Memorial Sloan-Kettering Cancer Center

David M. Rubenstein CPCR Center for Pancreatic Cancer Research

Pancreatic Adenocarcinoma: Current Treatment Approaches

Pancreatic Cancer Action Network Seminar
New York, Oct 24th, 2014

Eileen M. O'Reilly, M.D.
Associate Director, Clinical Research
Rubenstein Center for Pancreatic Cancer Research
Memorial Sloan Kettering Cancer Center

Agenda

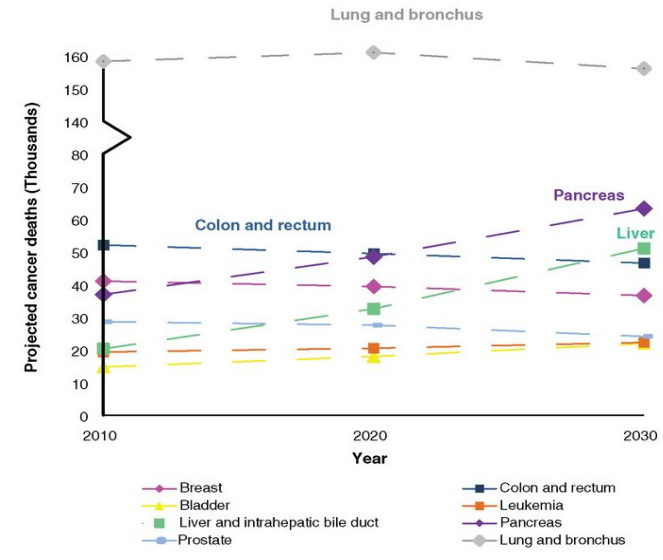
- Pancreas cancer epidemiology
- Early stage disease
- Advanced disease
- Clinical trials
- Novel agents in development

The Problem and Challenges

- New diagnoses – US 2014: 45,220
- 9th–10th most common cancer
- 3% of all new cancers
- Overall 5-year survival low and stable

American Cancer Society, 2014. www.cancer.org; SEER Cancer Statistics Review, 1975-2006. NCI. www.surveillance.cancer.gov; Hoos WA. J Clin Oncol, 2013; Siegel R. Ca Cancer J Clin, 2014

