New Agents / Strategies on the Horizon in Pancreatic Cancer

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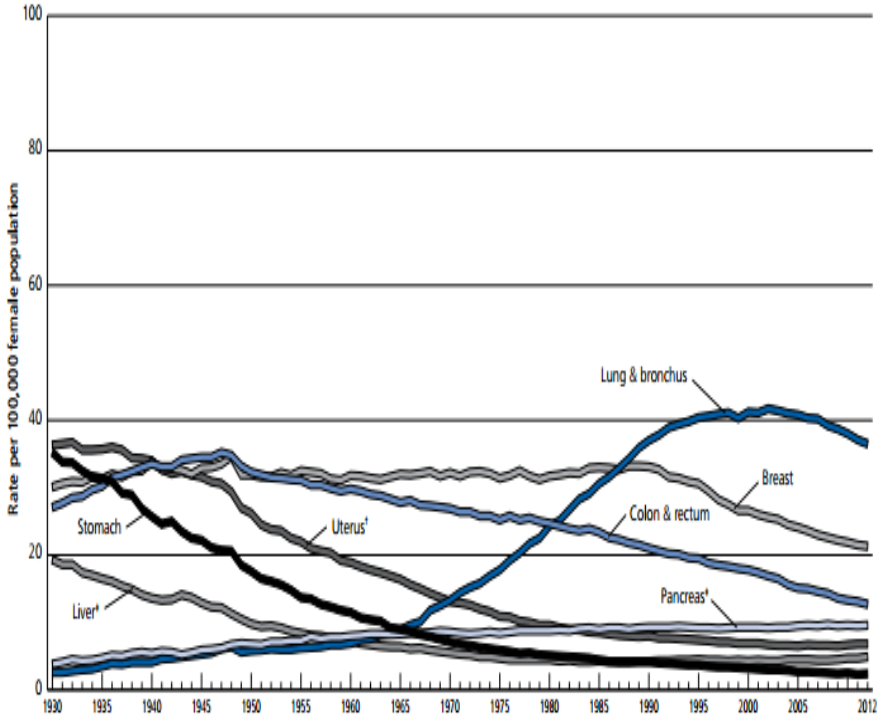
Director, UCSF Pancreas Center

UCSF Helen Diller Family Comprehensive Cancer Center

United States Cancer Statistics

Figure 2. Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2012

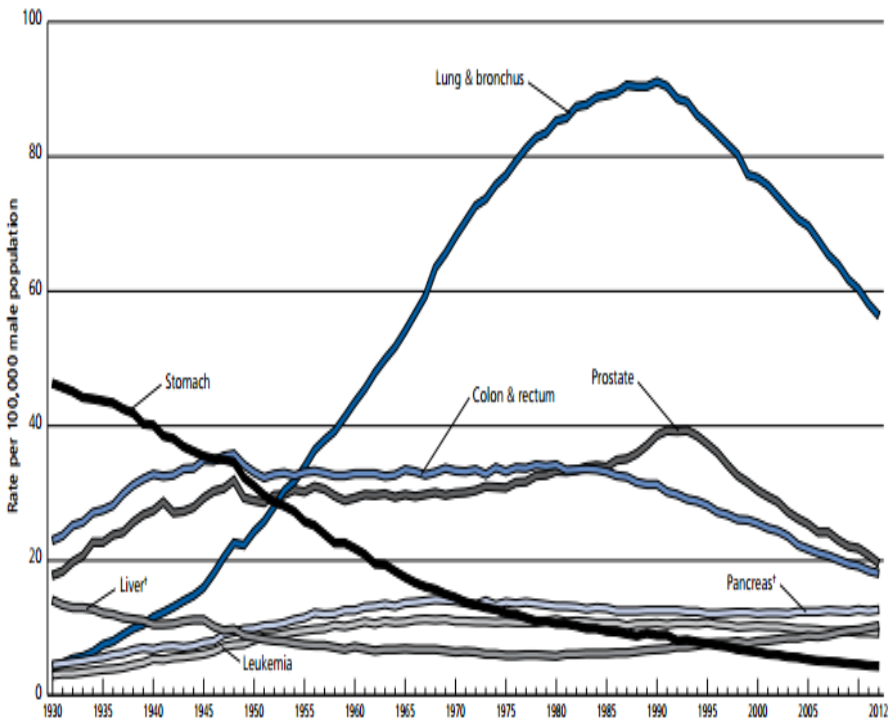


*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined. ‡Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2012, National Center for Health Statistics, Centers for Disease Control and Prevention.

Figure 1. Trends in Age-adjusted Cancer Death Rates* by Site, Males, US, 1930-2012



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Source: US Mortality Volumes 1930 to 1959 and US Mortality Data 1960 to 2012, National Center for Health Statistics, Centers for Disease Control and Prevention.

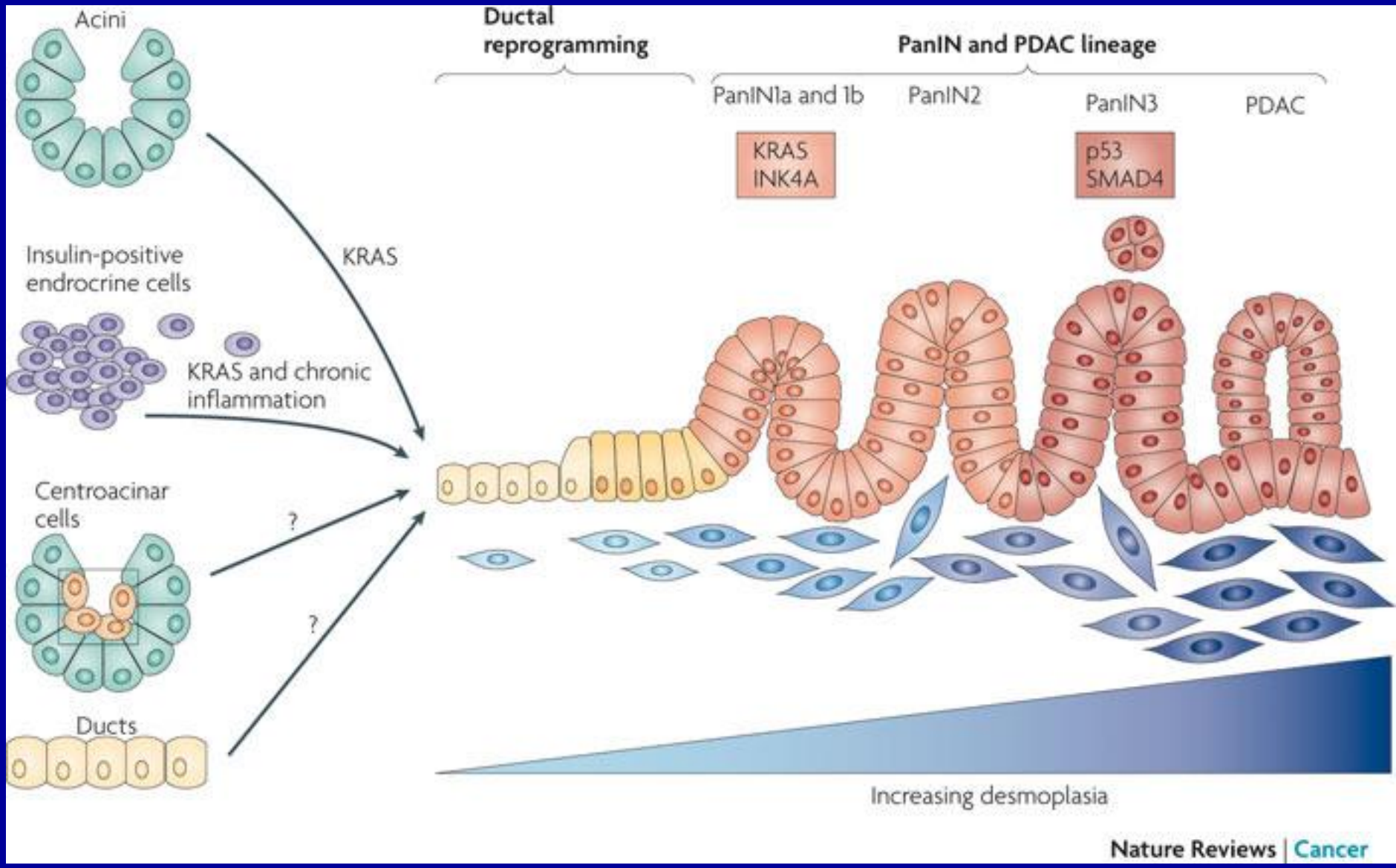
Progress in pancreatic ductal adenocarcinoma has been very slow.

This is a very tough disease!

- 80% of patients are diagnosed with advanced unresectable disease
- 80% of patients who have resection and adjuvant therapy relapse
- “Cure” rate is only 7%
- Median survival of patients with metastases without treatment is only about 3 months

Why is this disease so aggressive?

- No early symptoms
- Very early invasion and metastases
- Chemo-resistant (sanctuary?)
- Debilitating cytokine mediated symptoms



