Tackling Metastases
Opportunities and Challenges

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Why Target Metastasis?

- Leading cause of cancer deaths
- 90% patients die of metastases – but half present with localised disease
- Adjuvant (post-op) therapy of presumed micro-metastatic disease – biggest impact on overall survival in many tumour types
- We could have an even bigger survival benefit with agents designed to inhibit metastases (rather than chemotherapy of modest activity)
- But at what stage of development of metastases can we and should we intervene?

CRT / CDD WORKSHOP – FOCUS ON METASTASES
OCTOBER 2015

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Workshop Overview

- Lessons learned from the past

  e.g. MMPIs
- Motility and Invasion Targets

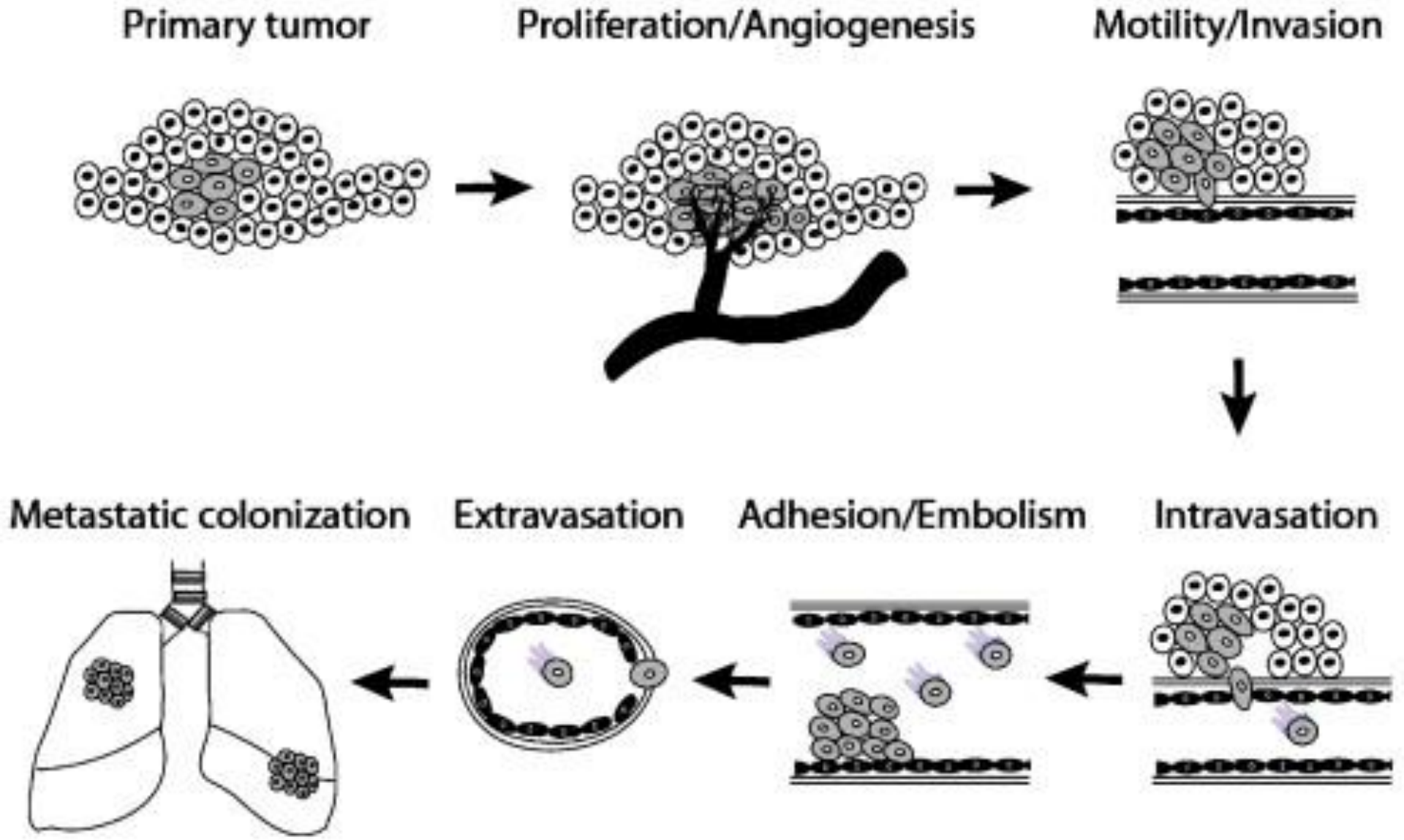
  e.g. Integrin internalization, MRCK, CLIC3
- Angiogenesis Targets

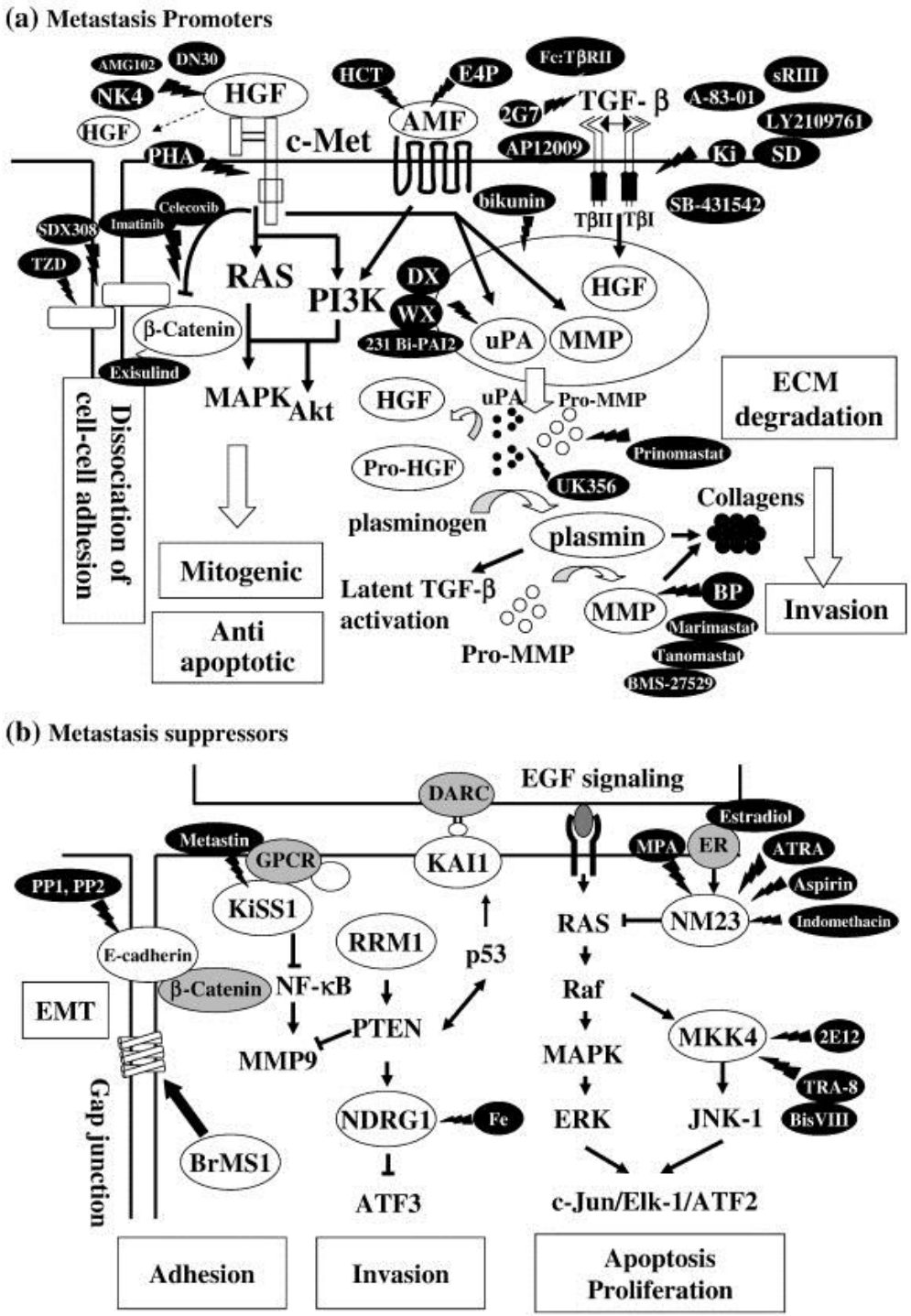
  e.g. VEGFR, RhoC, ROCK, HIF-1alpha
- ***Metastases Targets***