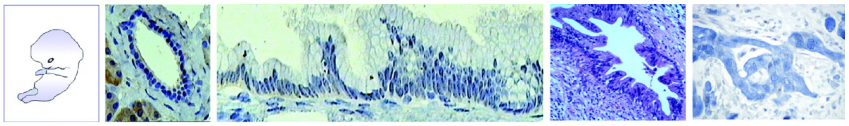
Projected Burden of Cancer



Rahib L et al. Cancer Res 2014

American Association for Cancer Research

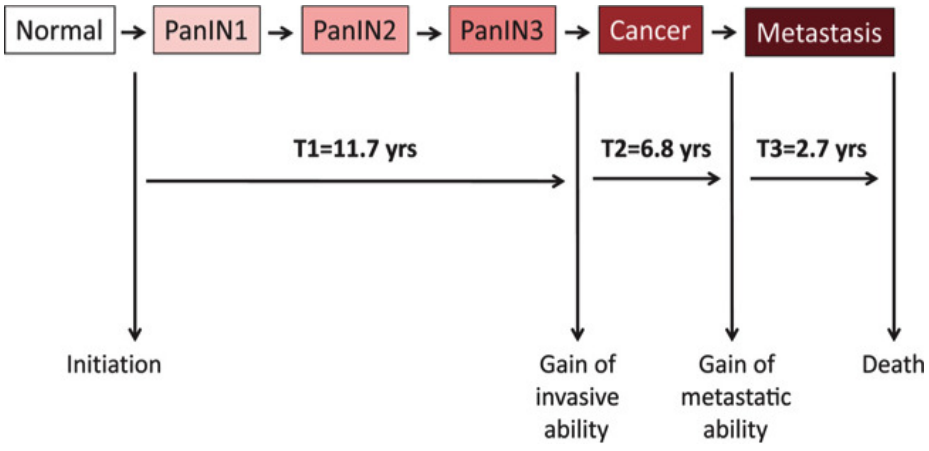
Development of Pancreas Ca



Embyro	Benign ductal cells	PanIN-1	PanIN-2	PanIN-3	Invasive carcinoma
Pdx-1 Sonic hedge-hog (SHH) Serine/threonine kinase 11 (STK11/LKB1)		K-ras Telomere shortening p21 (WAF1/CIP1) Human epidermal growth factor receptor 2 (HER2/neu) Mucin 1 (MUC1) MUC 6 Trefoil factor 1 (TFF 1) p16 (INK4a) S100A11 MUC5AC S100A6	Cyclin D1 Cyclo-oxygenase-2 (COX-2) Hes1 (Hair and enchancer-of split 1) Notch 1 Pepsinogen C Kruppel-like factor 4 (KLF4) HOXA5 GATA5 Gastrin Villin-1 Villin-2 Cellular retinoic acid binding protein 1 (CRABP1)	p53 SMAD4 BRCA2 S100P SHH SialyT (Mucin-associated-carbohydrate antigen) Maspin MUC4 Tumour suppressor in-lung cancer-1 (TSLC-1) Familial adenamatous-polyposis (FAP)	

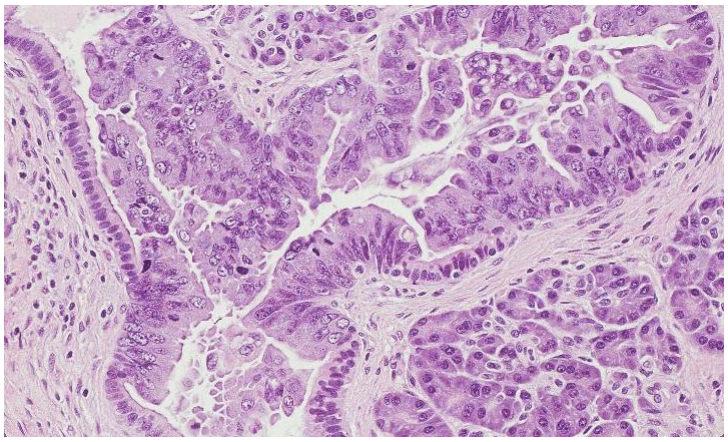
Ghaneh, et al. Gut, 2007

Genetic Evolution of Pancreas Ca



Yachida S, et al. *Nature*. 2010. Iacobuzio-Donahue C. *Gut*. 2012

Pancreatic Ductal Adenocarcinoma



A Formidable Tumor Biology…

- Complex microenvironment
- Physical barrier to effective drug delivery (stroma)
- Relative immune suppression
- Multiple gene mutations
- Key genes can't be targeted

Localized Pancreas Cancer

3 Key groups:

- Localized, operable (stage I-IIB)
- Localized, 'borderline' operable
- Locally advanced, non-operable (stage III)

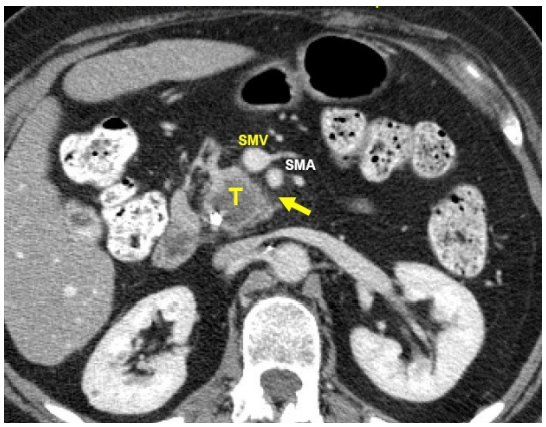
Clinical Features & Presentation

- Common symptoms: weight loss, appetite loss, jaundice, pain, malabsorption, new diabetes
- Symptoms depend on primary tumor location
  - Head tumors: weight loss, jaundice
  - Body/ tail tumors: weight loss, back/flank pain
- Blood clots: DVT or PE, presenting symptom in advanced disease (Trousseau)

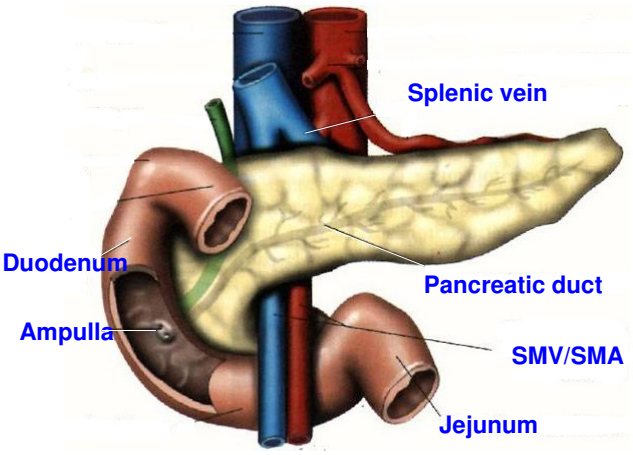
Surgical Considerations

- Absence of spread of cancer
- Key issue is the relationship of primary tumor to blood vessels
  - CT pancreas angiography – most useful
- Confirmed diagnosis of malignancy not necessitated in right clinical setting
- Laporoscopy – used selectively

