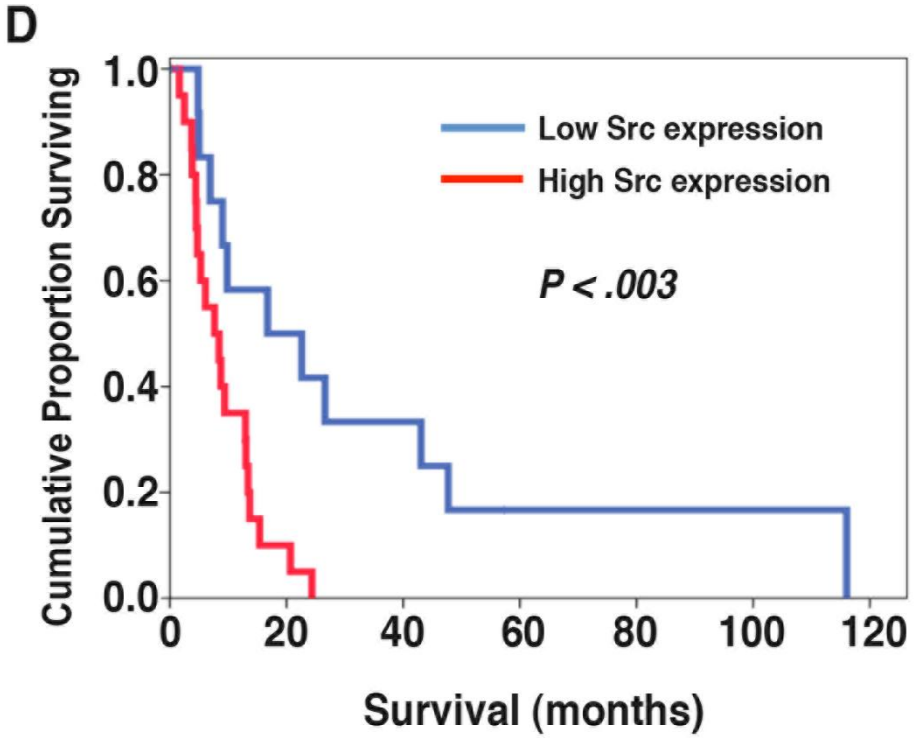
4-6 wks

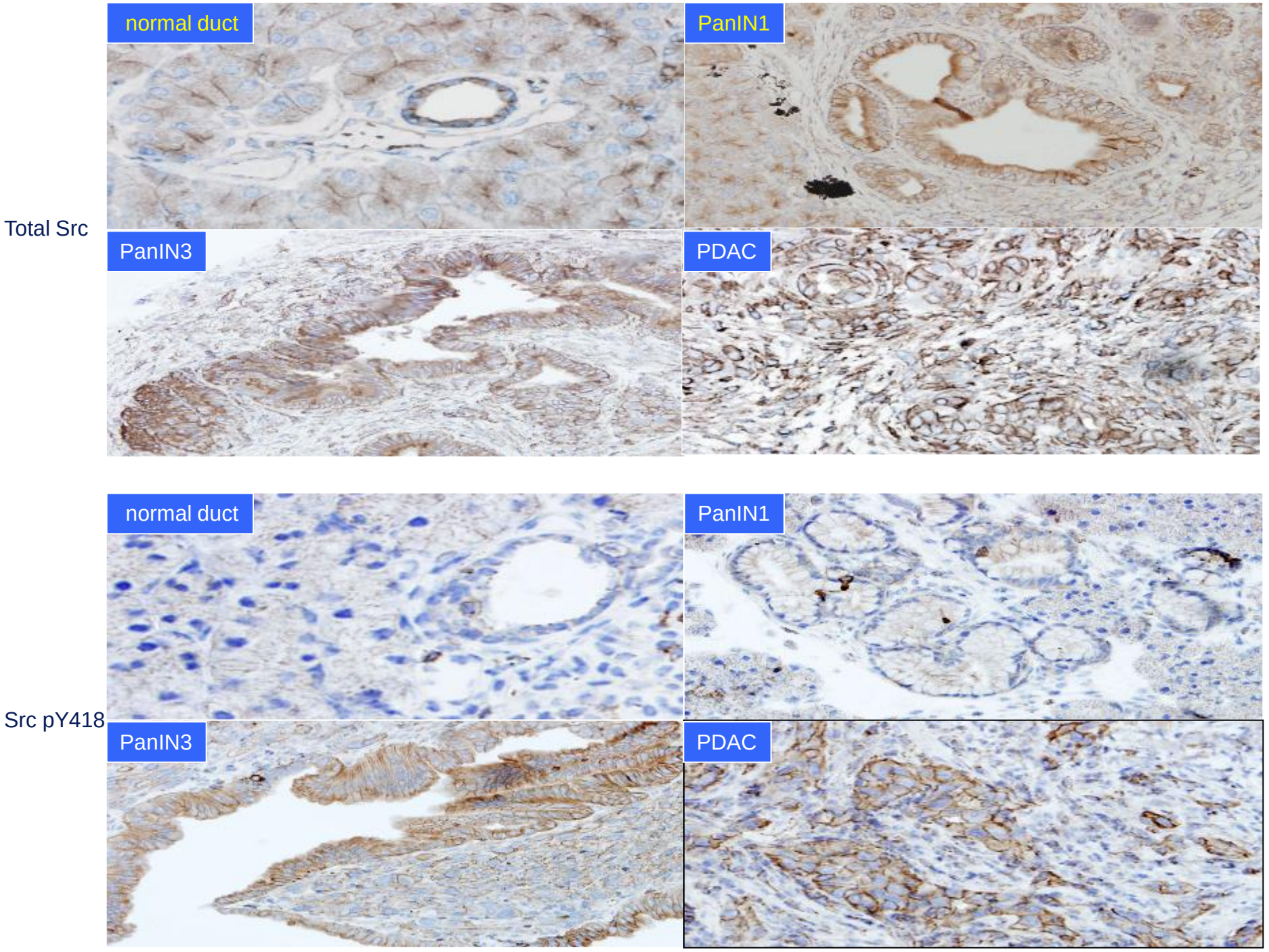
Primary Tumour (2)