  e.g. HSP90, FAK, BMP4, CSF-1R
- ***(Pre)-Clinical Development***

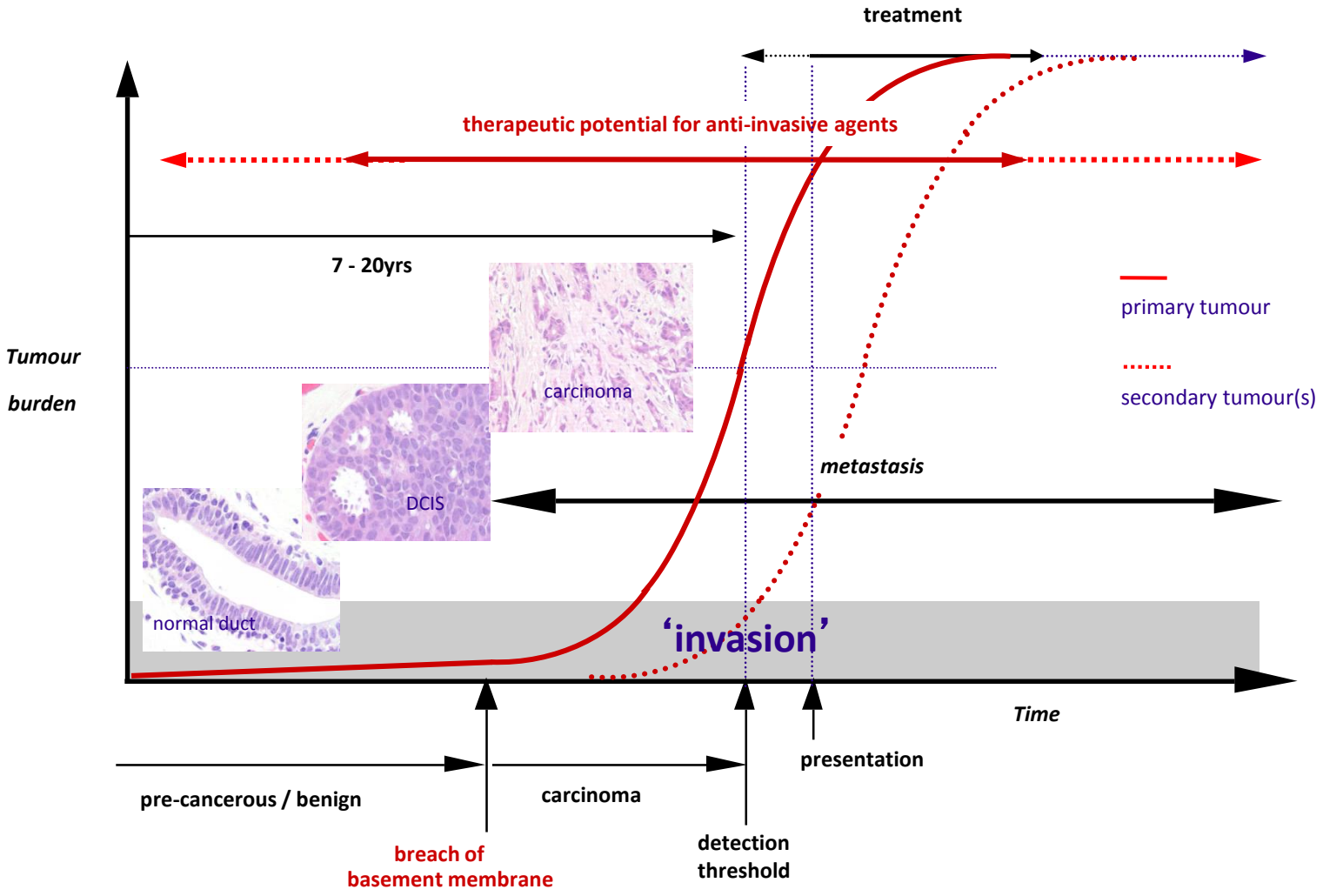
  murine models, trial designs
- ***Biomarkers***

  predictive, proof-of-concept, PD
- ***Regulatory Challenges & the way ahead***


Primary tumor
Proliferation/Angiogenesis
Motility/Invasion
Intravasation
Adhesion/Embolism
Extravasation
Metastatic colonization