Operable Pancreas Cancer



Surgery for Pancreas Adenoca



Pancreaticoduodenectomy (Whipple) 80%
Distal Pancreatectomy +/- Splenectomy 20%

Adjuvant (Postoperative) Therapy

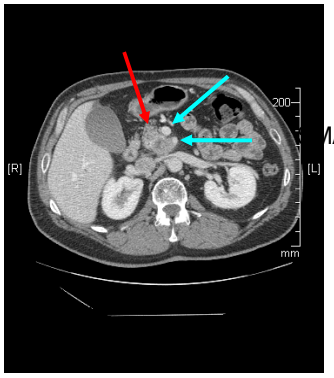
- Gemcitabine or 5-fluorouracil (5-FU) for 6 months
- Data for inclusion of combined chemotherapy and radiation – more controversial
  - US – often included
  - Europe, Japan – typically chemotherapy alone
  - Large study underway to define absolute benefit of chemotherapy + radiation (RTOG 0848)
- Other trials evaluating adding agent to gemcitabine

Why Neoadjuvant (Pre-operative) Therapy?

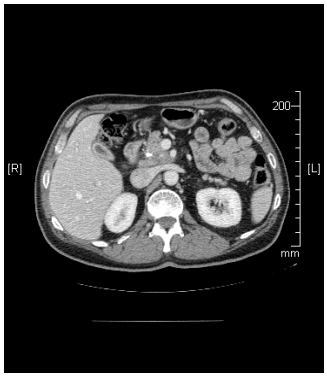
- Risk of recurrence
- Selects out cancer behaviour, avoidance of surgery
- Improved treatment delivery: 20-25% don't receive adjuvant therapy in view of post-op issues
- Improved margin negative operations, reduced local recurrence rate, 'downstaging'?
- Standard approach in other GI cancers