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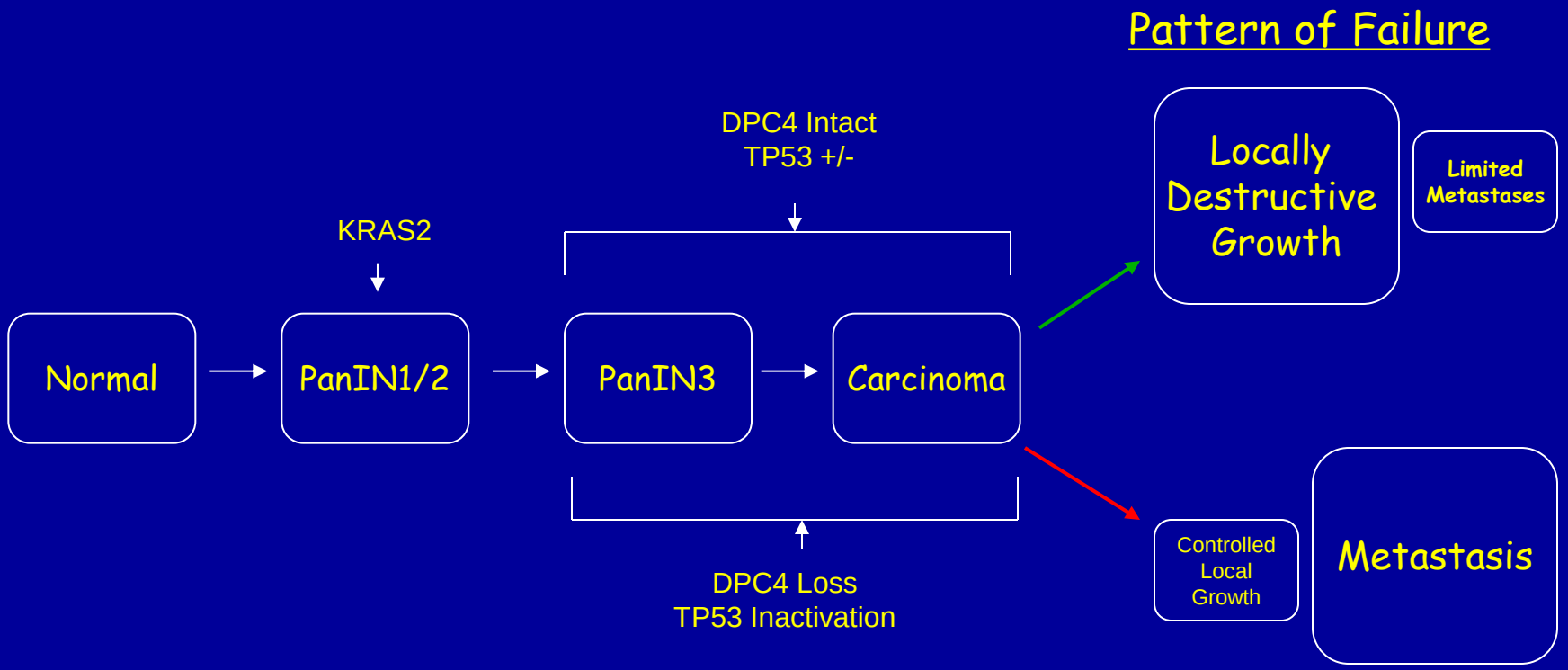
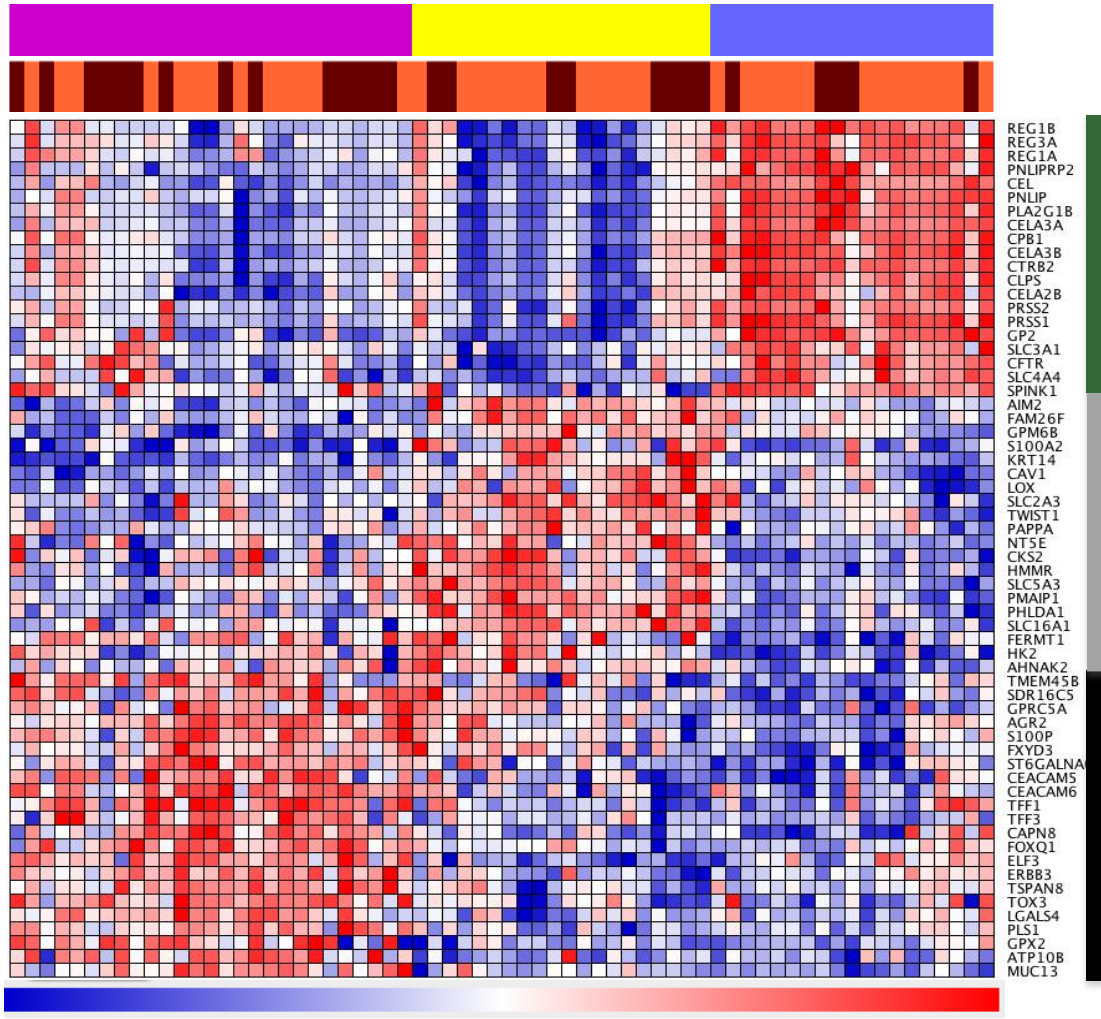
John P. Morris, IV, Sam C. Wang & Matthias Hebrok.*Nature Reviews Cancer* 10, 683-695 (October 2010) doi:10.1038/nrc2899