(a) Metastasis Promoters
AMG102
DN30
NK4
HGF
HGF
HCT
E4P
AMF
Fc:TβRII
TGF- β
sRIII
A-83-01
LY2109761
2G7
AP12009
Ki
SD
PHA
c-Met
bikunin
TβII
TβI
SB-431542
SDX308
Celecoxib
Imatinib
TZD
RAS
PI3K
DX
WX
231 Bi-PAI2
HGF
uPA
MMP
β-Catenin
Exisulind
MAPK
Akt
HGF
uPA
Pro-MMP
ECM degradation
Prinomastat
Pro-HGF
UK356
Collagens
plasminogen
plasmin
Dissociation of cell-cell adhesion
Mitogenic
Anti apoptotic
Latent TGF-β activation
MMP
BP
Marimastat
Tanomastat
BMS-27529
Pro-MMP
Invasion
(b) Metastasis suppressors
EGF signaling
DARC
Estradiol
Metastin
GPCR
KAI1
MPA
ER
ATRA
Aspirin
Indomethacin
PP1, PP2
KiSS1
RRM1
p53
RAS
NM23
E-cadherin
β-Catenin
NF-κB
Raf
EMT
PTEN
MMP9
MAPK
MKK4
2E12
TRA-8
BisVIII
Gap junction
NDRG1
Fe
ERK
JNK-1
BrMS1
ATF3
c-Jun/Elk-1/ATF2
Adhesion
Invasion
Apoptosis Proliferation

Cancer: Timeline



Adapted from Discovery and development of drugs targeting invasion and metastasis. Jones RJ, Green TP, Elvin P In Cancer Metastasis: Biologic basis and T herapeutics. Eds Lyden, Psalia, Welch Cambridge University Press 2011 pp600-611.

Methods for studying metastasis

- Discrete steps can be approached using *in vitro* assays – e.g. adhesion, motility/migration, invasion
- Best analysed in a 3D setting (ideally + host cell co-cultures)
- Essential also to study metastasis (and test potential inhibitors) *in vivo* in appropriate clinically-relevant models
- Need robust assays for accurate quantitation of metastatic tumour burden and location - preferably serial imaging
- Need early indications of response to treatment – CTCs / ctDNA?

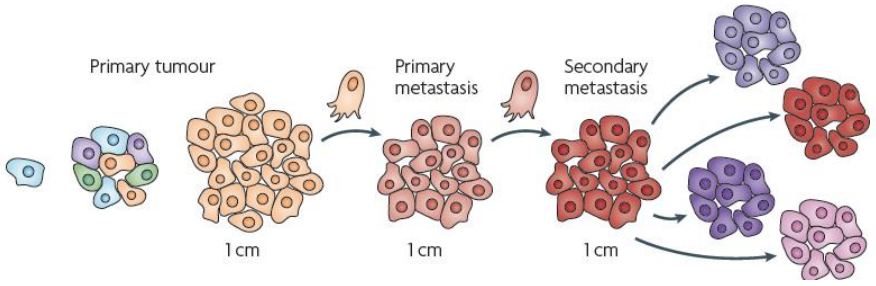
Suggested criteria for clinically relevant preclinical models

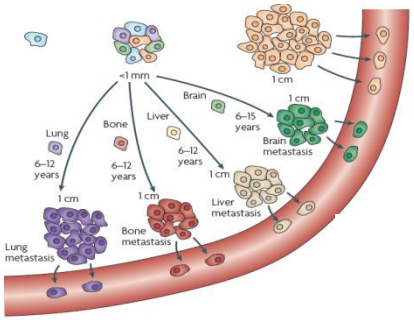
- Ideally driven by clinically relevant oncogenic events and representative of the type/subtype of the cancer in question
- Allow thorough validation of potential molecular mediators of metastasis - identifying requirement for maintenance as well as initiation.
- Adequately reproduce the dissemination route (regional, lymphatic, haematogenous), location of metastasis (nodes, brain, lungs, liver etc) and physiological properties;(e.g. drug access, sensitivity, vascularity etc)
- Provide objective and quantitative endpoints of therapeutic response.
- Reliable, reproducible, available and affordable

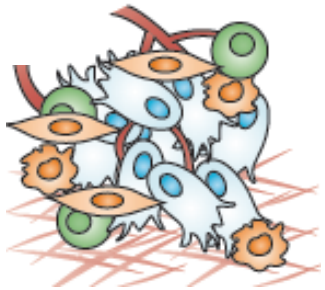
Select model(s) according to the scientific question: e.g. basic mechanisms of metastasis (early/late events?) preclinical testing of new agents?

Aspects of metastasis to consider when selecting preclinical metastasis models

- Key confounding factors: linear *vs* parallel progression of metastases; inter-and intra-lesion heterogeneity, clonal evolution; dormancy
- The different tissue microenvironments in which metastases develop influence their biology and therapeutic responses
- Need to consider the major contribution from stromal elements – vascular system, lymphatics, ECM, immune system







If dissemination occurs early (before diagnosis) need to develop therapies that prevent outgrowth of **existing** metastases.

Current Challenges

- **Phase I**: toxicity may be inappropriate surrogate for active doses (or may not occur)
- **Phase II:** Agents may not cause anatomical regression
- **Phase III:** metastatic population will not be optimal to assess efficacy
- There has not (yet) been an agent registered specifically as anti-metastatic

The Clinical Experiment

- Model in the laboratory (mouse) 1st
- Does the agent target pre-invasive - invasive or invasive – metastasis (or both)
- Assess toxicity, PK etc (if not already known)
- ***Proof of Concept study – clinical, with PD / biological +/- imaging read-out***
- "Definitive" Studies (large and long):

  Adjuvant (+ SoC or "maintenance") - RFS / FFDM

  Monitor with CTCs, cfDNA?