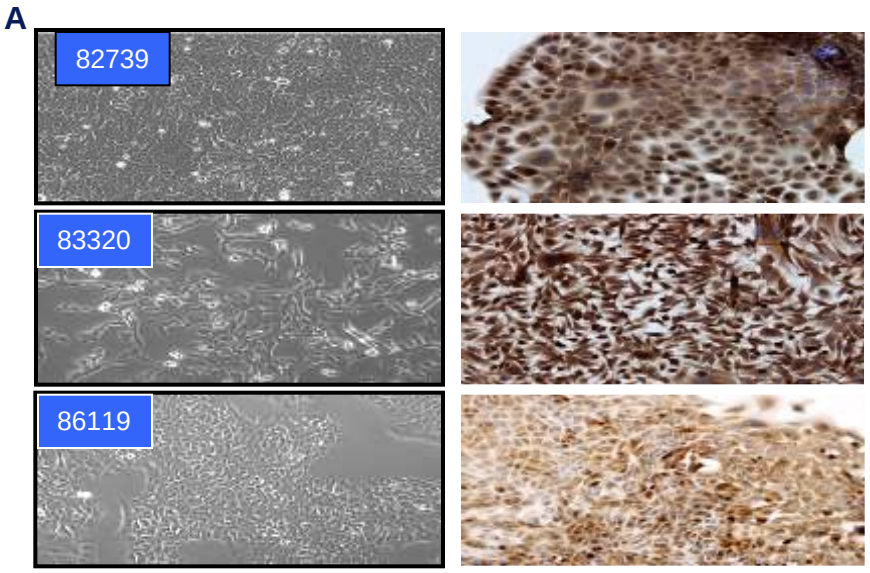
10 wks

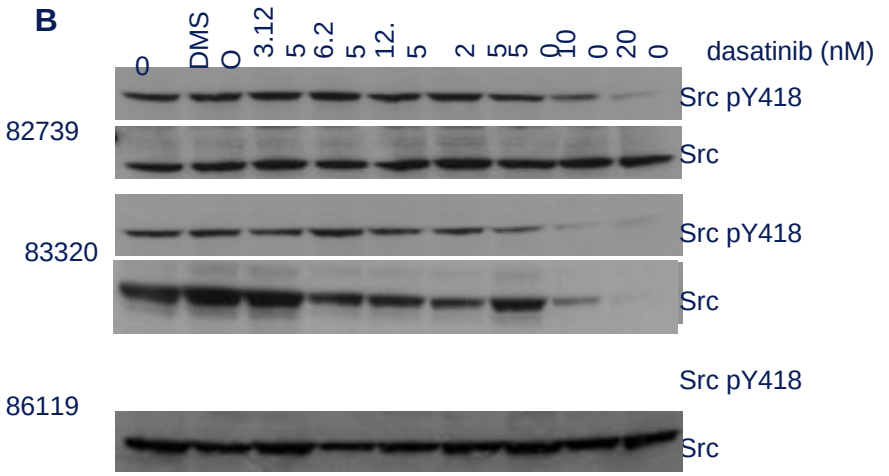
Metastasis (3)

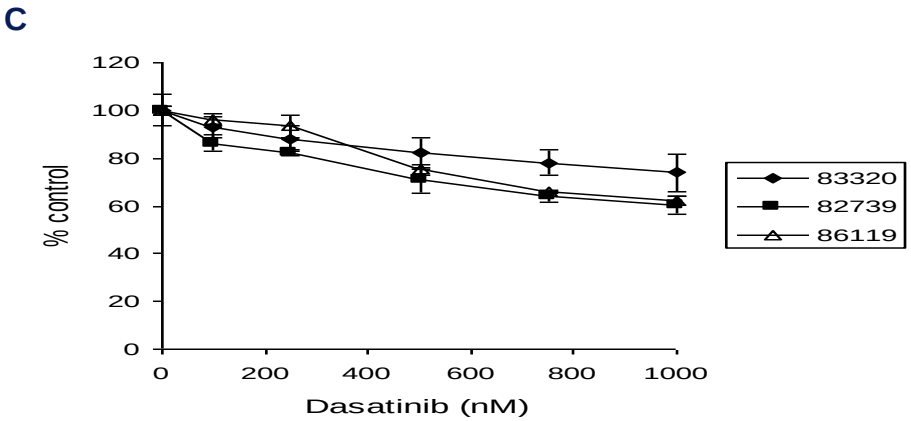
20 wks


D
Cumulative Proportion Surviving
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
Survival (months)
Low Src expression
High Src expression
P < .003