CT Pancreas Scan: Borderline Resectable

Hypovascular pancreas head tumor

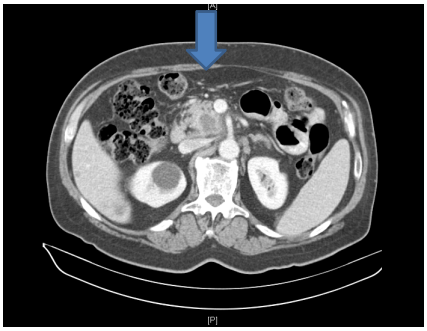


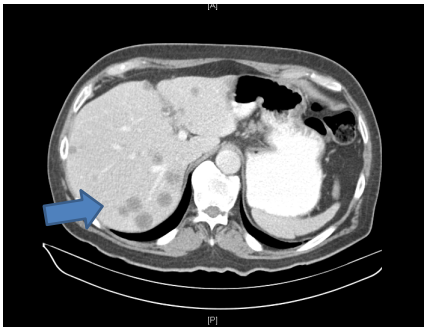
MA



Inoperable Pancreas Cancer

Head of Pancreas & Liver Metastases

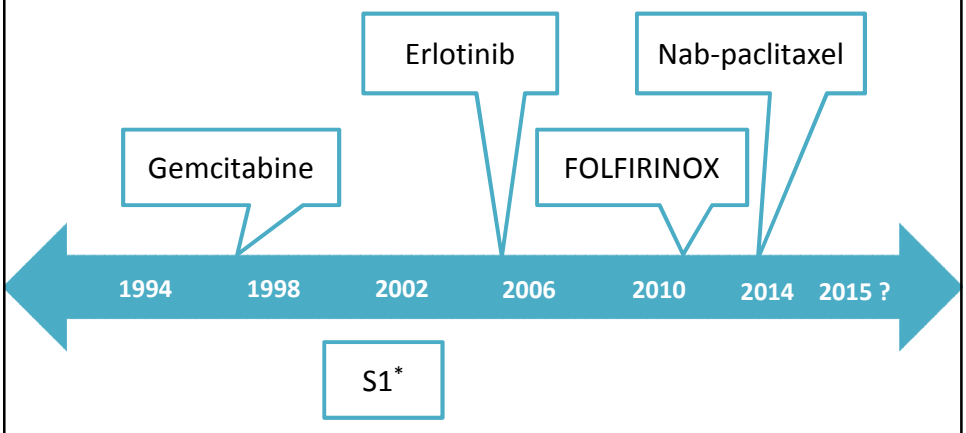




Multidisciplinary Management

- Pain management
  - Narcotics, nerve block
  - Supportive/ palliative care
- Jaundice
  - ERCP + bile duct stent, operative bypass
- Duodenal (gastric outlet) blockage
  - Stent, drainage tube (dPEG), rarely surgery
- Nutrition
  - Enzyme supplementation, appetite enhancement
- Blood clots > 30-50%
- Psychosocial care

'Approved' Treatments For PC



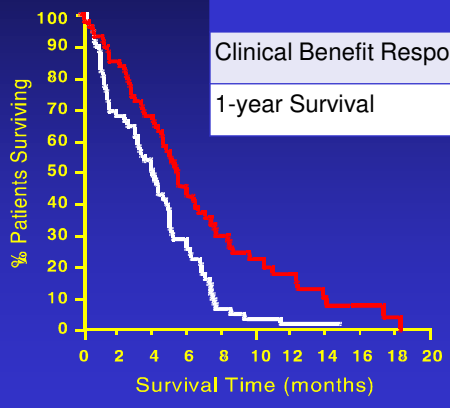
*Approved only in Japan

Goals of Treatment

- Control the cancer
- Ease symptoms
- Extend life
- Maintain/improve quality of life

FDA Approval 1996
Gemcitabine vs 5-FU Phase III Trial

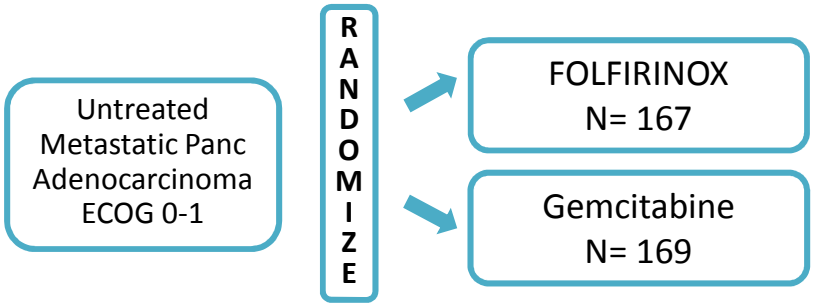
	Gemcitabine N= 63	5-FU N= 63
Clinical Benefit Response	24%	5%
1-year Survival	18%	2%