Progression Model of Pancreatic Cancer



Iacobuzio-Donahue et al. *J Clin Oncol 2009:27:1806-1813*

PDAC Subclasses



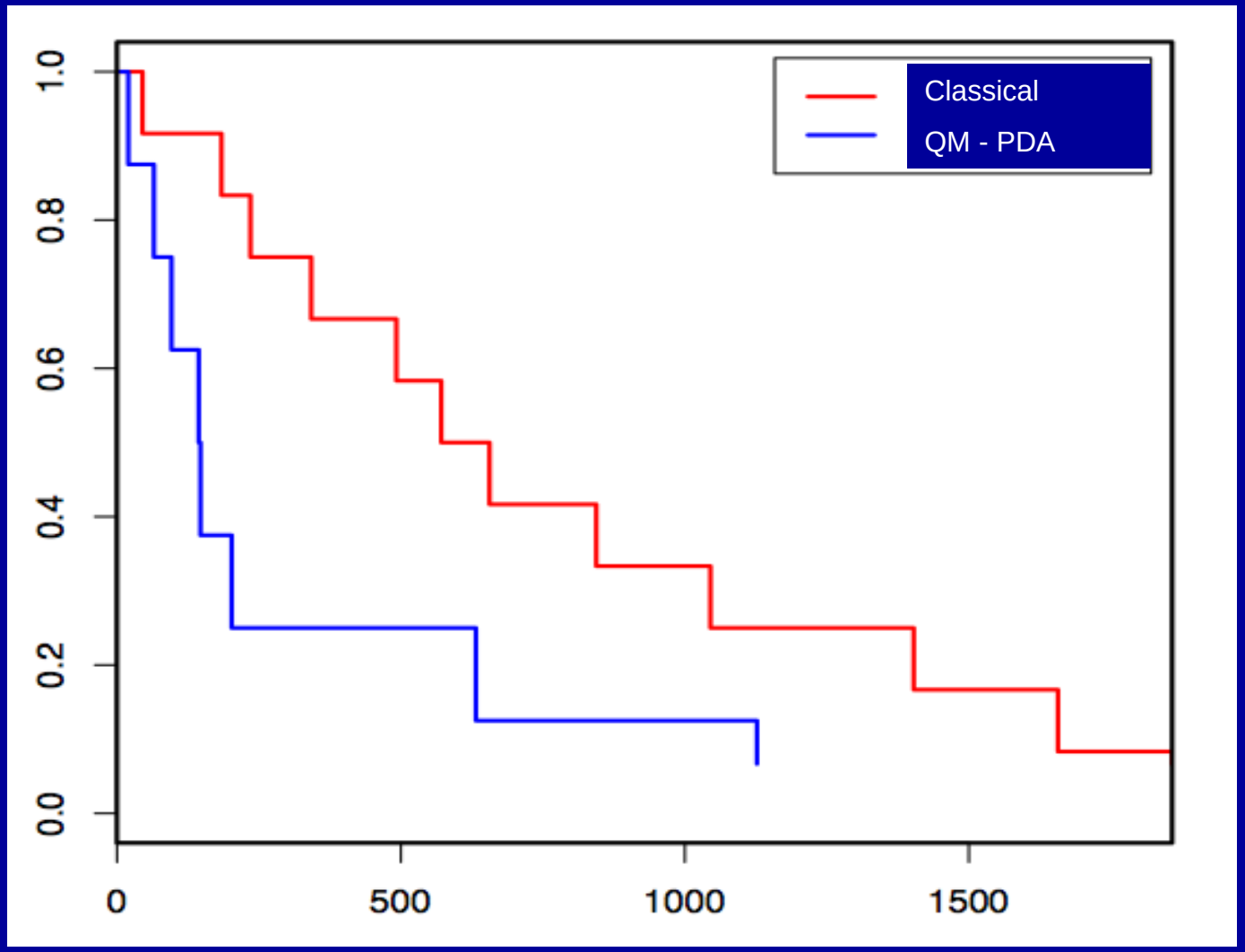
Acinar

Quasi-Mesenchymal

Classical

Collisson EA et al. Nature Medicine April 2011

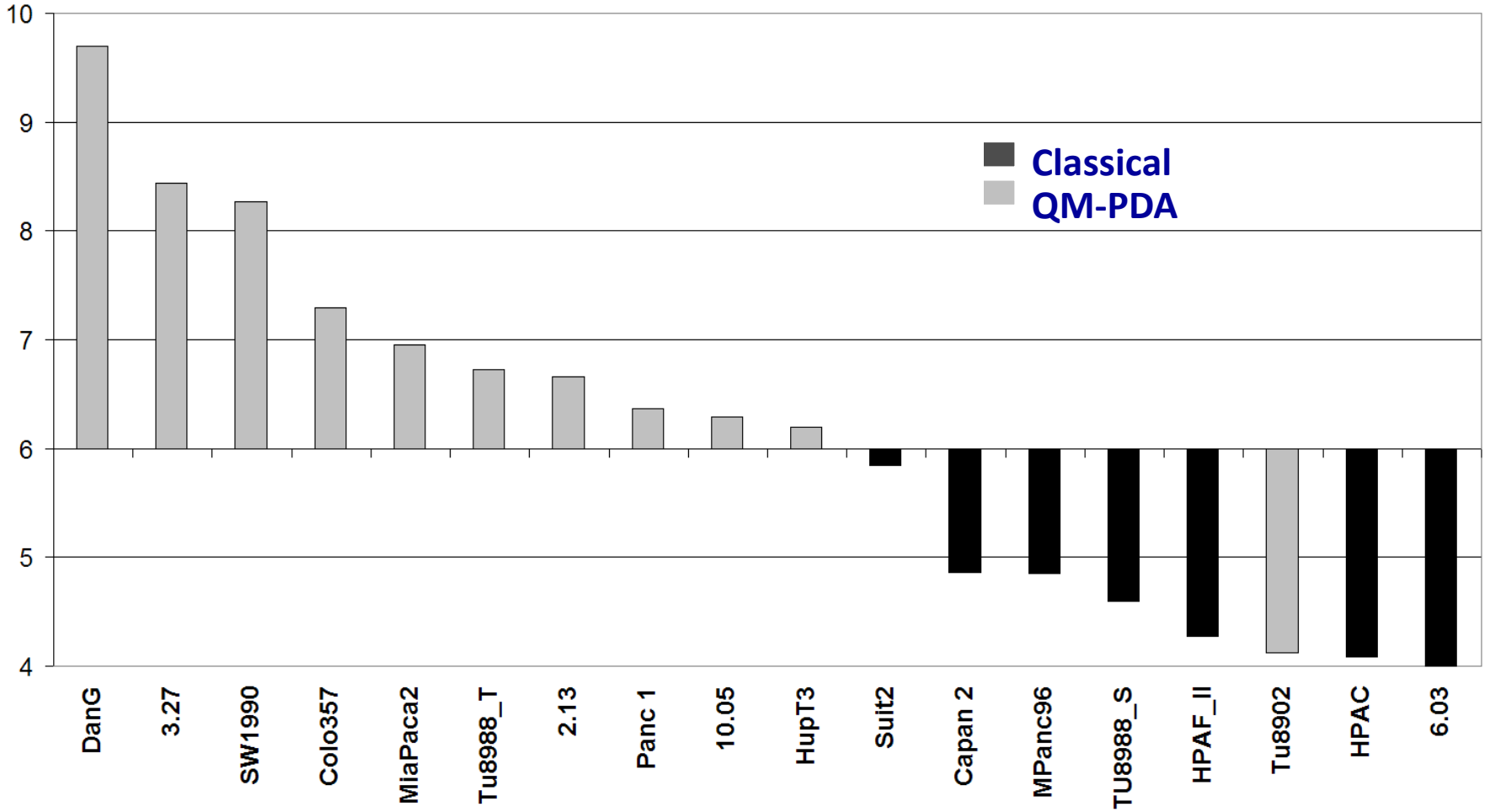
Prognostic Implications



p=.037

Collisson EA et al. Nature Medicine April 2011

Differential Drug Responses by Subtype in Cell lines

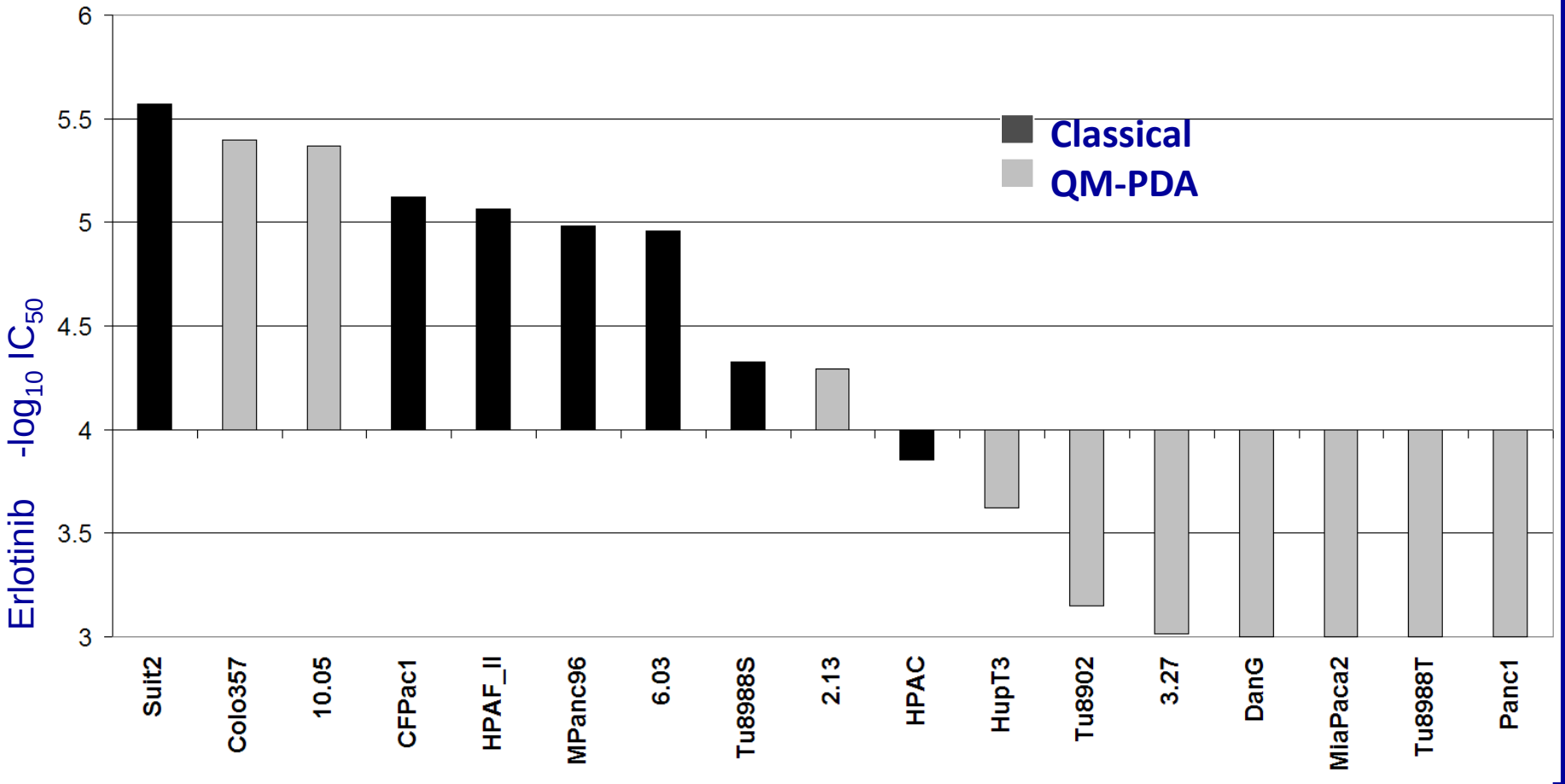


Quasi - Mesenchymal PDA cells are gemcitabine sensitive

Cancer Center

Collisson EA et al. Nature Medicine April 2011

Differential Drug Responses by Subtype in Cell lines



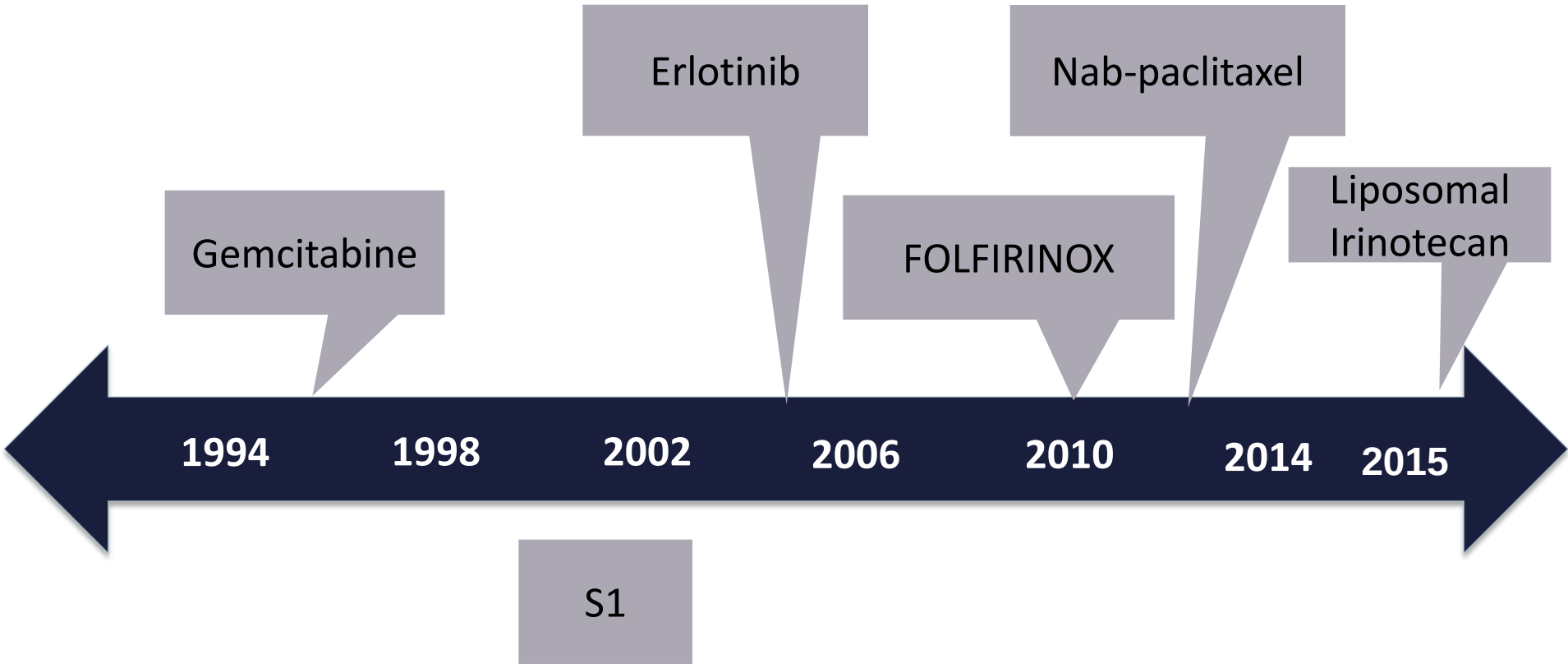
Classical PDA cells are erlotinib sensitive

Collisson EA et al. Nature Medicine April 2011

We still do not have a clinically useful biomarker for treatment selection in this disease.

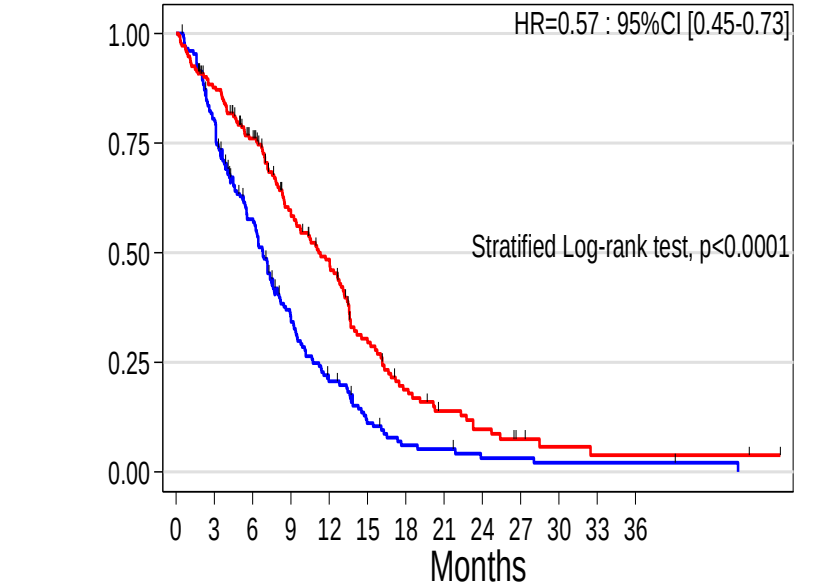
This is about to change!