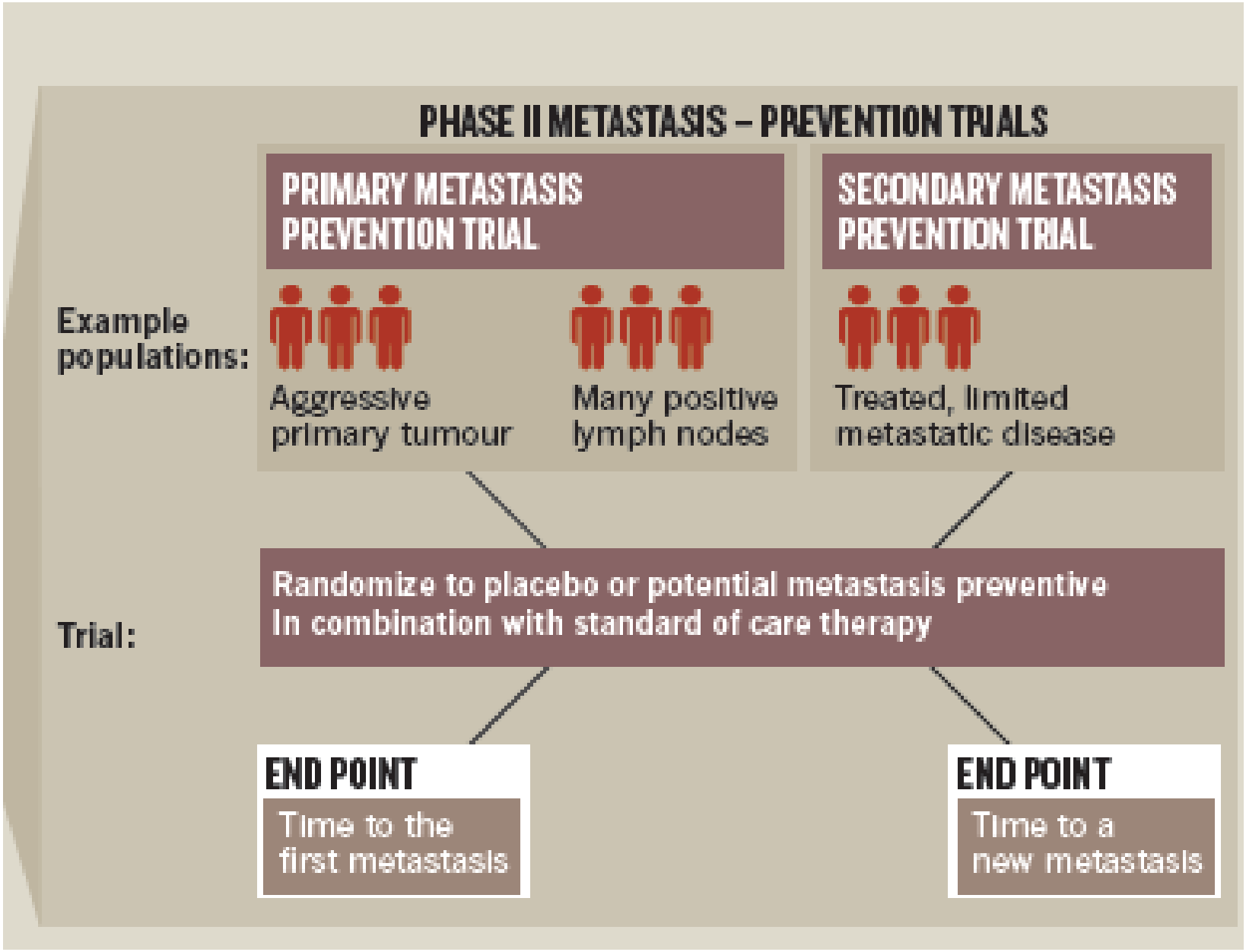
  Patient selection?

Proof of Concept

- “Quicker” (neo) adjuvant studies (e.g. PDAC)
- Locally advanced inoperable disease - optimal local treatment but high risk of metastases (e.g PDAC… and others)
- Freedom from distant mets (ie not local relapse)
- Patient selection

  at risk of mets

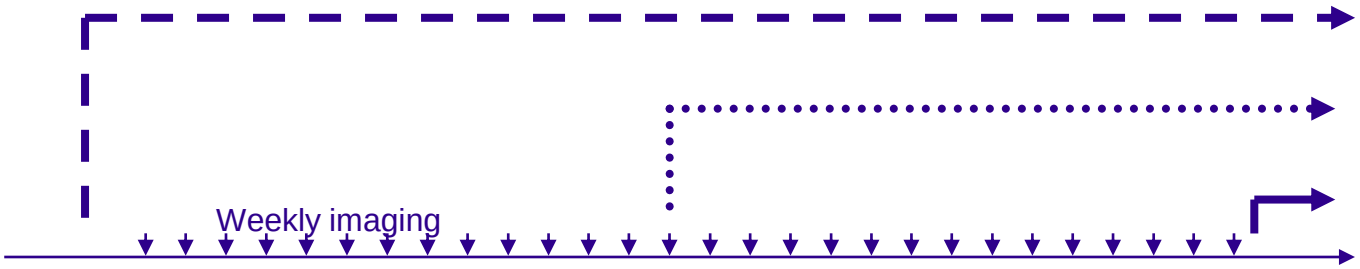
  have the relevant target / selection signature
- PD / biological “read-out”



Nature 485:S58, 2012

Clinical indication and scenario	Proof of concept end-points	Pre-clinical *in vivo* models and associated BICR group	Target validation resources
Colorectal cancer: post liver metastasectomy •Patients with complete surgical macroscopic clearance of metastatic disease (any prior therapy on completion of adjuvant chemotherapy). Randomized trial.	Primary endpoint: disease free survival	VilCreER+/T, $Apc^{+/fl}$ – K-$ras^{+/LSLG12D}$, $p53^{R172H/fl}$ (Owen Sansom)	Mouse tumour samples and cell lines, human cell lines, human tumour TMAs.
Advanced prostate cancer: minimum residual disease •Randomize at first nadir during intermittent androgen deprivation. Randomized trial against placebo.	Primary endpoint: time to biochemical progression. Markers of bone destruction.	PB-Cre4 x $PTEN^{(loxP/loxP)}$/β-$catenin^{exon3/exon3}$, orthotopic prostate models (Owen Sansom, Hing Leung)	Mouse tumour samples and cell lines, prostate cancer cell lines, human tumour TMAs
High-risk early-invasive bladder cancer •Single agent treatment post cystectomy/radical XRT/Adjuvant/neo-adjuvant therapy complete. Randomized trial.	Primary endpoint: relapse–free survival	UroIICRE $PTEN^{-/+}$/$p53^{-/+}$ UroIICRE β-$catenin^{exon3/exon3}$ H-Ras^{Q61L} (Owen Sansom)	Mouse tumour samples, human cell lines, human biopsy samples and TMAs
Pancreatic cancer: post-pancreatectomy	Primary endpoint: relapse–free survival	Pdx1-Cre-GFP, LSL-$Kras^{G12D}$, LSL-$Trp53^{R172H/+}$ (Jeff Evans)	Mouse tumour samples and cell lines, human pancreatic cell lines, human tumour TMAs

Experiment Plan



Weaning
Pan (1)