Burris, et al. J Clin Oncol, 1997

FOLFIRINOX vs Gemcitabine

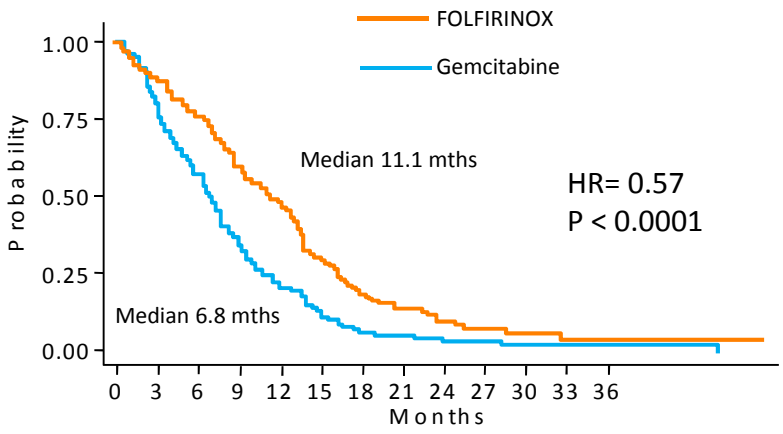
Prodige 4- ACCORD 11



Primary Endpoint: Overall Survival

Conroy, et al. NEJM, 2011

FOLFIRINOX vs Gemcitabine
Overall Survival



Conroy, T. NEJM, 2011

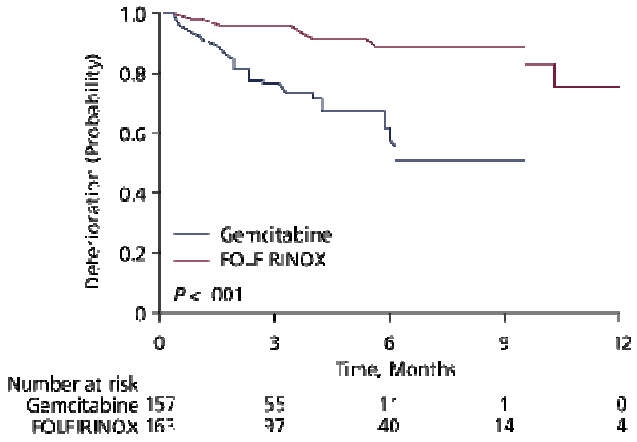
FOLFIRINOX vs Gemcitabine

Other Trial Endpoints

	FOLFIRINOX N= 167	Gemcitabine N= 169
Low white cells + fever	5 %	0.6%
Low platelets	9%	2%
Nerve effects	9%	-
Vomiting	14%	5%
Diarrhea	13%	1%
White cell booster needed	43%	5%
Tumor Shrinkage	32%	9%
Cessation tumor growth	6.4 m	3.3 m

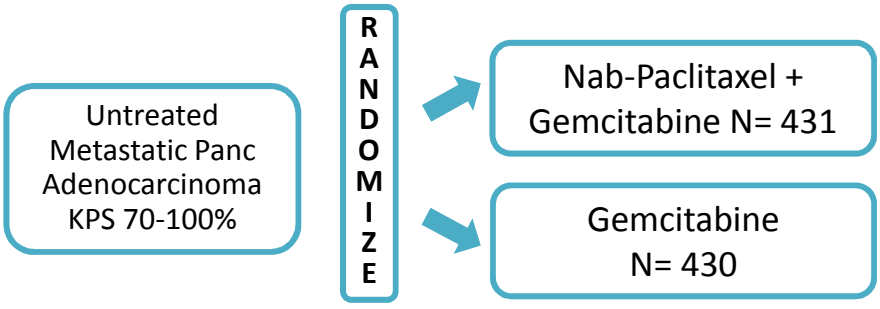
Conroy T, et al. NEJM, 2011

FOLFIRINOX Delays Worsening Quality of Life



Gourgou-Bourgade S et al. J Clin Oncol, 2013

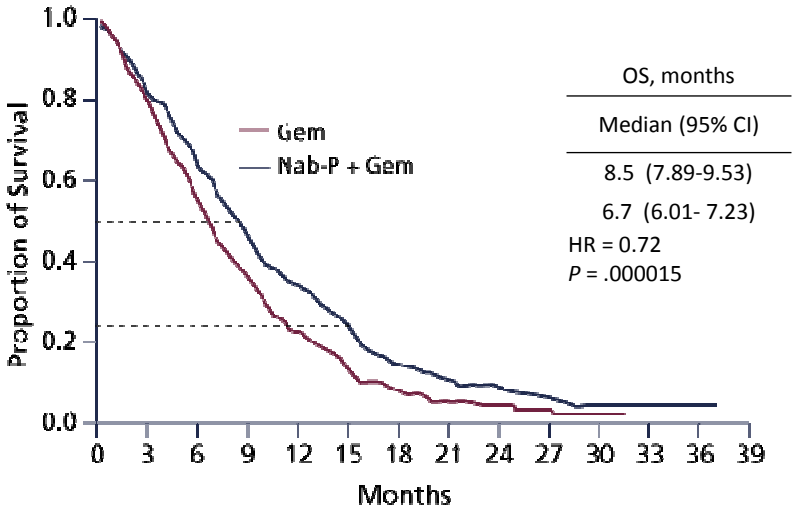
Metastatic Pancreas Adenoca Trial (MPACT)



Primary Endpoint: Overall Survival

Von Hoff, D. NEJM, 2013

MPACT Trial: Outcome



Von Hoff DD et al. N Engl J Med. 2013

Which Treatment First For PC?