Treating Pancreatic Cancer: Increasing Availability of Therapies



FOLFIRINOX

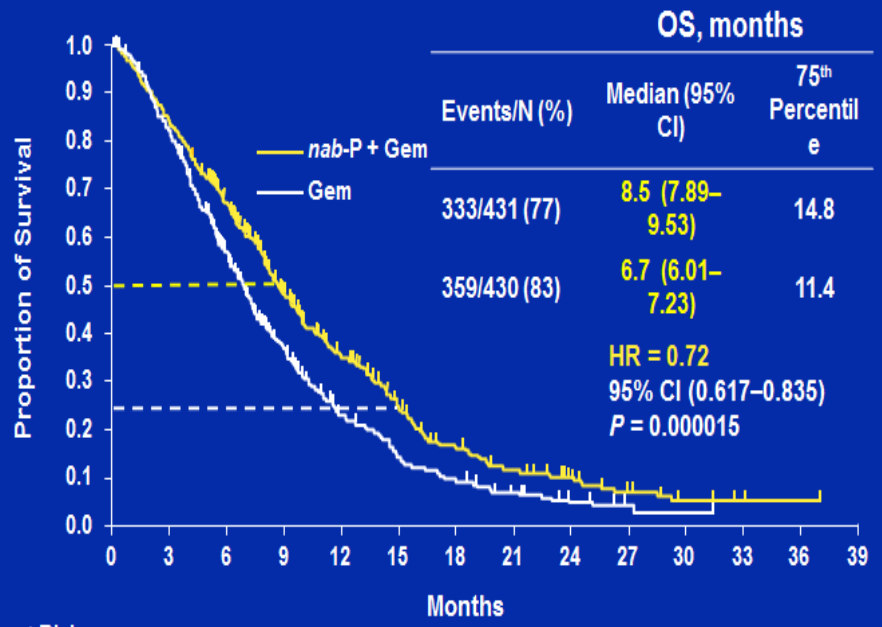
Overall Survival Curve



Slide courtesy of Thierry Conroy

UCSF Helen Diller Family Comprehensive Cancer Center

APACT Overall Survival



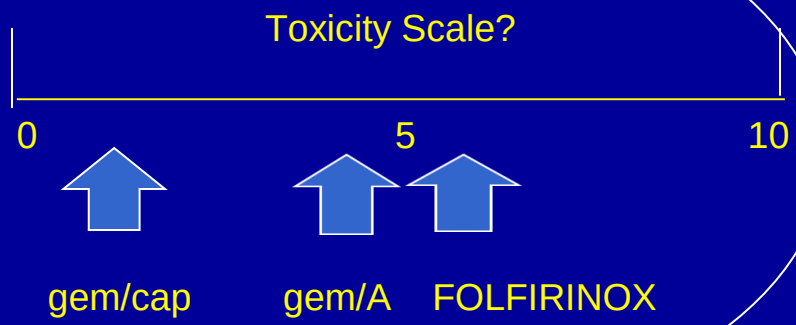
Von Hoff et al., ASCO GI 2013 LBA148

Which is better?

These studies cannot be compared.

One was regional (1 country) and one was global. Eligibility was slightly different. In a global trial, patients in some countries may have less optimal supportive care and fewer opportunities for second line treatments.

This is not a “contest”!



OS, PFS.
Objective RR

FOLFIRINOX > gem/A
but comparisons like this
are hazardous!

Selecting Treatment

Consider comorbidities
Patient preference
Goal of treatment
Compatibility with investigational agents
Predictive biomarkers

Other Options

1. gemcitabine and capecitabine
2. gemcitabine and cisplatin
3. GTX
4. gemcitabine and erlotinib

Moving Forward?

Let's build on both FOLFIRINOX and gemcitabine plus albumin bound paclitaxel.

Give special consideration to gemcitabine and cisplatin in selected individuals.

Randomized Phase II or First Line Phase III Studies

FOLFIRINOX: PEGPH20 (hyaluronidase)

Gemcitabine + Nab-P: ibrutinib
demcizumab
MM-141
PEGPH20

There are 54 open Phase 1 - 3 trials in the US for metastatic disease – only 2 trials incorporate FOLFIRINOX

Maintenance?

What can you do when patients have good disease control

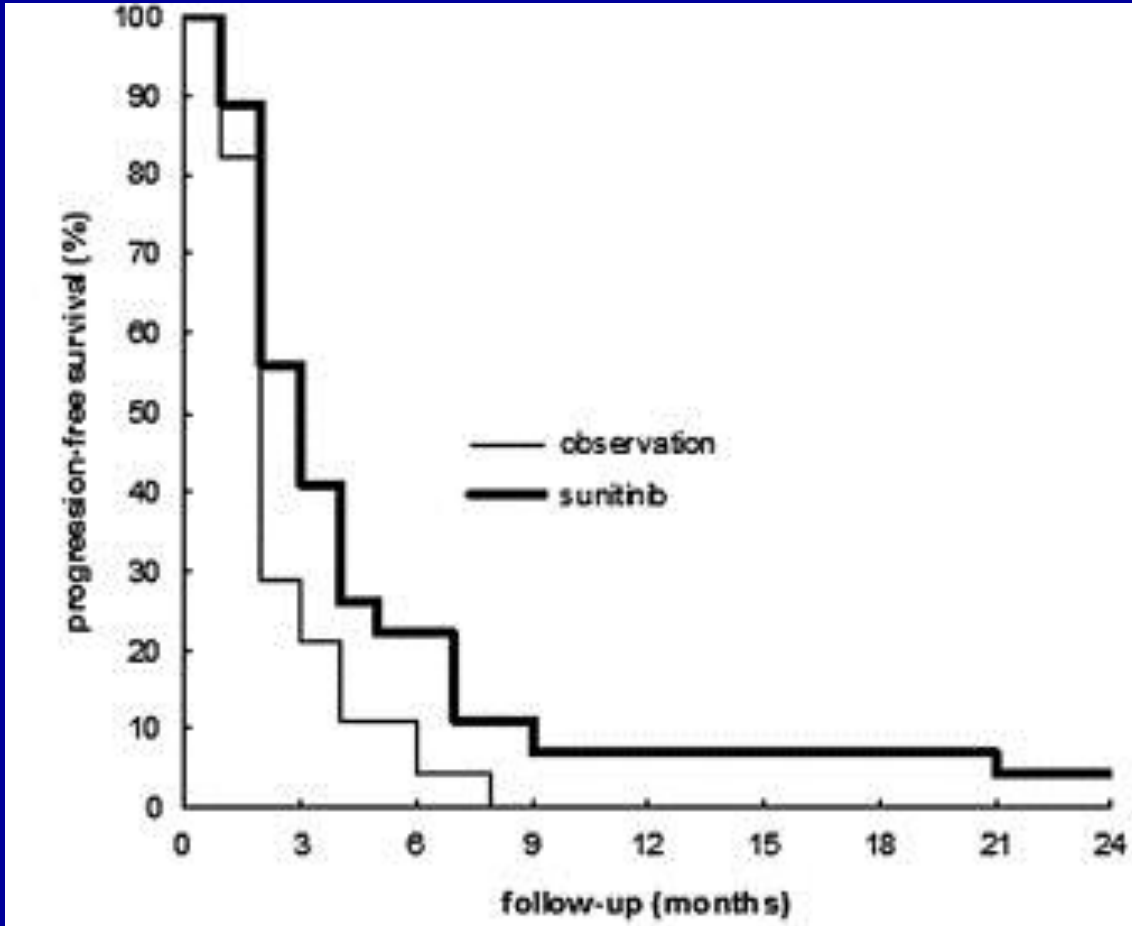
but can’t tolerate

continued treatment?

Maintenance sunitinib or observation in metastatic pancreatic adenocarcinoma: A phase II randomised trial

Michele Reni [a,*], Stefano Cereda [a], Michele Milella [b], Anna Novarino [c], Alessandro Passardi [d], Andrea Mambrini [e], Giuseppe Di Lucca [f], Giuseppe Aprile [g], Carmen Belli [a], Marco Danova [h,k], Francesca Bergamo [i], Enrico Franceschi [j], Clara Fugazza [a], Domenica Ceraulo [a], Eugenio Villa [a]

Eur J Cancer. 2013 Nov;49(17):3609-15



Number at risk:

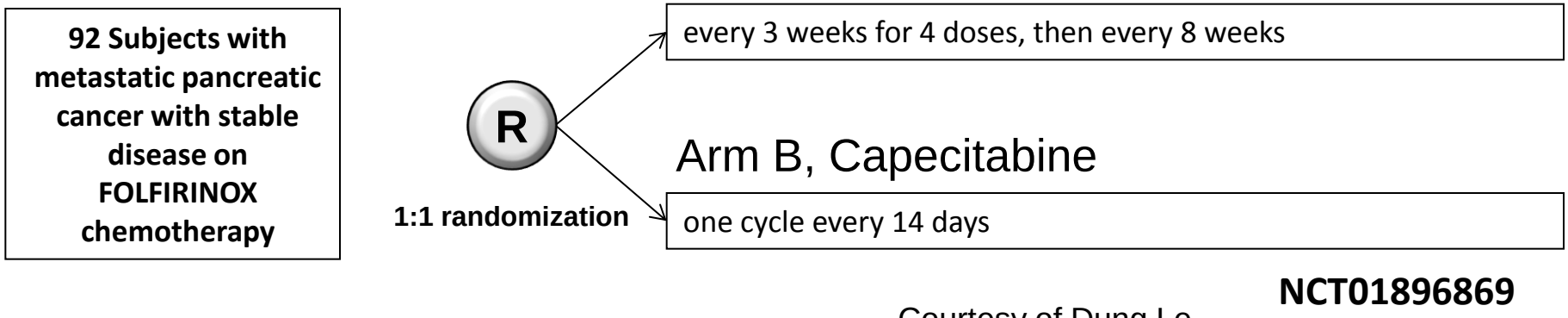
observation	28	7	1	0	0	0	0	0	0
sunitinib	27	15	6	2	2	2	2	2	1