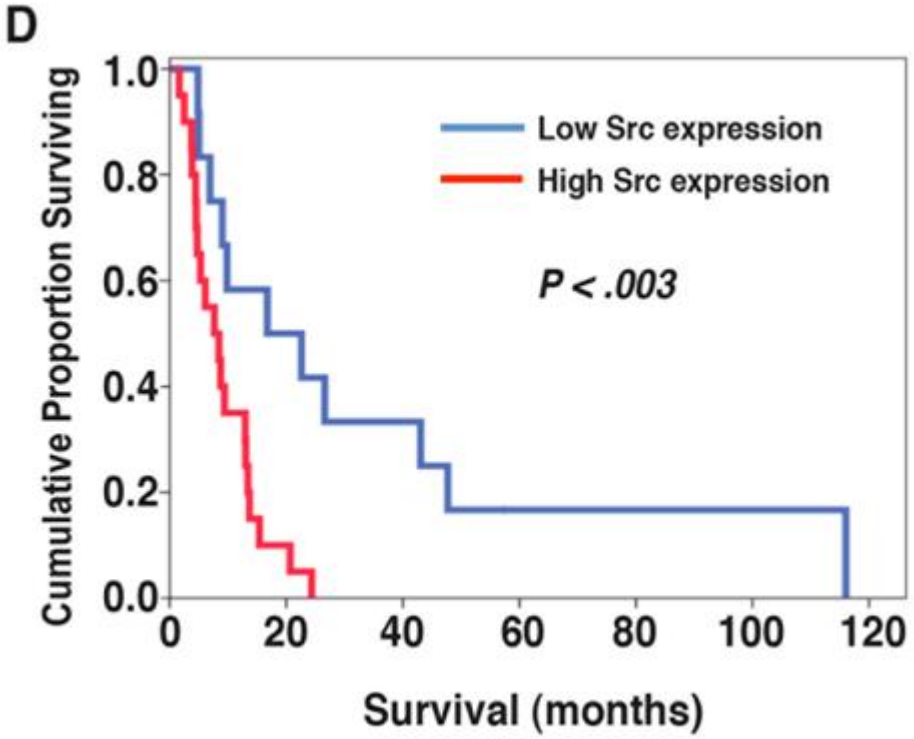
4-6 wks
“chemo-prevention”

Primary
Tumour (2)

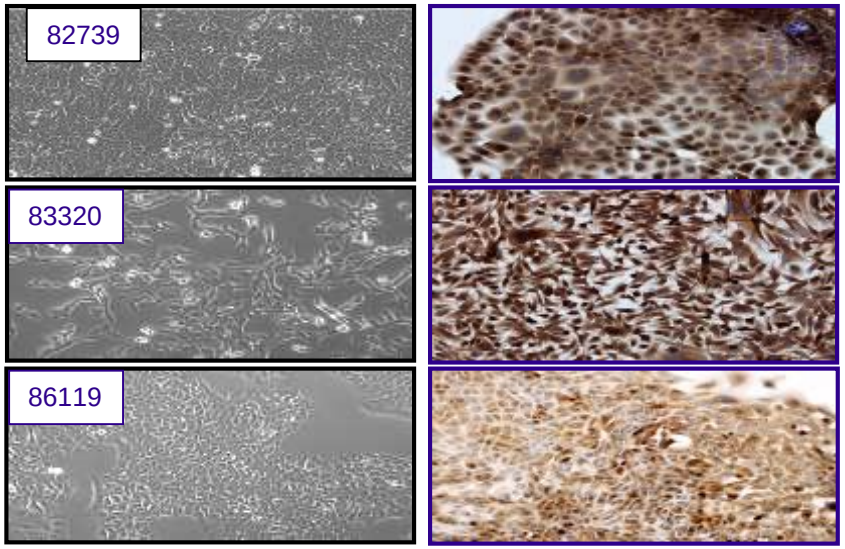
10 wks
“adjuvant therapy”

Metastasis (3)

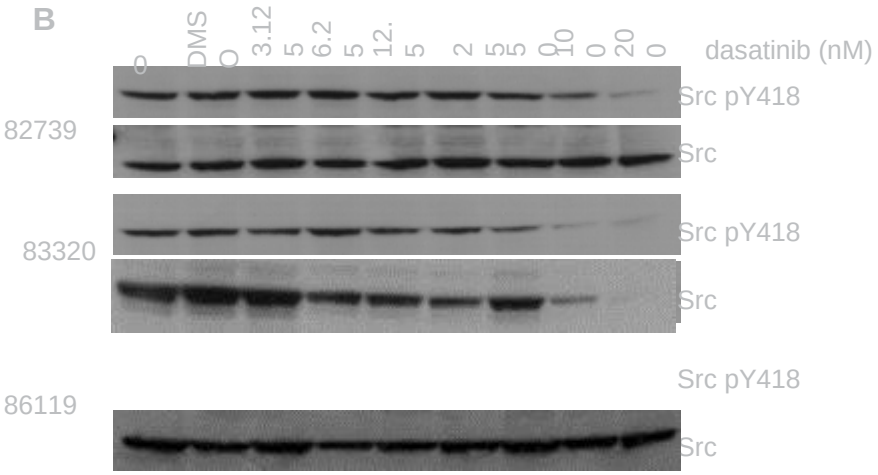
20 wks
Metastatic disease


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

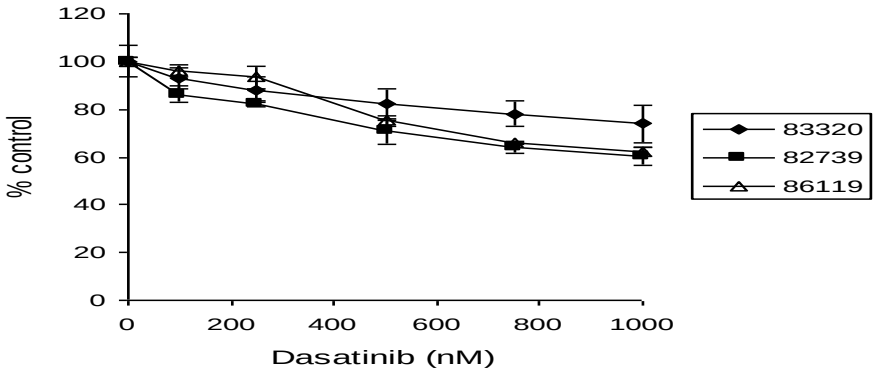
A



B



C

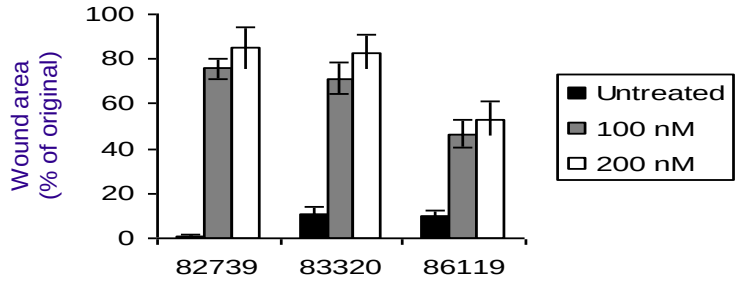


A. Pdx1 IHC - mouse PDAC cell lines

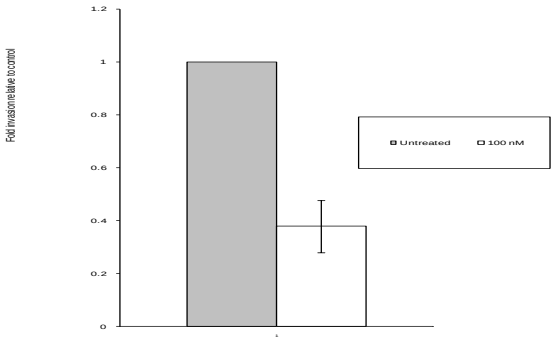
B. Inhibition of Src kinase activity by dasatinib in mouse PDAC cells