normal duct
PanIN1
Total Src
PanIN3
PDAC
normal duct
PanIN1
Src pY418
PanIN3
PDAC



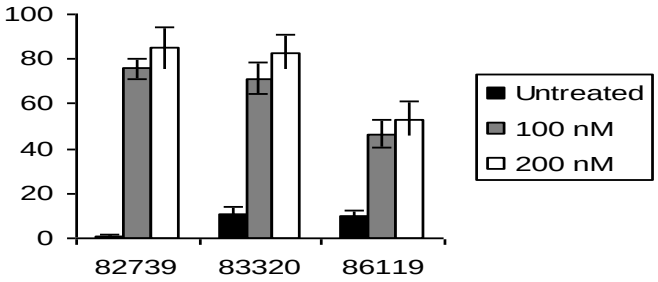


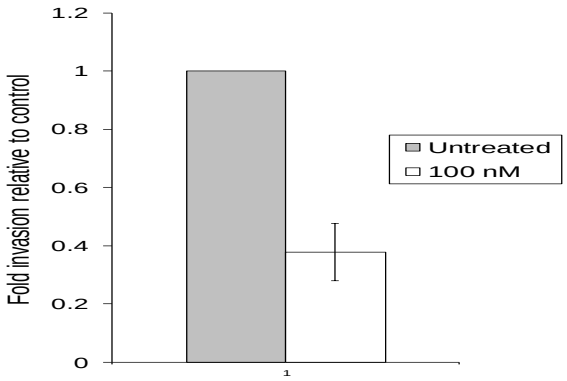


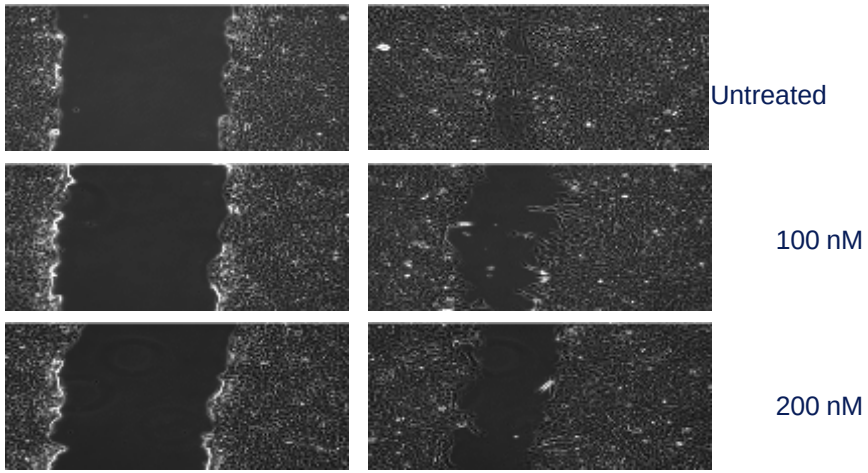
A. Pdx1 IHC - mouse PDAC cell lines

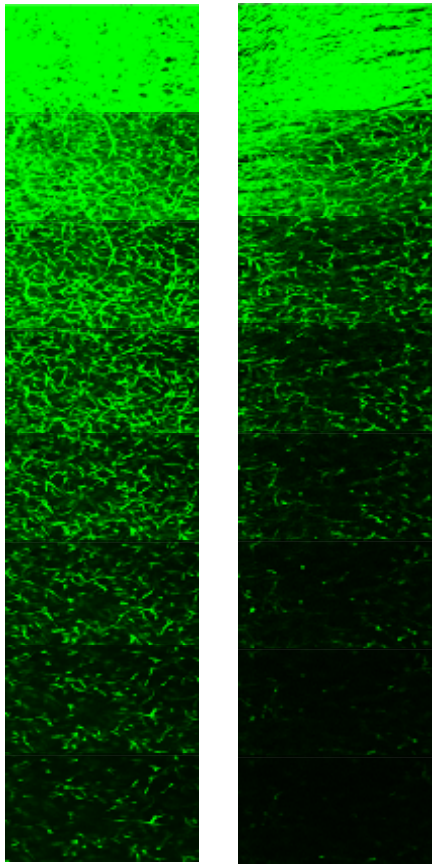
B. Inhibition of Src kinase activity by dasatinib in mouse PDAC cells

C. Dasatinib inhibits proliferation of mouse PDAC cell lines at high concentrations (1 uM), but not at a Src kinase – inhibitory dose (100 – 200 nM)