Eur J Cancer. 2013 Nov;49(17):360

GVAX/Ipi Frontline Maintenance Study

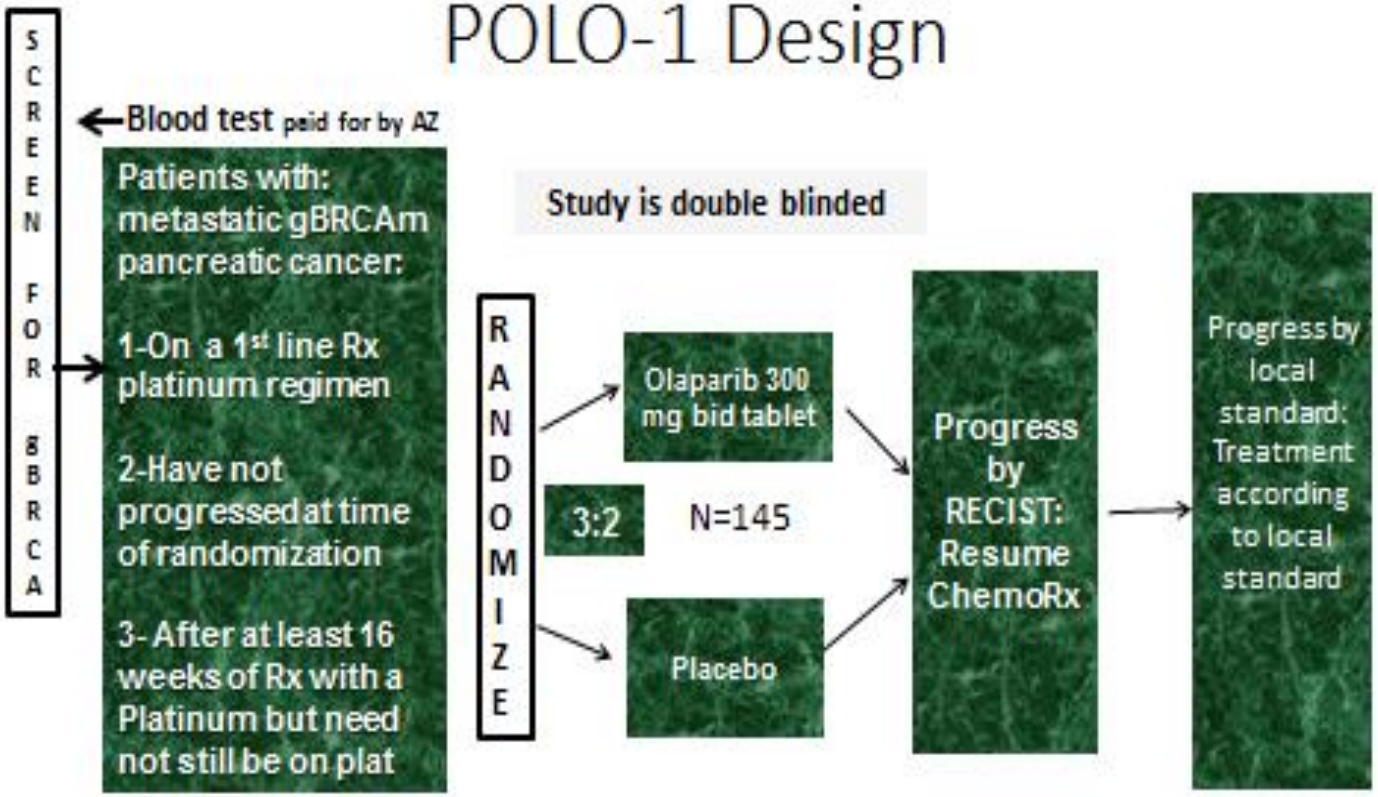
GVAX Pancreas + Ipilimumab vs. FOLFIRINOX

- Stable metastatic pancreatic cancer after 8-12 cycles of FOLFIRINOX; ECOG 0 or 1
  - Investigator-sponsored (PI: Dung Le)
  - Multi-Center, open-label, randomized, controlled
- Objectives
  - Primary objective: Overall survival
  - Secondary objectives: number of adverse events; progression-free survival; immune-related progression-free survival; objective response rate; duration of response; and tumor marker (CA 19-9) kinetics



Courtesy of Dung Le

POLO-1 Design



- Primary Endpoint is PFS (by central review) with intent to apply for accelerated approval based on target endpoint
- Secondary Endpoints are OS (basis of permanent registration), PFS2 by investigator assessment, ORR, DCR, safety, quality of life, and exploratory studies

Courtesy of Talia Golan

PRECISION PROMISE

Revolutionizing
treatment for every
pancreatic cancer patient.

Precision Promise

Mission Statement: To transform outcomes for all pancreatic cancer patients through a research and clinical trials platform that creates a culture of cooperation and learning among clinicians, researchers and drug developers, and puts the patient at the center of every decision.

PANCREATIC CANCER ACTION NETWORK®

Guiding Principles

- Patient centricity - through the entire journey
- Audacious goals
- Sense of urgency
- Flexibility
- Iterative between science and medicine
- Sustainability

PANCREATIC CANCER ACTION NETWORK®

Precision Promise **structure**

Coordinating center

- Executive Committee
- Working Groups including industry
- Infrastructure for communication & information exchange

Translational Research Grants Program

- Support for translational and clinically relevant research identified by Coordinating Center
- Projects competitively reviewed through Research Grants department processes

Clinical Trials Consortium

- 10 sites initially in US
- Know Your Tumor
- Just-in-time feature to be developed
- Other Consortia to join in future

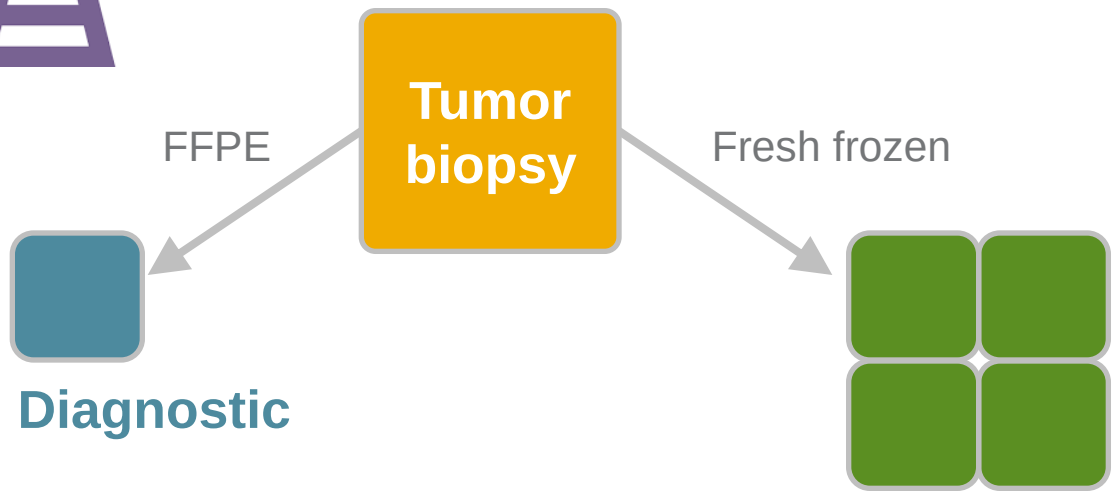
PANCREATIC CANCER ACTION NETWORK®

Master Protocol with Sub-studies

- Molecularly stratified
- Small “signal seeking” studies
- Adaptive design
- Multiple “shots on goal” for each patient
- Flexible - changes in sub-studies do not affect master protocol
- Rapid transfer of patient to next sub-study when indicated
- Learn as we go
- Start with 3 sub-studies
  - Stromal Disruption
  - DNA Damage Repair
  - Immunotherapy

PANCREATIC CANCER ACTION NETWORK®

Master Protocol Molecular Profiling



Diagnostic

Immunohistochemistry

- HA
- Immunotherapy markers
- Other

Genome sequencing

In order of priority based on DNA quantity and tumor cellularity:

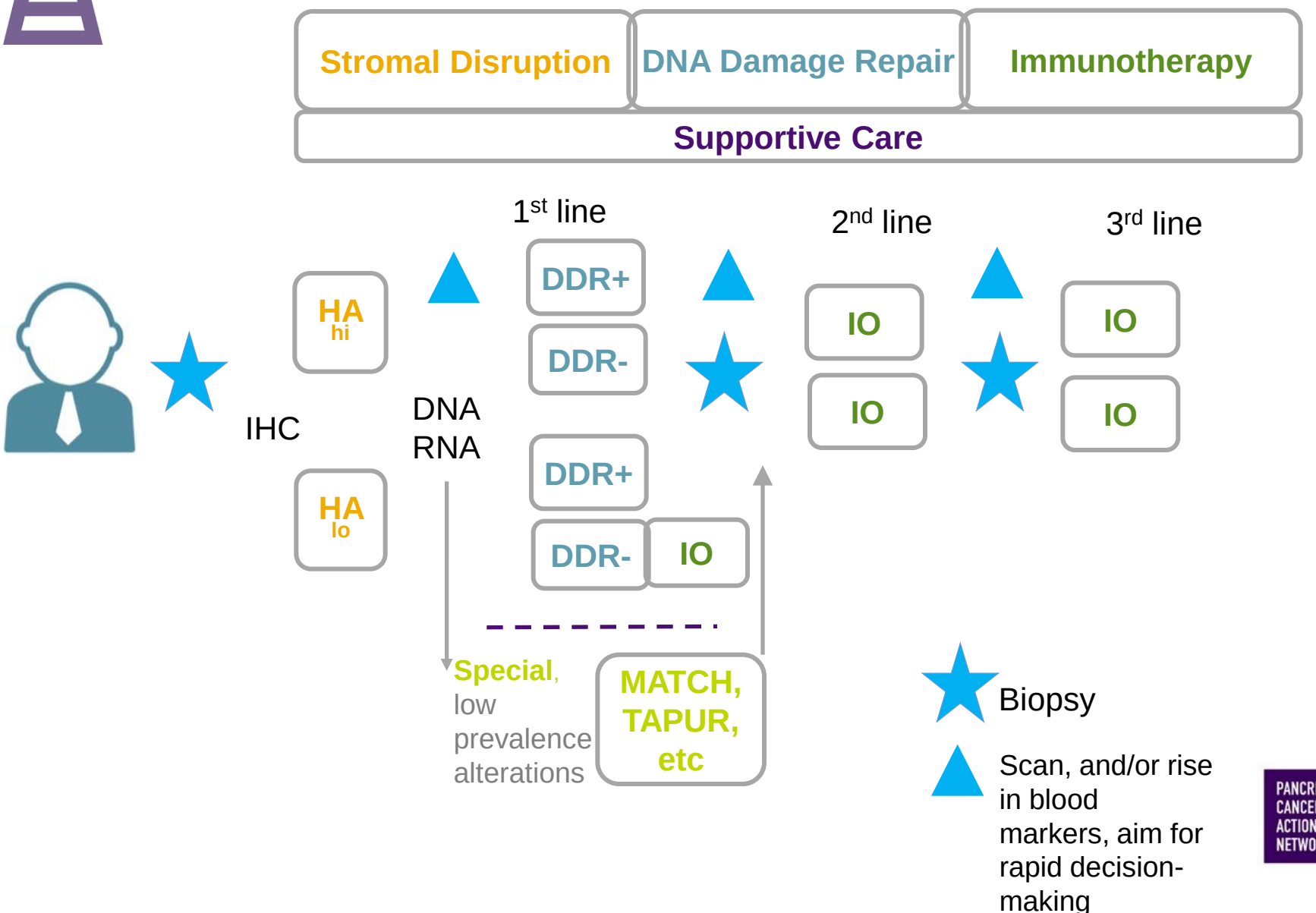
1. Cancer gene panel
2. WGS 80X, Normal 40X (Deeper if low cellularity or of significant interest)
3. WES 100X (only if min DNA left after panel)