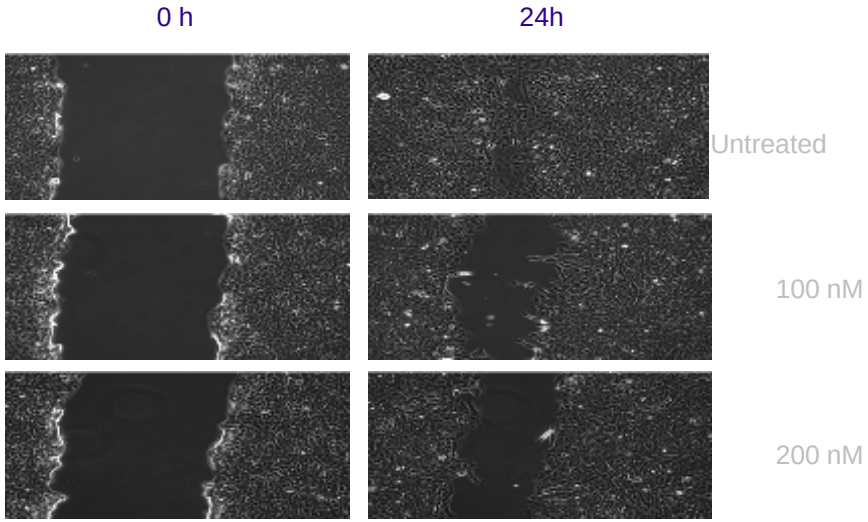
C. Dasatinib inhibits proliferation of mouse PDAC cell lines at high concentrations (1 uM), but not at a Src kinase – inhibitory dose (100 – 200 nM)