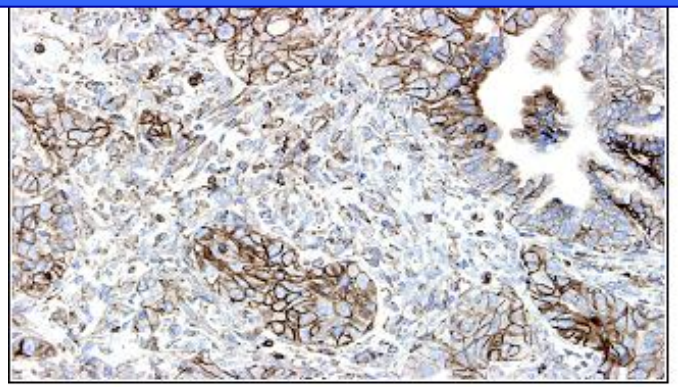


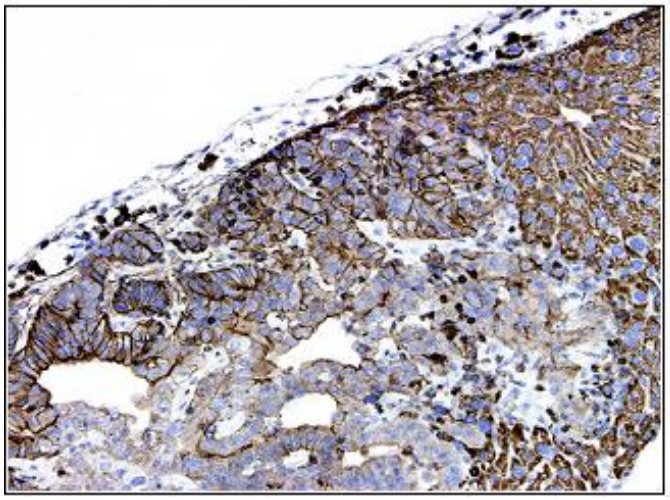
A. Dasatinib inhibits mouse PDAC cell migration (wound assay)

B. Dasatinib inhibits mouse PDAC cell invasion

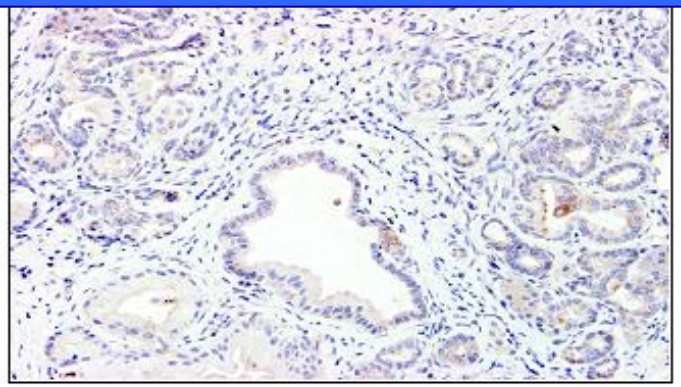
phospho-Src^{Y416} expression

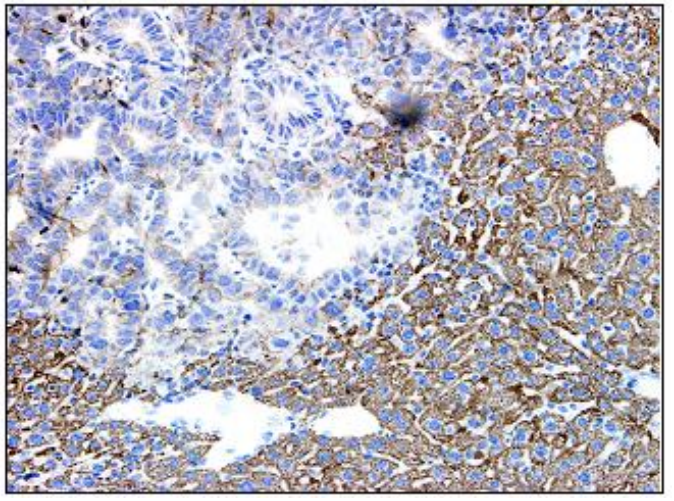
Pdx1-Cre GFP Kras$^{G12D/+}$ Trp53$^{R172H/+}$
Vehicle treated