Transcriptome sequencing

RNAseq on all patients
(50-135M reads depending on cellularity)

PANCREATIC CANCER ACTION NETWORK®

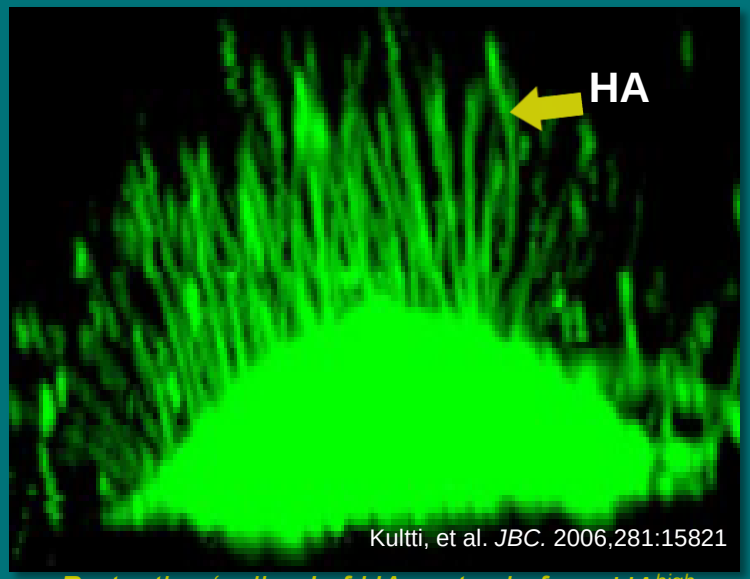
General Concept for Trial Design



Hyaluronan (HA): A Barrier to Therapeutic Access

- **Highly hydrophilic, megadalton glycosaminoglycan (GAG) that can generate large immobile fluid phase**
- **Compromises Access to the Tumor**
  - Increased tumor interstitial fluid pressure [1,2]
  - Compresses vasculature [2-4]
  - HA-rich tumor cell "coat" can hinder host immune cell access
- **HA also signals through surface receptors**
- **PEGPH20 degrades HA**

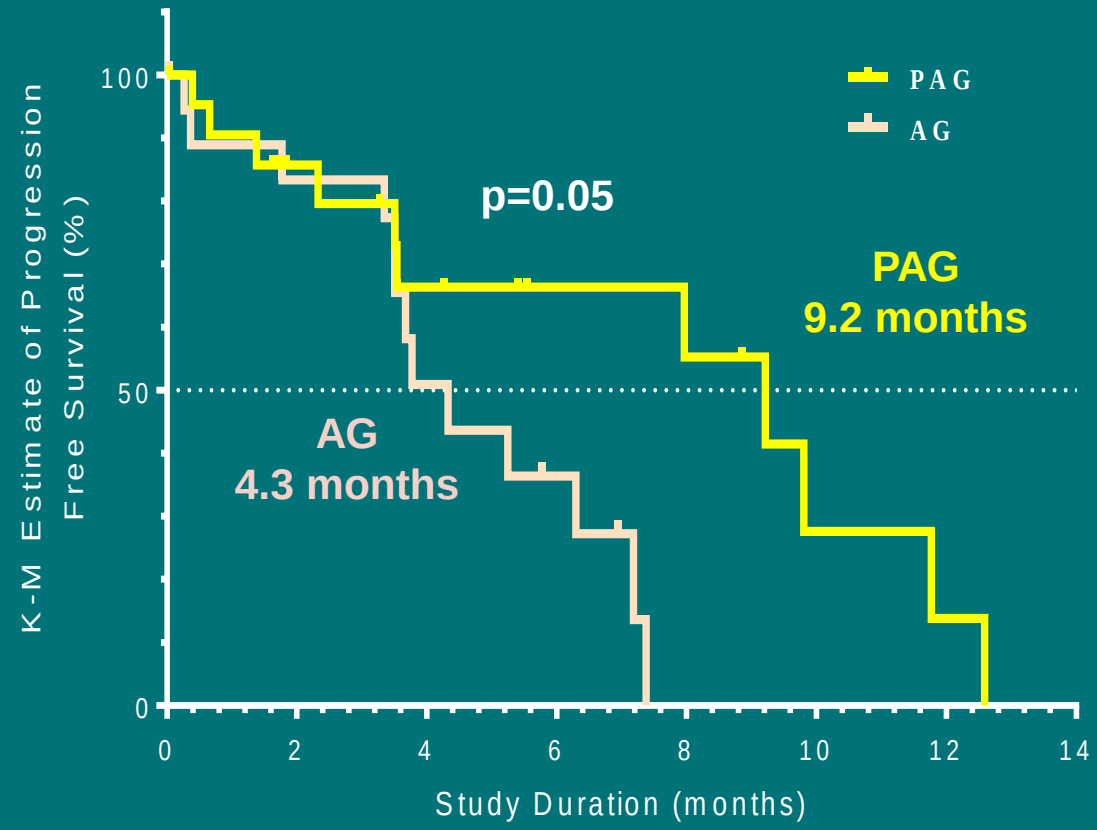
HA^{High} Cancer Cell



Protective 'spikes' of HA protrude from HA^{high} tumor cell in culture

1. Brekken, et al. *Anticancer Res.* 2000,20:3503. 2. Provenzano and Hingorani, *Br. J. Cancer.* 2013,108:1.
3. Thompson, et al. *Mol Cancer Ther.* 2010,9:3052. 4. Stylianopoulos, et al. *PNAS. 2013,*110:18632.

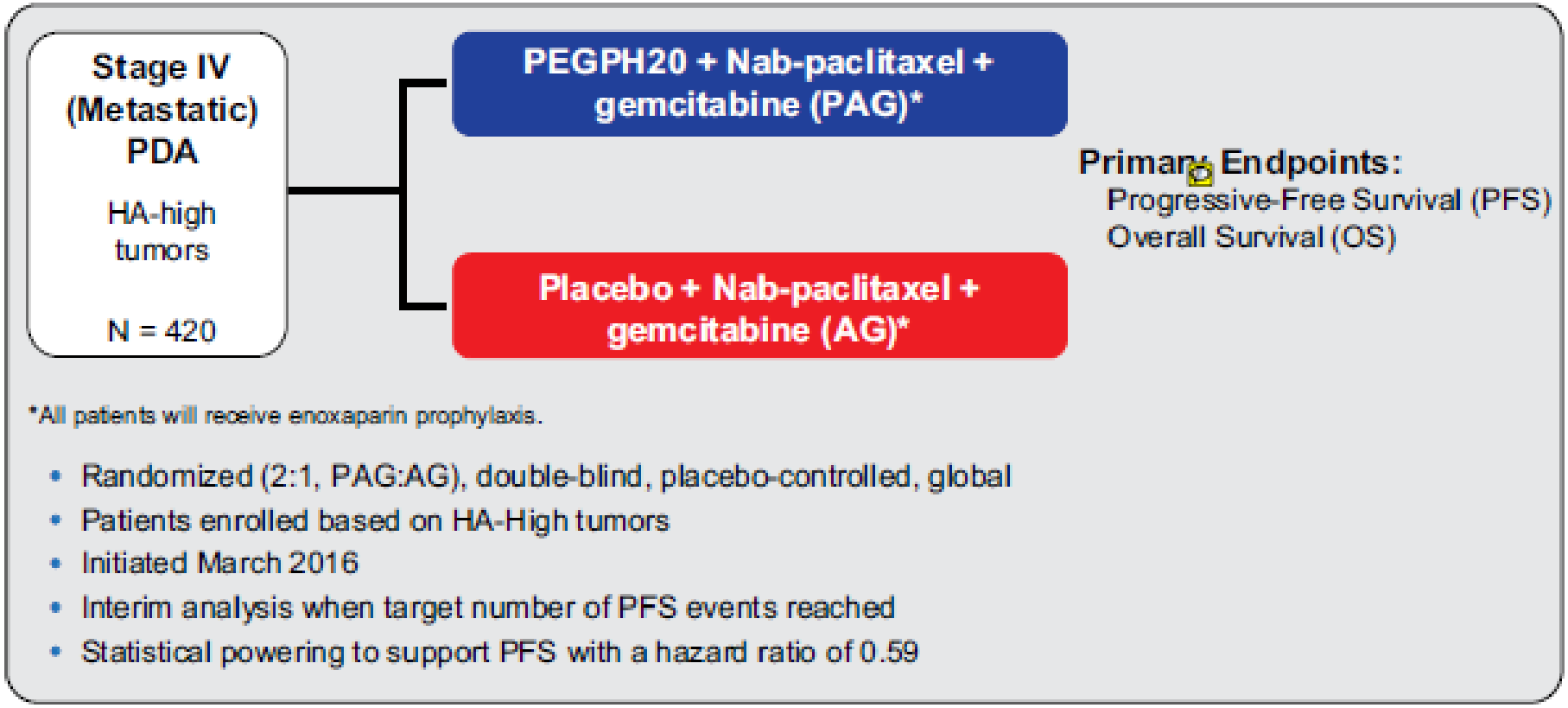
PFS in HA-High Patients



HR
0.39 (0.15, 1.04)