- No clear data to guide
  - Age, level of well-being, patient preference
- Nab-paclitaxel and gemcitabine – applicable to broader patient population
  - Older, less robust
  - Easier to add other agents?
- Ability to select which regimen first will be useful

Second-Line Therapy in Pancreatic Adenocarcinoma

- No standard/ approved therapy for second line (yet…)
- Data to support gemcitabine-based treatment for patients with disease growth on 5-FU-based regimen
- Data to support 5-FU-based therapy for patients with disease growth on gemcitabine-based therapy
- Relatively few patients enrolled on trials in a second-line setting

Targeting Inflammation in PC RECAP Trial

- Randomized phase II capecitabine ± ruxolitinib
- N= 138 with progressive met PDAC following prior gemcitabine-based therapy
- Primary endpoint: Survival

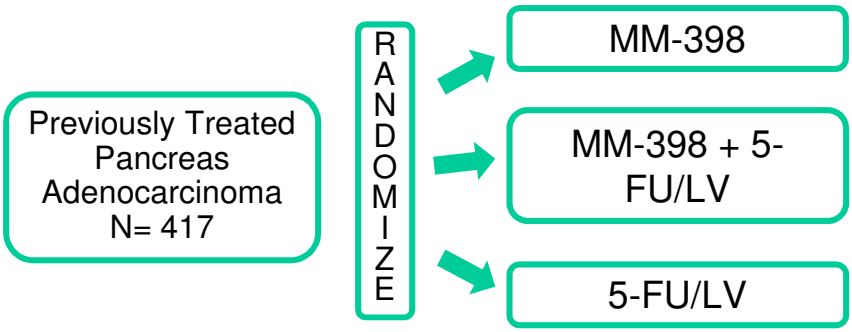
- Subgroup: 50% with elevated C-reactive protein (CRP)
  - Improvement in outcome with addition of ruxolitinib

ASCO, 2014

MM-398: New Chemotherapy

- Irinotecan – encapsulated for improved delivery/ efficacy (lipid nanoparticle)

Randomized Phase III Trial
Previously Treated Pancreas Cancer



Combination of MM-398 + 5-FU/LV – most beneficial
Under FDA review – 2015?

Wang-Gillam. World GI Symposium, 2014.

Where Do We Go From Here?

- Interfering with the stroma
- Targeted therapy for genetic subgroups
- Targeting cancer stem cells
- Immune therapies
- Specific inhibitors of key signaling pathways
- New chemotherapy (cytotoxic) agents

Clinical Trials

- Phase I
  - Dosing, schedule, side effects, hints of efficacy
- Phase II
  - Typically restricted to a specific disease
  - Estimation of the effectiveness of the therapy
  - Fuller understanding of side effects
- Phase III
  - Comparison to best standard treatment
  - Gold standard approach for drug approval
- Phase IV
  - Post FDA drug approval assessment

Clinical Trials II

- Support for clinical trials
  - Government (NCI)
  - Pharmaceutical industry
  - Philanthropy,
  - Academic Institutions
- Regulatory control/ support for clinical trials
  - Institutional Review/ Privacy Board
  - Large trials – Data & Safety monitoring committee
  - Principal investigator - responsibility

Types of Clinical Trials

- Therapeutic
  - Treat the cancer
  - Treat the symptoms
- Non-therapeutic
  - Data collection
  - Investigate biology, outcomes in subgroups

Considering a Clinical Trial

- Things to think about…
  - Goal of study and your goals
  - State-of-the-art care
  - Better than state-of-the-art?
  - Advancing knowledge
- Appropriate for your setting?
  - Mostly for patients without prior treatment
  - Adequate general health (aside from cancer)

Pancreatic Cancer Trial Accrual 2011

(Courtesy Pancreatic Cancer Action Network)

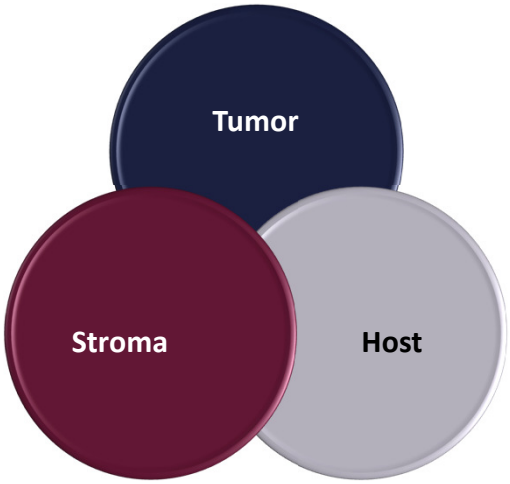
	TOTALS
Number patients participating in phase I-III pancreatic trials	1,794
Pancreatic Cancer Trial Participation	4.54%
Other Adult Cancers	~2%