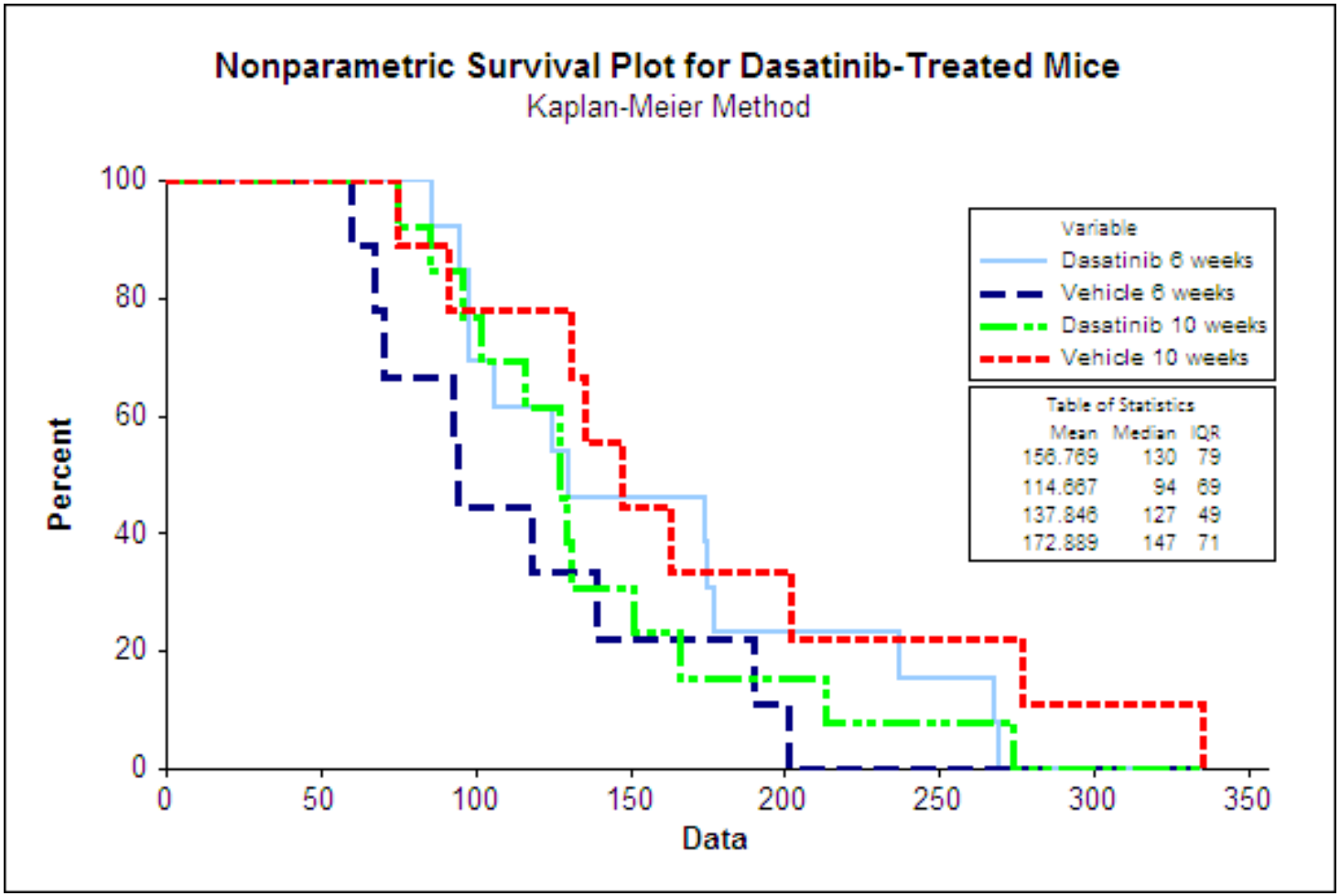




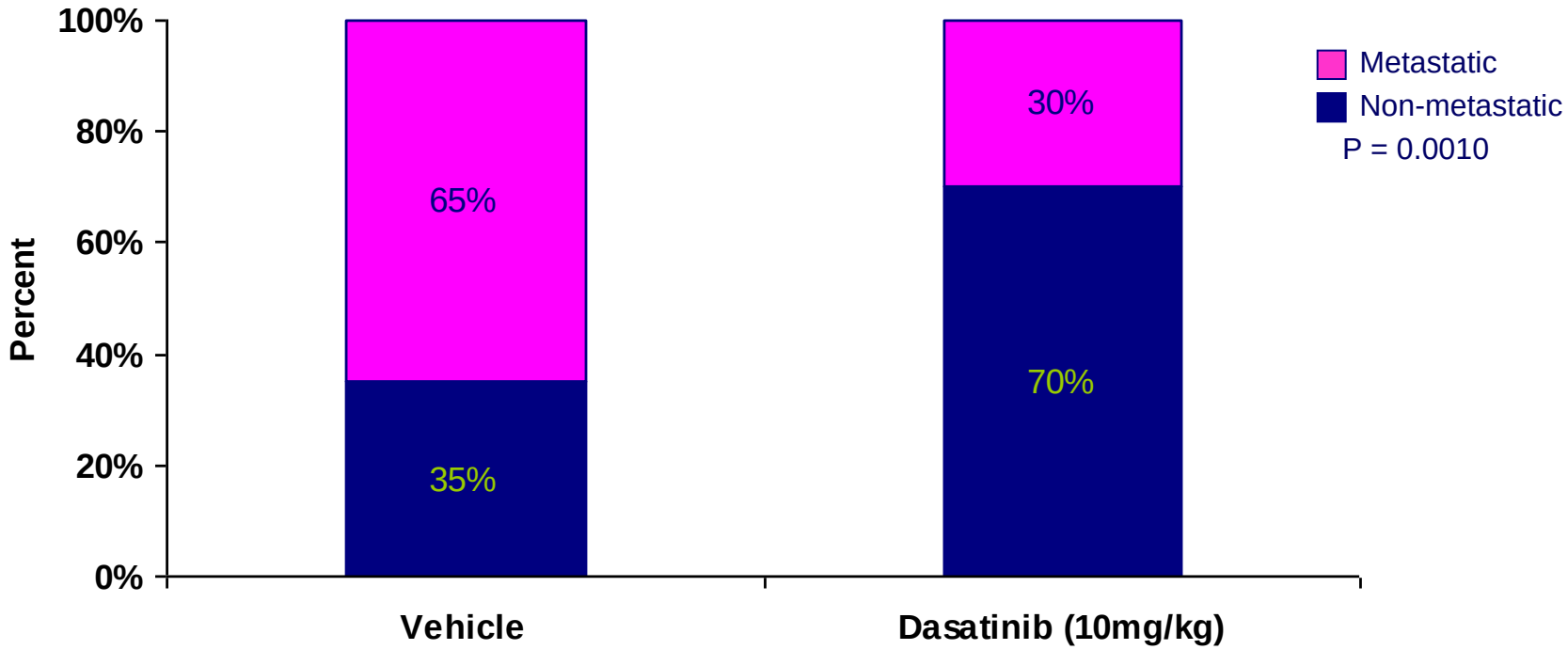
Pdx1-Cre GFP Kras$^{G12D/+}$ Trp53$^{R172H/+}$
Dasatinib treated