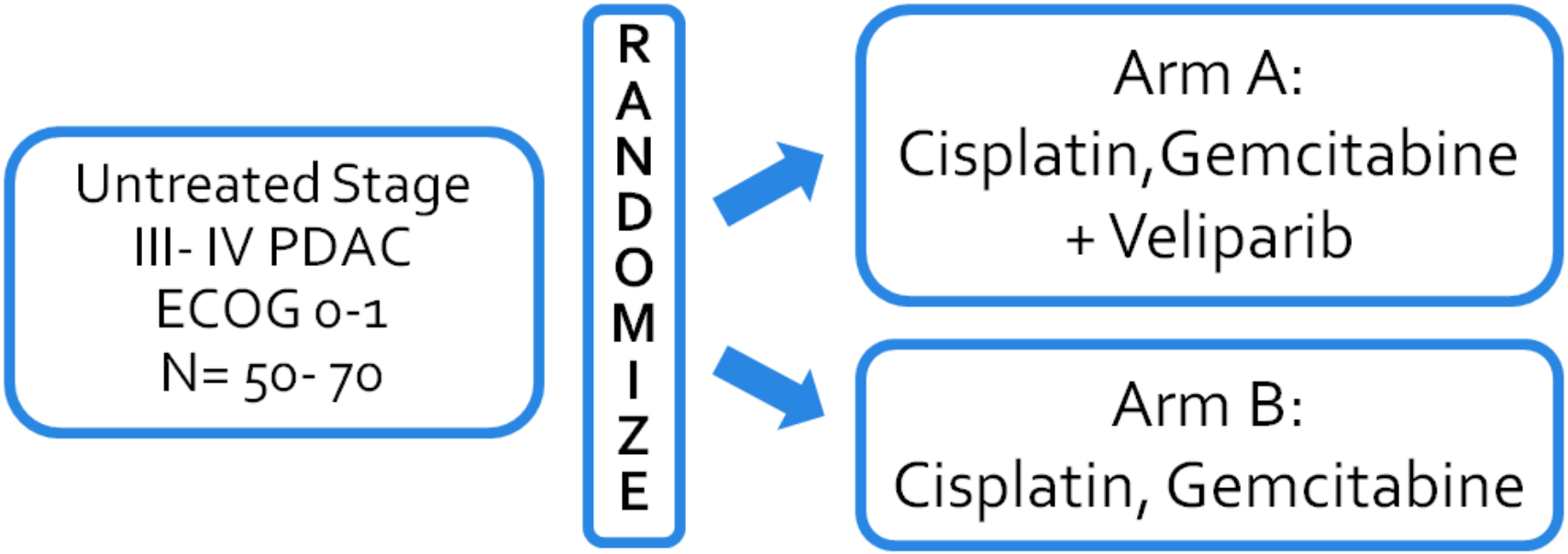
At Risk								
PAG	23	14	10	6	5	2	1	0
AG	21	14	7	4	0	0	0	0

Global Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Compare Efficacy and Safety of PEGylated Recombinant Human Hyaluronidase (PEGPH20) Plus Nab-Paclitaxel and Gemcitabine vs Placebo Plus Nab-Paclitaxel and Gemcitabine in Patients With Previously Untreated, Hyaluronan (HA)-High, Stage IV Pancreatic Ductal Adenocarcinoma



Courtesy of Halozyme

Randomized Phase II Cisplatin, Gemcitabine +/- Veliparib Germline BRCA/PALB2



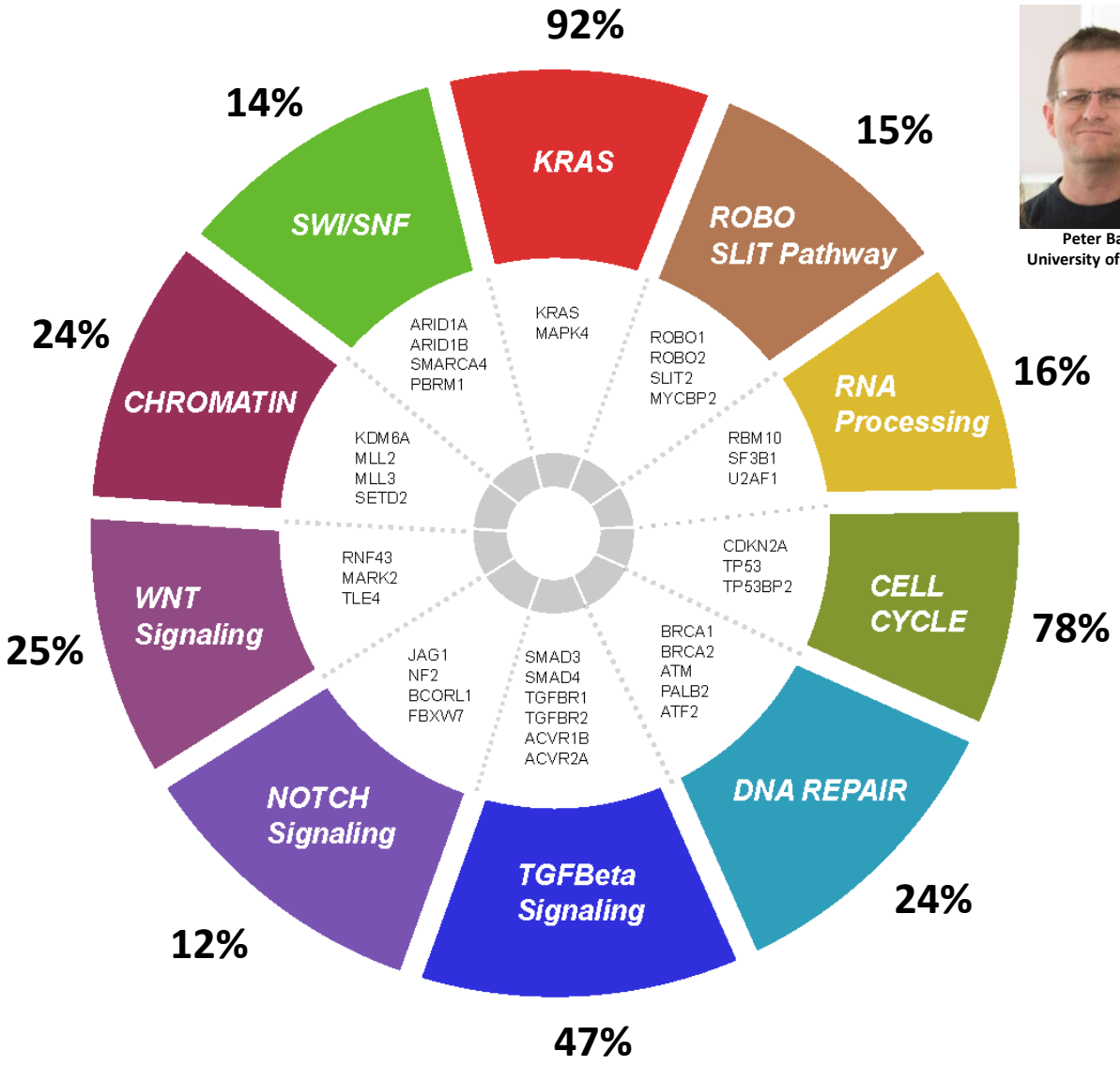
Randomization 1:1

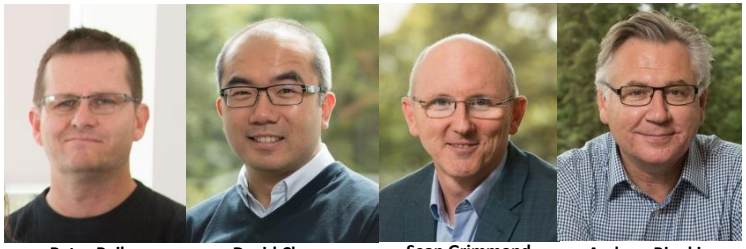
Primary Endpoint: Response Rate

NCT01585805 O'Reilly, EM, Lowery, MA, Kelsen, DP

Memorial Sloan Kettering Cancer Center

Key Molecular Mechanisms and Potential Novel Vulnerabilities (n = 457 multiplatform -omic analysis)





Peter Bailey
University of Glasgow

David Chang
University of Glasgow

Sean Grimmond
University of Glasgow

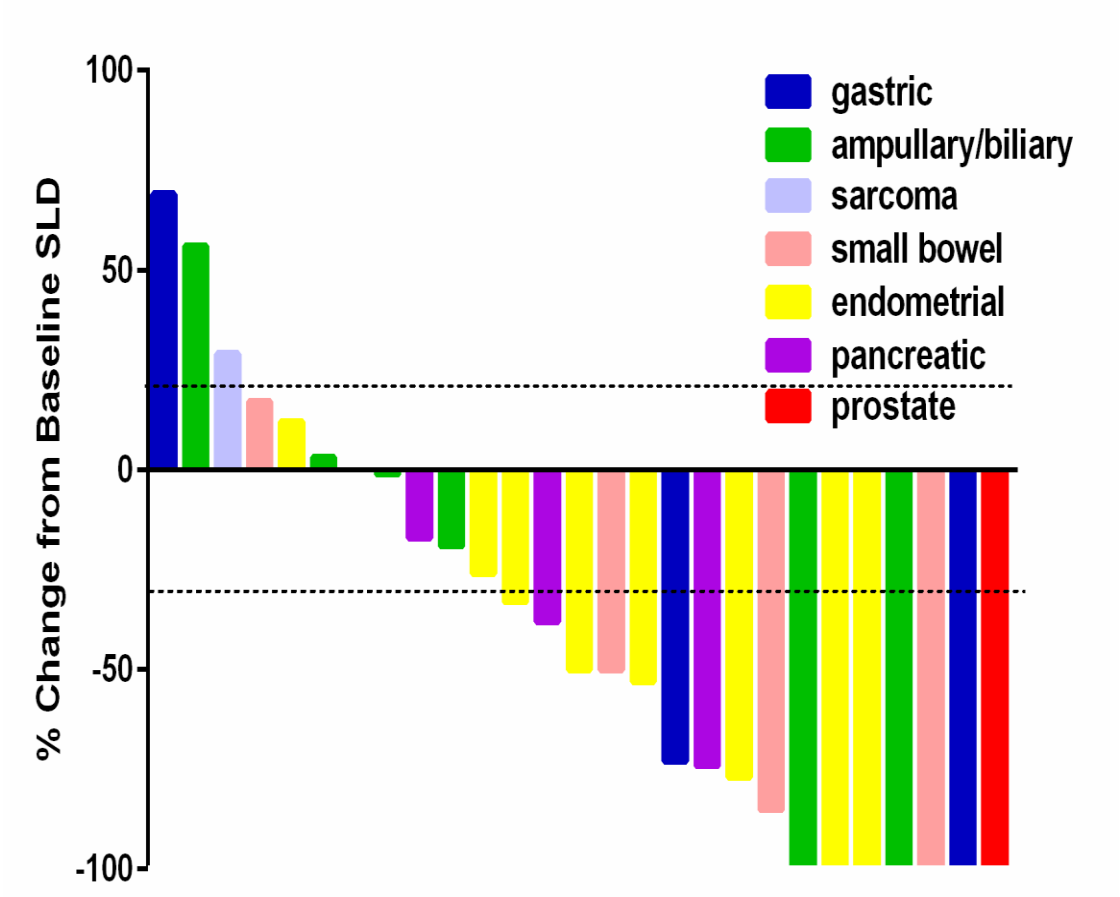
Andrew Biankin
University of Glasgow

Hudson et al. Nature 2010
Biankin et al. Nature 2012
Perez-Mancera et al. Nature 2012
Mann et al. PNAS 2012
Alexandrov et al. Nature 2013
Weissmueller et al. Cell 2014
Waddell et al. Nature 2015
Biankin et al. Nature 2015
Bailey et al. Nature 2016