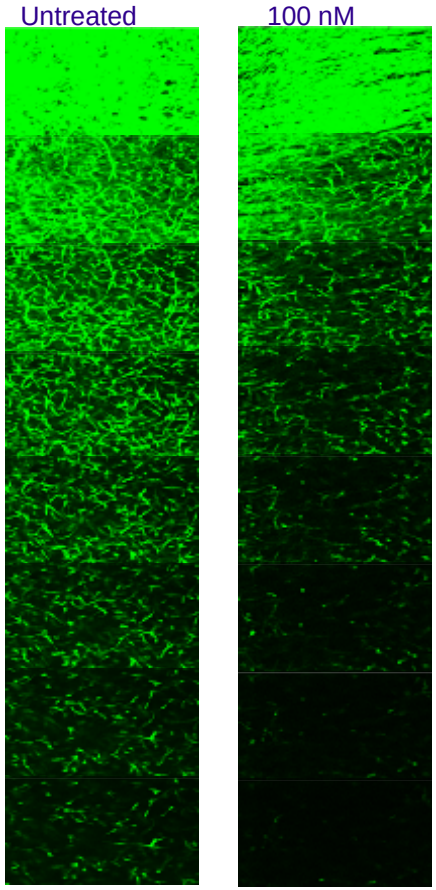
A



B

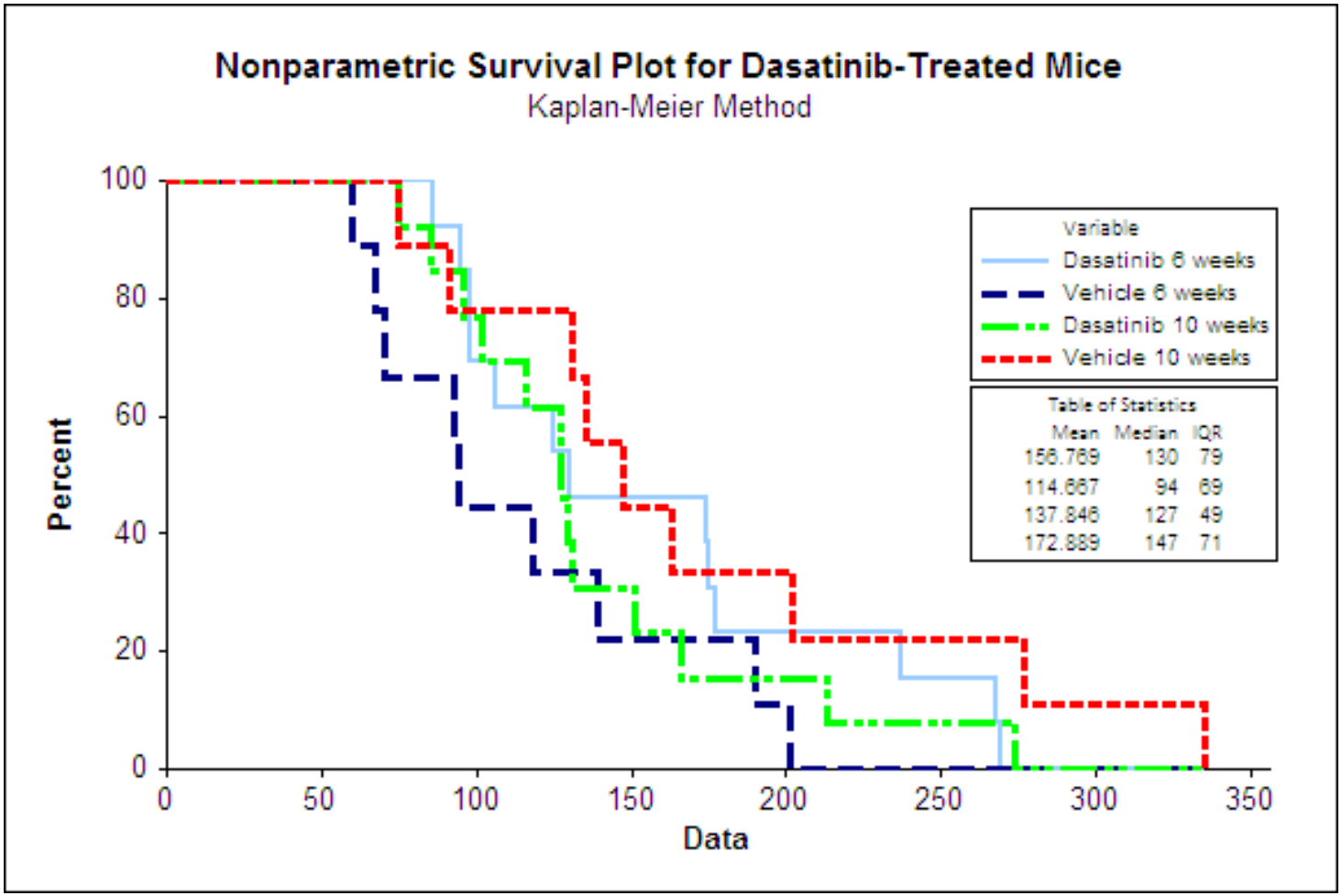




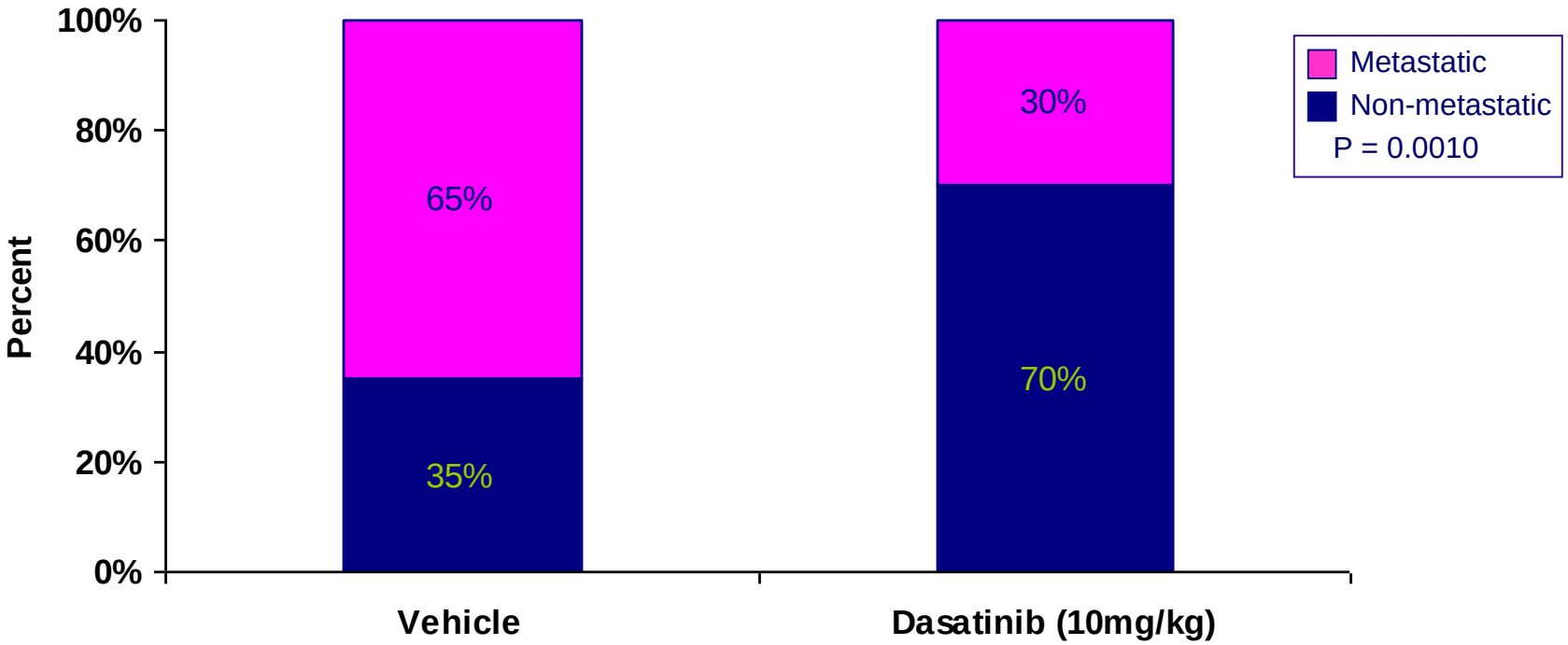


A. Dasatinib inhibits mouse PDAC cell migration (wound assay)

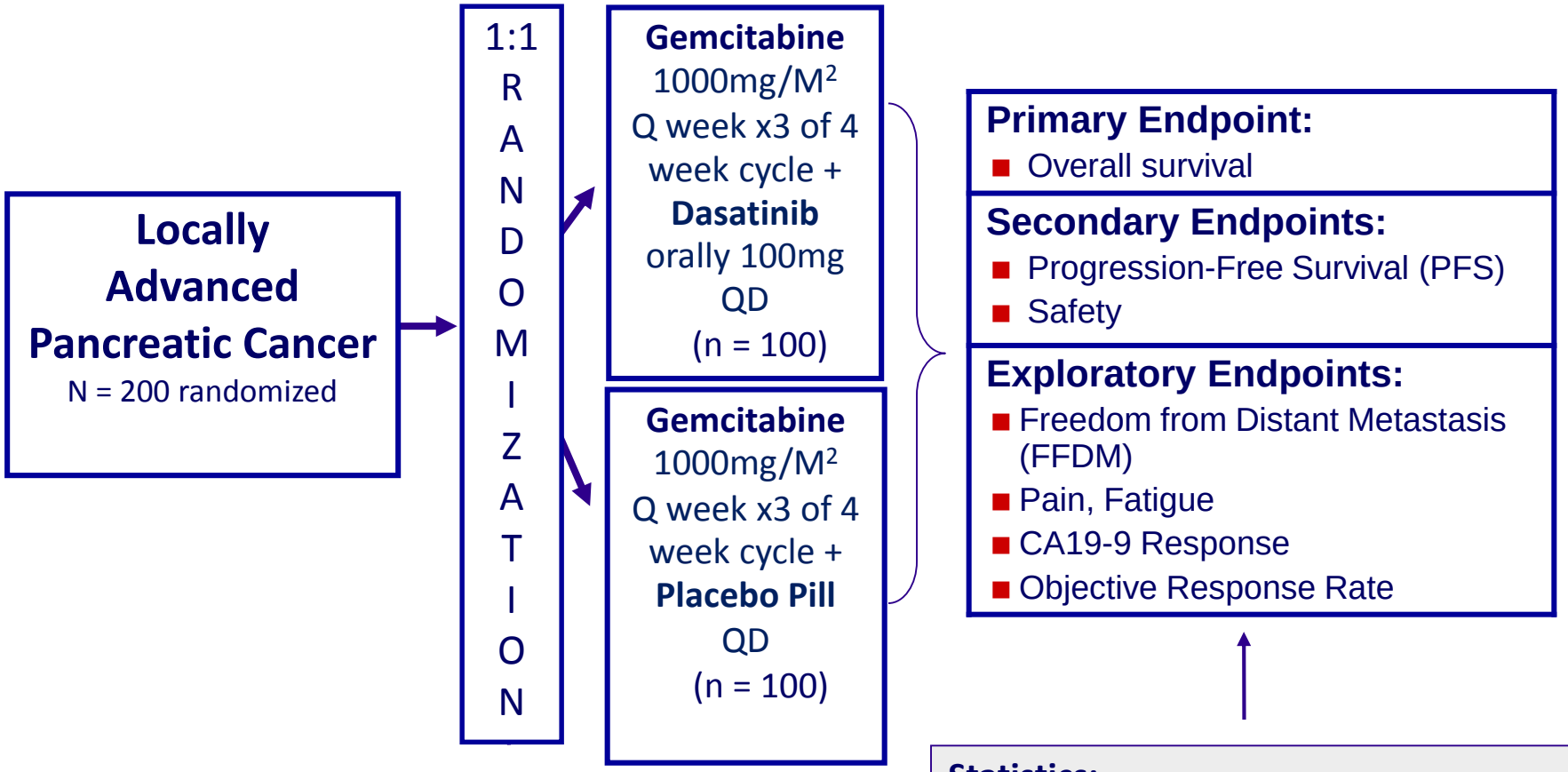
B. Dasatinib inhibits mouse PDAC cell invasion