Nonparametric Survival Plot for Dasatinib-Treated Mice
Kaplan-Meier Method
Percent
Data
100
80
60
40
20
0
0
50
100
150
200
250
300
350
Variable
Dasatinib 6 weeks
Vehicle 6 weeks
Dasatinib 10 weeks
Vehicle 10 weeks
Table of Statistics
Mean Median IQR
156.769 130 79
114.667 94 69
137.846 127 49
172.889 147 71

Incidence of Metastasis in Dasatinib-Treated *Pdx1-Cre* *Kras*$^{G12D/+}$ *Trp53*$^{R172H/+}$ Mice



Study - Design

Locally Advanced Pancreatic Cancer
N = 200 randomized

1:1 RANDOMIZATION

Gemcitabine
1000mg/M^2
Q week x3 of 4 week cycle +
Dasatinib
orally 100mg QD
(n = 100)

Gemcitabine
1000mg/M^2
Q week x3 of 4 week cycle +
Placebo Pill
QD
(n = 100)

Primary Endpoint:
- Overall survival

Secondary Endpoints:
- Progression-Free Survival (PFS)
- Safety

Exploratory Endpoints:
- Freedom from Distant Metastasis (FFDM)
- Pain, Fatigue
- CA19-9 Response
- Objective Response Rate

Stratification factors:
- Site intent to provide radiotherapy (Y or N)
- ECOG PS (0 or 1)

Statistics:
- OS: median 10 to 13.3 mos; 79% power
  - 1-sided $\alpha = 0.2$ (HR = 0.75)
- PFS: median 5 to 7 mos; 88% power
  - 1-sided $\alpha = 0.15$ (HR = 0.714)

A Phase I study of olaparib in combination with chemo-radiation in locally advanced pancreatic cancer

Jeff Evans on behalf of the Glasgow ECMC and
Glasgow Pancreatic Cancer Research Group

Will Steward and the Leicester ECMC

Martin Eatock and the Belfast ECMC

Olaparib + Chemo-Radiation (LAPC)

SCIENTIFIC RATIONALE FOR THE COMBINATION

	Agent A	Agent B
Name	Olaparib	Chemo-Radiation (fluoro-pyrimidine based)
Mechanism	PARP inhibitor (potentiates radiation – induced DNA damage)	Cytotoxic & DNA Damage (single and double strand breaks)
Preclinical / clinical data available	Yes (pre-clinical for PARPi + RT, although not in PDAC)	Yes – "SOC" for LAPC (NB SCALOP)
Rationale for Combination *<Comment on any potential overlapping toxicity or predictive PK interactions from preclinical or single agent studies. Insert trial schema if available >*	PDAC – 5th commonest cancer; 4th commonest cause of cancer deaths in the UK 30% are locally advanced inoperable (anatomical; MDT) – overall survival < 1 year NB "Borderline" resectable (AHPBA-SSO-SSAT criteria)	

Rationale for Combination

- Chemo-radiation superior to RT (meta-analysis) – increasingly used in UK for LAPC ("SOC" in USA, EU)
- RT up-regulates thymidine phosphorylase (xenograft studies)
- Capecitabine superior 1-year survival & toxicity profile to gemcitabine + RT
- Multi-centre studies feasible in UK (SCALOP)
- RT causes SSBs and DSBs
- PARP enzymes – critical role in signalling SSBs as part of the BER pathway, also bind strongly to DSBs
- *In vitro* and *in vivo* data to support that PARP inhibition potentiates cytotoxicity of DNA – damaging agents, including radiation
- PARPi radio-sensitising mediated during S phase – potential synergy 5-FU / RT
- Emerging clinical data on olaparib + radiation
- NB: IMRT and IGRT may allow improved tumour response without increased normal tissue toxicity