Hoos WA, et al. *J Clin Oncol.* 2013;31(27):3432-3438

New Targets, New Drugs…

Target/ Frequency	Class of Drug	Example of Drug
RAS (90%), RAK, MEK	FT inhibitor; Oncolytic virus C-Met	Tipifarnib, Salarasib; Reovirus, Selumetinib, Onartuzumab
EGFR (40-70%)	TKI's, monoclonal Antibodies	Erlotinib
mTOR/ P13K/ AKT/ MEK	mTOR inhibitor AKT, P13K, MEK	Everolimus, temsirolimus MK-2206, XL-765, BKM-120, Selumetinib
Hedgehog (70%) Notch (60-70%)	Small molecule Shh inhibitor Gamma-secretase inhibitor	GDC-0449, IPI-926, LDE-225 R04929097, OMP-59R5
PSCA	Antibody to PSCA	AGS-1C4D4
SRC	SRC, bcr-abl inhibitor	Dasatinib, AZD 0530
PARP/BRCA/PALB2	PARP inhibitors	AZD 2281, Veliparib, BSI-201
Vaccines/Immune	CTLA4, PD-1, PD-L1, CD40 CAR mesothelin	Ipilumumab, Nivolumab, CRS-207, GVAX, Algenpantucel-L

Targeting the Tumor Microenvironment



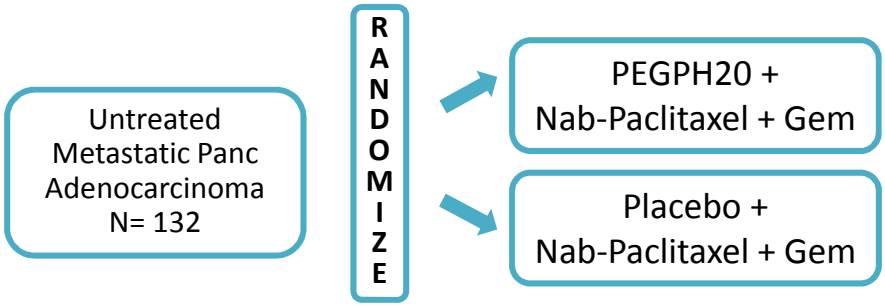
Hyaluronan in the Stroma as a Target in Pancreatic Cancer

- Hyaluronan increased in >80% of pancreatic cancers
- Tumors that accumulate hyaluronan develop high pressure and drug resistance
- Hyaluronan is associated with disease progression and poor prognosis

1. Theocharis AD et al. *Biochim Biophys Acta*. 2000;1502:201-206. 2. Jacobitz MA et al. *Gut*. 2013;62:112-120. 3. Provenzano PP et al. *Cancer Cell*. 2012;21:418-429.

Nab-Paclitaxel + Gemcitabine +/- PEGPH20

Randomized Phase II Trial



Primary Endpoint: Disease control

http://clinicaltrials.gov/show/NCT01839487

Pancreatic Cancer, BRCA, and PARP Inhibition

- 5%-10% of pancreatic cancer patients have inherited BRCA-1 or -2 gene mutation
  - Ashkenazi Jewish, Scandinavian, Icelandic, others
- BRCA-1, -2 involved in DNA repair
- PARP inhibition established value in ovarian/breast cancer with BRCA-related mutations
- Emerging data in pancreatic cancer supports targeting genetic vulnerabilities related to BRCA gene mutations

Randomized Phase II Trial in BRCA-Mutated Pancreas Adenoca

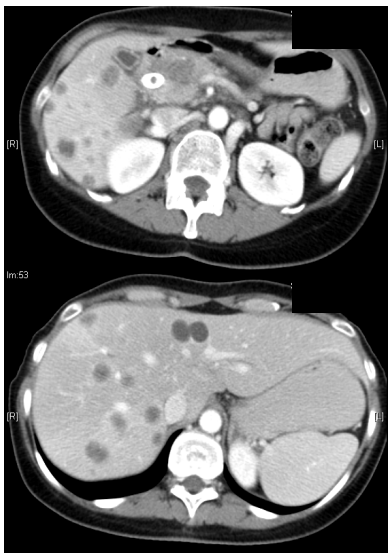
Pancreas cancer with BRCA1-2, PALB2 mutation