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



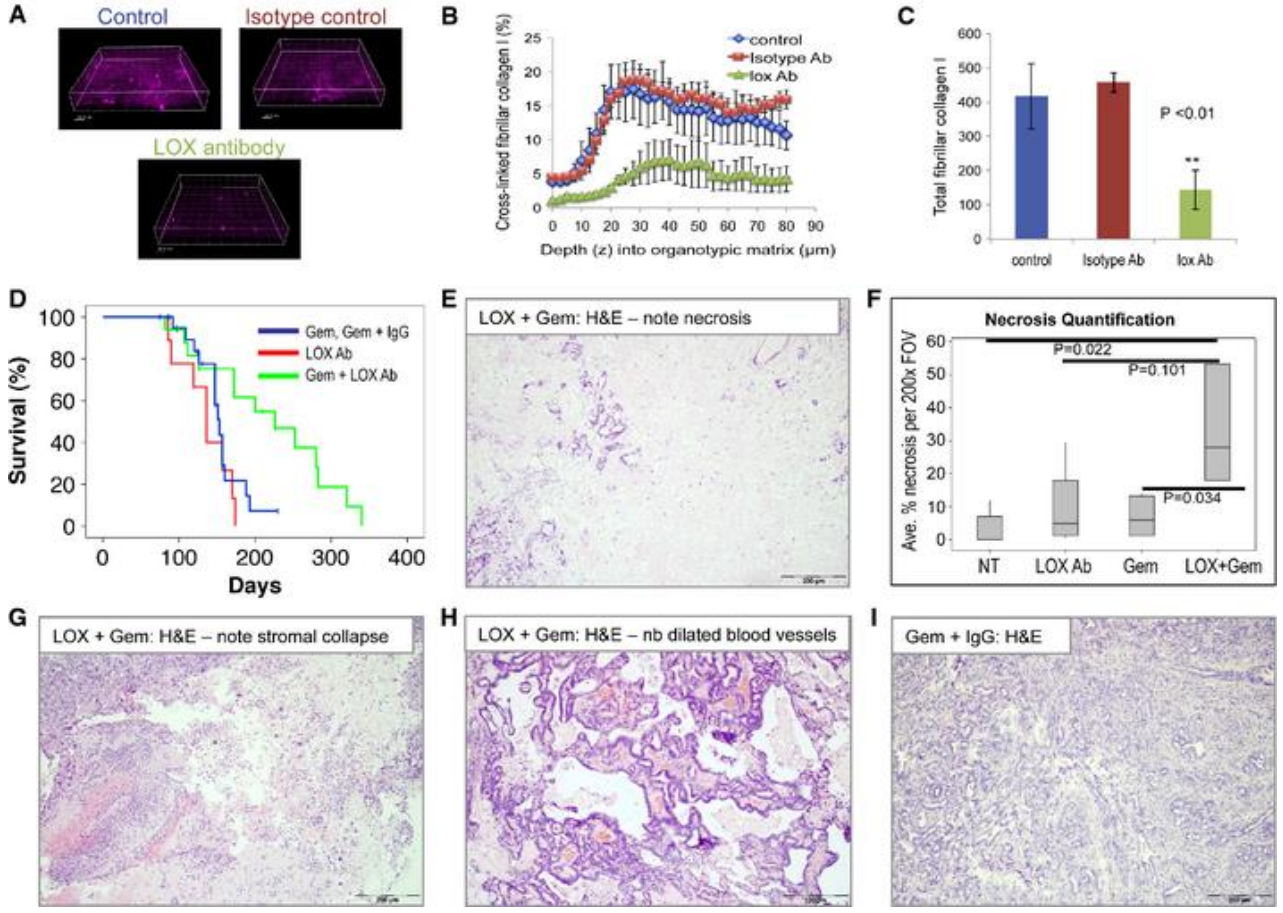
Stratification factors:

- 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)

Targeting the LOX/hypoxia axis : inhibition of LOX abrogates metastasis and enhances drug efficacy



DEVELOPING A FRAMEWORK FOR ANTI-METASTATIC DRUG DEVELOPMENT

CONCEPT DEVELOPMENT	PRECLINICAL DEVELOPMENT	CLINICAL TRIAL
Target identified Prevention or established metastasis? Clinical indication(s) of interest? Tailored target validation package	Clinical route of spread? Select most appropriate preclinical models Validation of pharmacodynamic, predictive and/or enrichment biomarkers Imaging?	Drug development plan: • What is the label? • Fit with standard of care? Right drug profile: • Therapeutic index required? • Healthy volunteer Ph I? • MTD appropriate? • Test more than one dose? Patient compliance? Appropriate side effect profile?

Next Steps

- Poster presentation – TAT Congress 2016
- Manuscript in preparation
- “Metastatic Niche” Consortium Funding
  - tumour microenvironment
  - immunotherapy
  - metabolism
  - *in vivo* models
  - patient selection markers
  - proof – of concept markers
- Clinical evaluation