TRIAL DESIGN (1) - Phase I

Proposed trial design	
Dose escalation model?	**Phase I:** rolling 6 design
Dosing regimen?	**Induction chemotherapy** Weeks 1 – 12 **Chemo-Radiation** **Capecitabine**: 830 mg / m2 po (Monday – Friday) with RT **RT**: 50.4 Gy in 28 fractions (Monday – Friday) **Olaparib:** start 3 days prior to chemo-radiation then Monday – Friday with RT 100 mgs bid; 150 mgs bid; 200 mgs bid; 250 mgs bid; 300 mgs bid (tablet formulation);

TRIAL DESIGN (2)-Phase I

PATIENTS	Dose ESCALATION *(complete as applicable)*	Dose EXPANSION *(complete as applicable)*
Patient Population	Locally advanced inoperable (anatomical; MDT) PDAC	“Borderline” resectable PDAC (anatomical; MDT)
No. Patients (approx range is acceptable)	12 - 18	12
All comers?	LAPC suitable for chemo-radiation	Suitable for neo-adjuvant chemo-radiation
Specific tumour group?	LAPC suitable for chemo-radiation	Borderline resectable for neo-adjuvant chemo-RT
Stratified patient group?	No	No
By Genotype?	No – not restricted to BRCA or DDR (n)	No – not restricted to BRCA or DDR (n)
By biomarker profile?	No – not restricted to BRCA or DDR deficiency	No – not restricted to BRCA or DDR deficiency

Trial Endpoints

Endpoints

- **Primary Endpoints**
- Optimal dose of olaparib in combination with capecitabine-based chemo-radiation based on clinical and laboratory toxicity (NCI-CTC version 4.0).

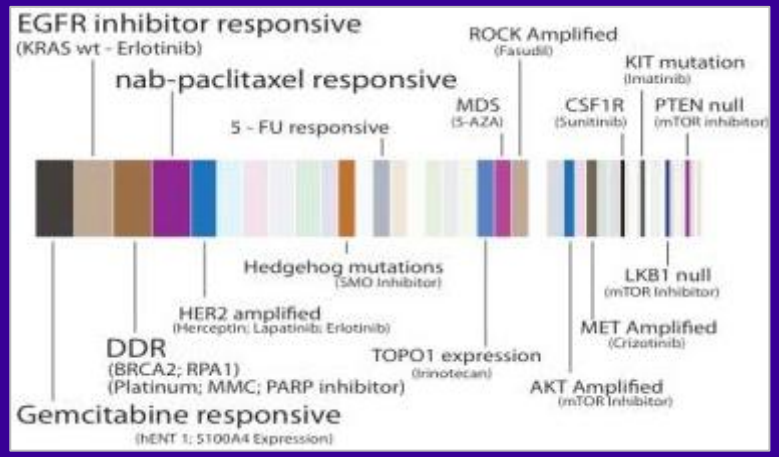
- **Secondary Endpoints**
- Safety and tolerability of olaparib in combination with capecitabine-based chemo-radiation

- **Research (tertiary) endpoints**
- PD effects of the combination of olaparib with capecitabine-based chemo-radiation in blood and, where available, in tumour samples

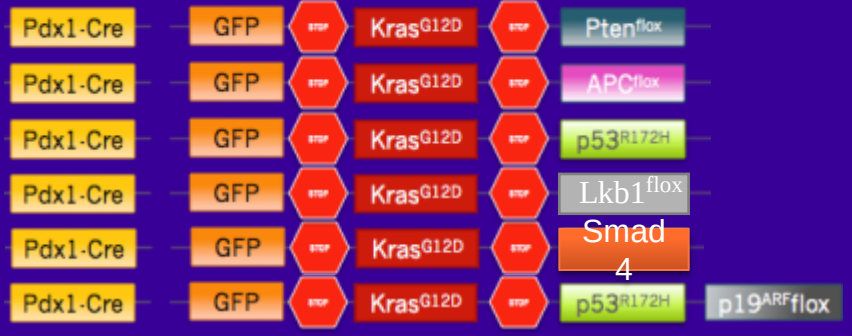
- **PD Studies**
- PARP in PBMCs; DNA damage (y-H2AX in hair follicles); CK-18 (treatment - induced cell death by apoptosis – blood); path of resected specimens
- Predictive: DNA damage repair (Kennedy); genomics

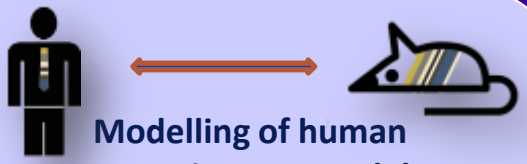
Preclinical mouse models: GEMM and Patient Derived Xenografts (PDX)

Identification of molecular subtypes



Development of GEM models





Modelling of human cancer in GEM models

- Accurate genetics & pathology
- Fundamental biological questions *in vivo*
- Dissect all stages of the cancer process (driver mutations, invasion, metastasis)