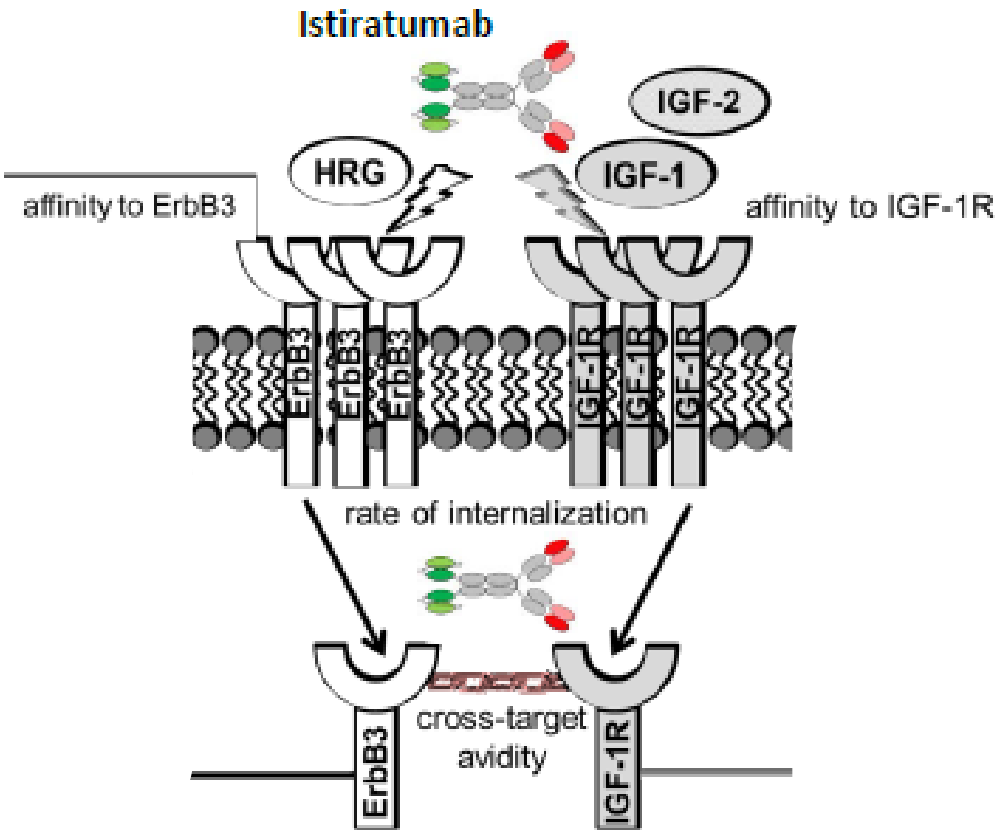
Bailey *et al. Nature* 2016

MMR Deficient non CRC - Pembrolizumab Rx

Target Lesion Measurements

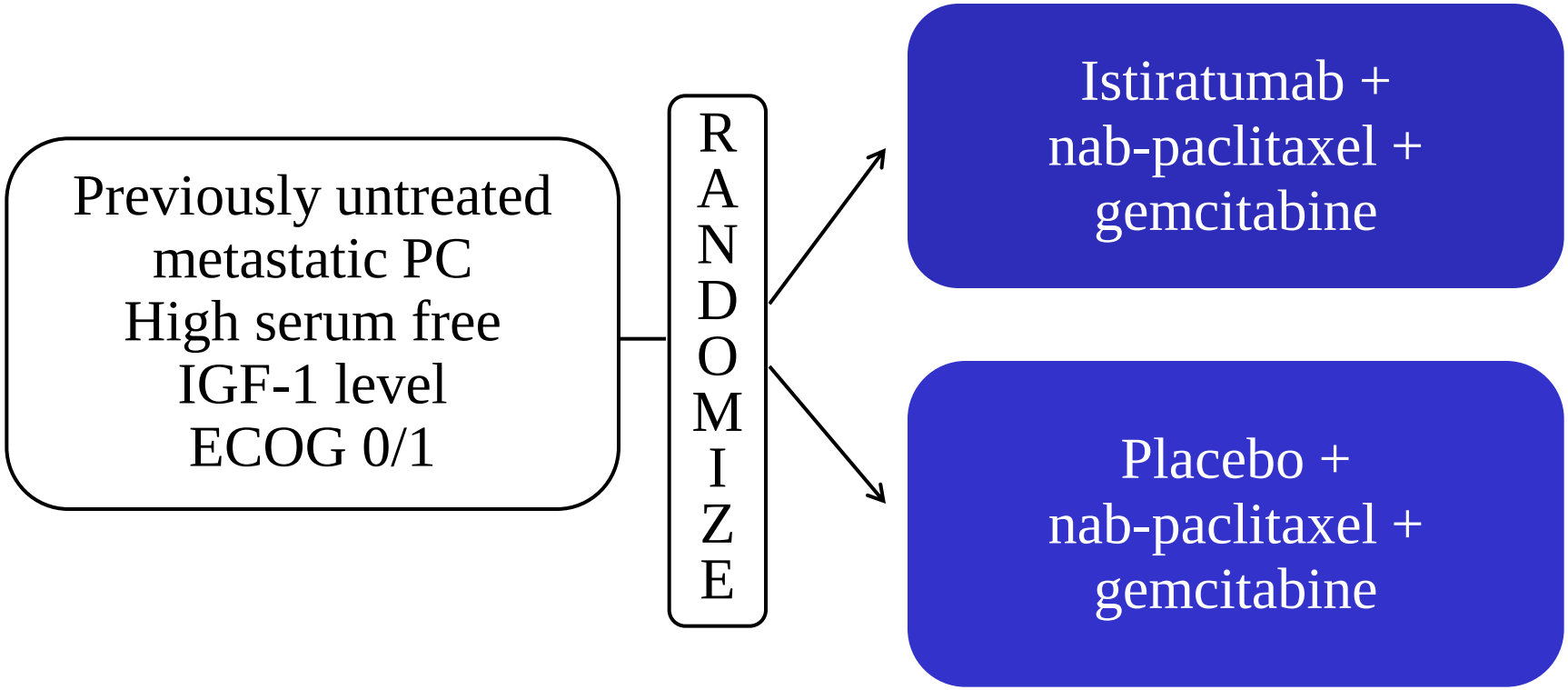


Istiratumab (MM-141)
(bispecific antibody vs. IGF-1R and HER3)



Ko, ASCO GI 2016 (abstract)

Randomized phase 2 study (CARRIE) of istiratumab for metastatic pancreatic cancer



Primary endpoint: PFS
Screened 260 patients to identify ~146 eligible subjects

https://clinicaltrials.gov/ct2/show/NCT02399137. Accessed May 20, 2016.

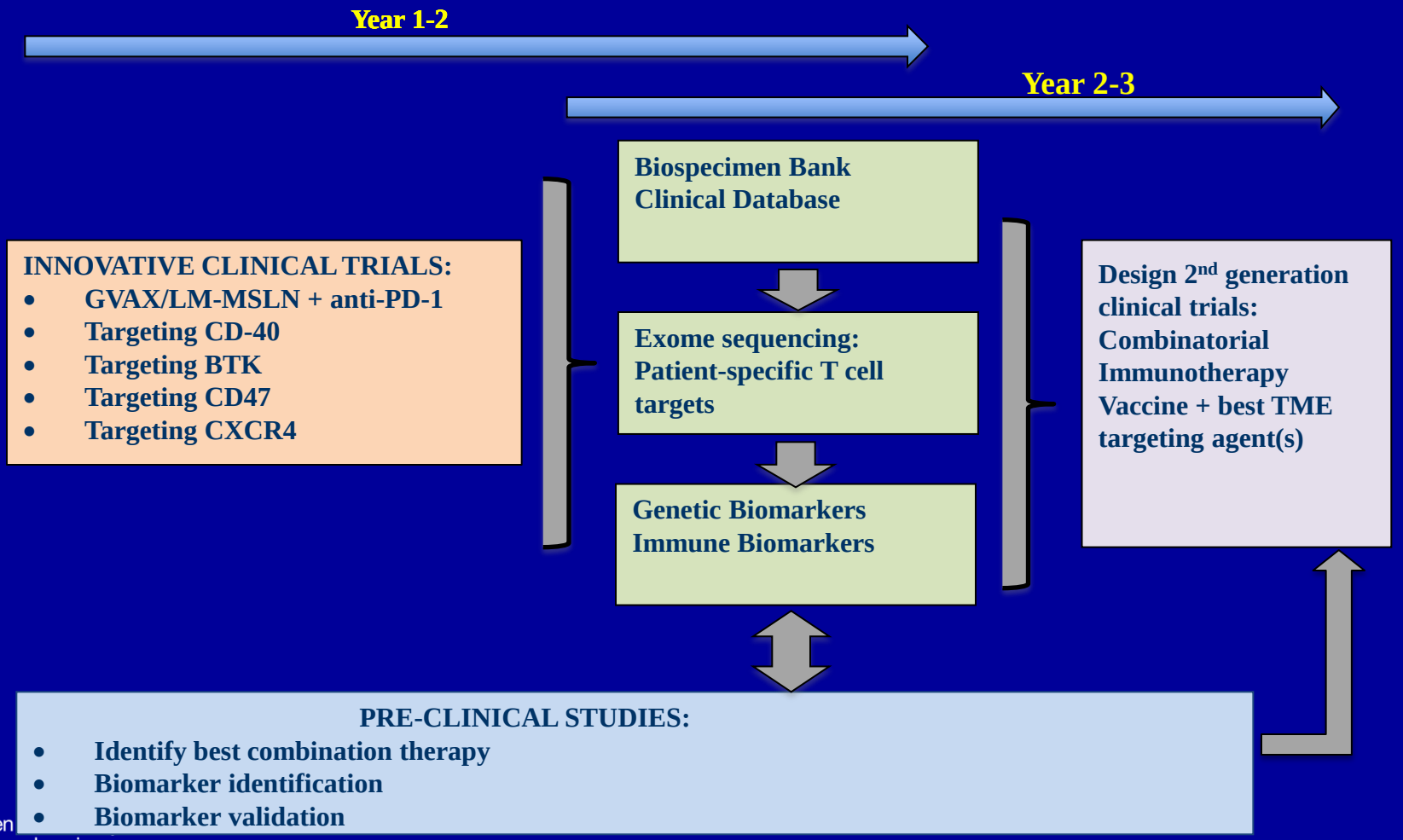
Considering genetic heterogeneity in cancer, adaptive immunity may be our best asset in controlling disease progression.

However, PDAC is not enriched with CD8 T cells, so standard approaches with checkpoint inhibitors do not work.

SU2C Collaboration

SU2C Dream Team: "Transforming pancreatic cancer from a death sentence into a treatable disease"

Figure 4. Schematic of Tiered Approach



Summary

- We now have multiple options for stabilizing chemotherapy
- Robust efforts underway to target RAS
- Biomarker driven trials are now in progress
- Precision Promise will launch in 2017
- Stromal associated targets, especially immune targets, are being addressed
- Windows of opportunity trials are feasible after response to chemotherapy


Thank you!