Arm A: Cisplatin + gemcitabine + veliparib
Arm B: Cisplatin + gemcitabine

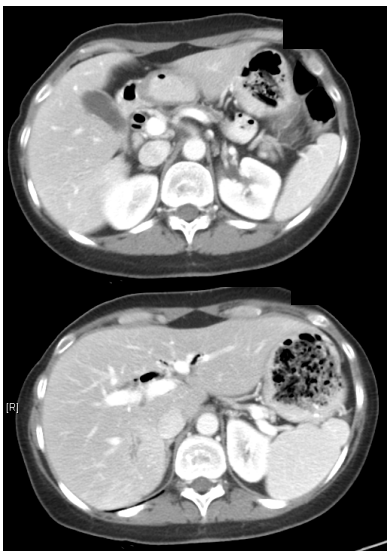
Gemcitabine + cisplatin d3+10, q21
Veliparib dosing, day 1-12 twice daily by mouth

http://clinicaltrials.gov/show/NCT01585805. Accessed 2014

Pancreas Cancer BRCA Mutation



Ca 19-9 2660; CEA 229

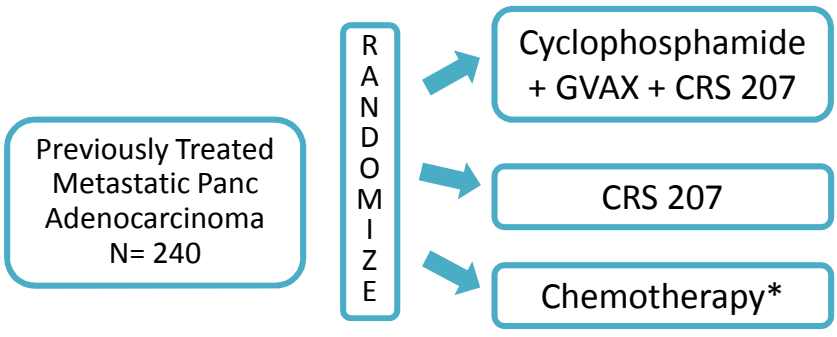


Ca 19-9 42; CEA 4.3

Immunotherapy Trials in PC

- Algenpantucel-L (NewLink Genetics): human PC cell lines genetically engineered to express αGal
  - Completed study in surgically removed pancreas cancer
- Nivolumab (PD1) ± ipilimumab (anti-CTLA4)
- MEDI4736 (PDL1)
- Engineered T-cells (CAR)
  - Mesothelin, CEA
- Clivatuzumab – mAb hPAM40 + ^{90}Y (radioimmunotherapy)

ECLIPSE Trial
Randomized Phase IIB



*Gemcitabine/ Capecitabine/ Erlotinib/ Irinotecan
Primary Endpoint: Overall Survival

NCT02004262

Front-Line Metastatic Trials
Selected Randomized Phase II

NCT	Trial Design	N	Target	Sponsor
01839487	Gem + nab-paclitaxel ± PEGPH20	132	Hyaluronan	Halozyme
01621243	Gem + nab-paclitaxel ± M402	148	Anti-stromal	Momenta
01647828	Gem + nab-paclitaxel ± OMP-59R5	140	Notch, stem cell	OncoMed
01844817	Gem + nab-paclitaxel ± OGX-427	132	HSP27	OncoGenix
01016483	Gem ± MSC1936369B	174	MEK	Merck, EU
01728818	Gem ± afatinib	117	EGFR, HER2,4	Boehringer, EU
01509911	Gem ± TL-118	80	Angiogenesis	Tiltan Pharma
01505530	LY249555 + chemo (investig choice)	120	Myostatin	Eli-Lilly
01280058	Carbo + paclitaxel ± reovirus	70	RAS	NCI
01585805	Gem + cisplatin ± veliparib	~70	PARPi (BRCA+)	NCI, Lustgarten
01209111	Gem + erlotinib ± metformin	120	Multiple	U. Amsterdam
01167738	PEXG ± metformin	82	Stem cells	San Raffaele

Conclusions

1. Treament works in PC
2. Adjuvant therapy: Gemcitabine +/- chemoradiation
3. For high functioning individuals with metastatic disease
   Multi-drug combination, e.g.,
   FOLFIRINOX,
   Gemcitabine + nab-paclitaxel
4. For all – clinical trials where possible
5. Multiple interesting agents in development

Conclusions II

- Second-/third-line therapy trials feasible and area for drug development
- Ongoing needs
  - Validated markers for patient treatment selection
  - Enhanced clinical trial participation
- Future looks brighter…

Expectations For The Future

1) Improved understanding of who is at risk
2) Increased role of screening for PC
3) Improved model systems of PC
4) Improvements in treatment
5) Improvements in molecular classification