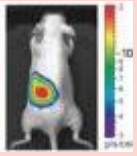
'Patient-derived' mouse models to explore concept of personalised medicine

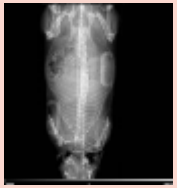
- Validation of targets (genetically)
- Test new drugs & inhibitors
- Xenograft (including PDX) & GEM models

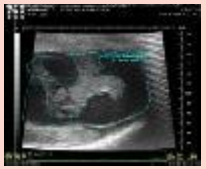
Fluorescence/ bioluminescenc

PET/SPECT/CT

Ultrasound of pancreatic tumour



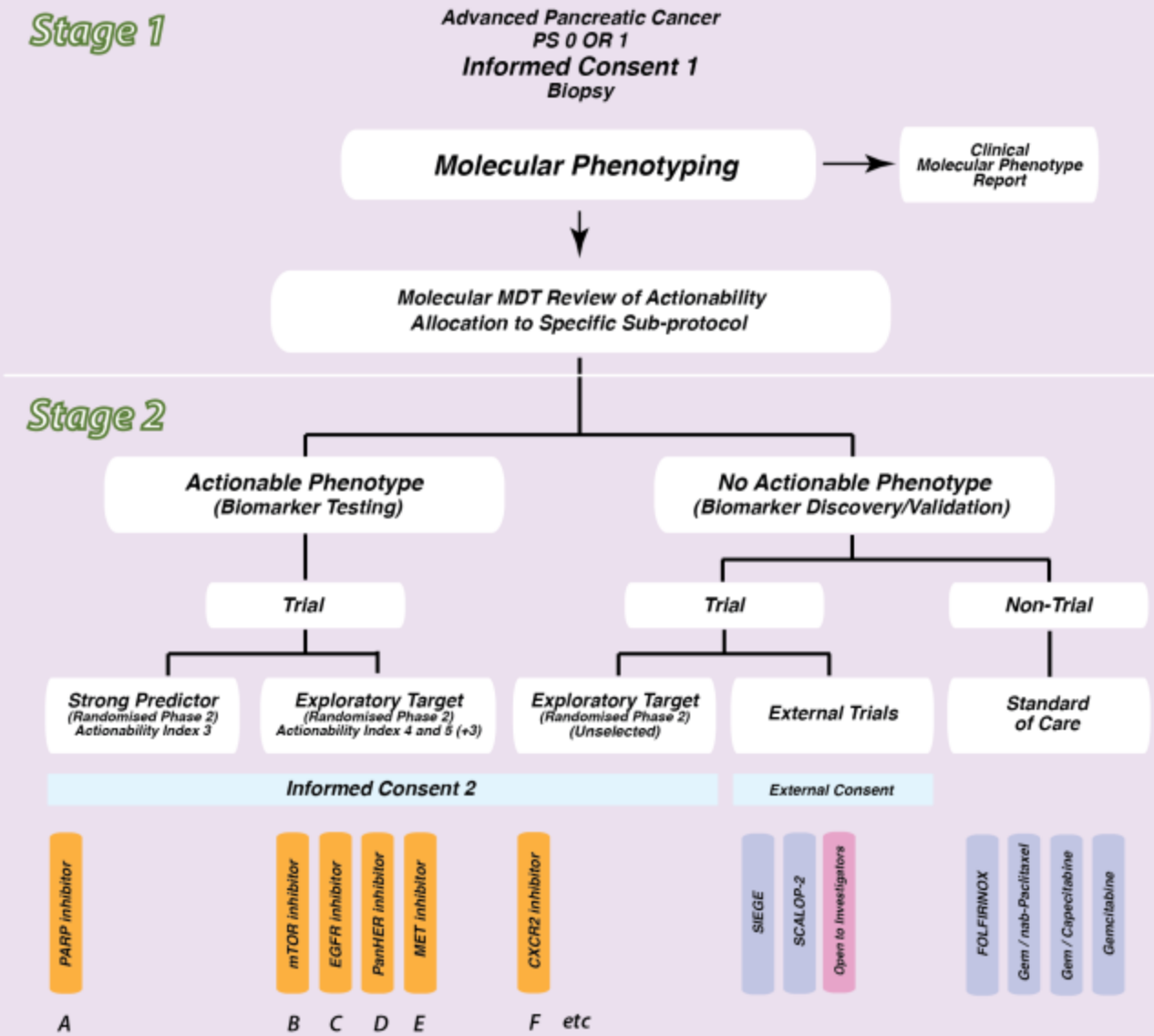




Preclinical Imaging

Primus

Pancreatic CanceR Individualised Multi-arm Umbrella Study

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institute for cancer research

NHS
Greater Glasgow
and Clyde

CANCER
RESEARCH
UK

ECMC

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SCIENTIST
OFFICE

pancreatic cancer
research fund

MRC | Medical
Research
Council

IRCI
International Rare Cancers Initiative

NCRN

wellcome trust


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