Promising Treatments for Pancreatic Cancer

Vincent Chung, MD, FACP
City of Hope
Multidisciplinary Approaches to Cancer Symposium
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Disclosures

Celgene – Speaker’s Bureau

Perthera – Medical review consultant
Overview

Pathogenesis of pancreatic cancer

Why does it take so long to make a diagnosis?

Progress in the treatment of pancreatic cancer

Future directions

Case Presentation
Pancreatic Cancer Is Typically Diagnosed at a Late Stage

Worst survival of any solid tumor
2016 US estimation
- 53,070 new cases
- 41,780 deaths


Development of Pancreatic Cancer

Clinical Presentation

Early stages are difficult to diagnose
  • most are asymptomatic

Later stages the symptoms depend on the location of the tumor

Symptoms of advanced disease
  • Fatigue, anorexia or weight loss
# Genetic Susceptibility to Pancreatic Cancer

<table>
<thead>
<tr>
<th>Genetic Mutations</th>
<th>Syndrome</th>
<th>Risk Level</th>
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<tbody>
<tr>
<td>BRCA1/BRCA2</td>
<td>Hereditary breast/ovarian cancer syndrome</td>
<td>- BRCA2 mutation is the most common known genetic cause for familial pancreatic cancer</td>
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<tr>
<td></td>
<td></td>
<td>- 3.6%-5% lifetime risk for developing pancreatic cancer</td>
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<tr>
<td>PALB2</td>
<td>Fanconi anemia</td>
<td>- Up to 3% of patients with familial pancreatic cancer</td>
</tr>
<tr>
<td>P16/CDKN2A</td>
<td>Familial atypical multiple-mole melanoma</td>
<td>- 10%-17% lifetime risk for pancreatic cancer</td>
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<tr>
<td>STK11/LKB1</td>
<td>Peutz-Jeghers syndrome</td>
<td>- 11%-36% lifetime risk for pancreatic cancer</td>
</tr>
<tr>
<td>PRSS1</td>
<td>Hereditary pancreatitis</td>
<td>- 25%-40% lifetime risk for pancreatic cancer</td>
</tr>
<tr>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td>Hereditary non-polyposis colon cancer (Lynch syndrome)</td>
<td>- Approx 4% lifetime risk for pancreatic cancer</td>
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Making the Diagnosis

- Ultrasound - limitations
- Pancreas protocol CT
  - Triphasic
  - Thin slices through pancreas
- MRI
- PET
PET-PANC: multi-centre prospective diagnostic accuracy and clinical value trial of FDG PET/CT in the diagnosis and management of suspected PANCreatic cancer.


ASCO, Chicago 06/06/2016 8:00 AM - 11:00 AM 4008

UKCRN: 8166
ISRCTN: 73852054
NIHR HTA programme: 08/29/02

LCTU NCRI UKCRC Registered Clinical Trials Units
Cancer Research UK National Institute for Health Research

Presented By Paula Ghaneh at 2016 ASCO Annual Meeting
Eligible patients with suspected pancreatic cancer standard work up, MDT discussion

Informed consent

Registration

PET/CT requested

PET/CT scan within 2 weeks of consent

Central PET/CT QA

D1

D2

D3

MDCT QA

Management and follow up decided by local clinician (12 month follow up)

D4

Pathology QA

Study design

<table>
<thead>
<tr>
<th>Diagnosis stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>D1</td>
<td>Diagnosis, staging, management decision made by clinician UNBLINDED using usual diagnostic strategy based on MDT outcome.</td>
</tr>
<tr>
<td>D2</td>
<td>Diagnosis, staging, management decision made by clinician UNBLINDED to PET/CT scan results based on investigator decision or 2nd MDT.</td>
</tr>
<tr>
<td>D3</td>
<td>Actual diagnosis and management.</td>
</tr>
<tr>
<td>D4</td>
<td>REFERENCE STANDARD for clinical judgement in all patients made by independent panel. Diagnosis made using reference standard BLINDED to D1 and D2 previous diagnoses and scan results.</td>
</tr>
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</table>

LCTU

Presented By Paula Ghaneh at 2016 ASCO Annual Meeting
PET-PANC Conclusions

1st prospective multicenter study of PET/CT in the diagnosis and management of patients with suspected pancreatic cancer

Corrected the staging in 56 patients (14%)

Prevented resection in 58 (20%)

Most cost effective in patients with suspected pancreatic cancer planned to undergo resection
**Tumor markers: CA19-9**

Most common elevated tumor marker in pancreatic cancer

May also be elevated with colorectal, lung, liver and ovarian cancer

Benign conditions can also elevate level
- Disease of hepatobiliary system, pneumonia, pleural effusion, renal failure and SLE

Generally CA19-9 >1000 implies advanced disease that is not amenable to resection (biliary obstruction can cause elevated CA19-9)
Pancreatic Cancer - Related Complications

**Gastrointestinal**
- Pancreatic Exocrine Insufficiency
- Malignant Biliary Obstruction
- Malignant Gastric Outlet Obstruction

**Constitutional**
- Pain

**Thrombotic**
- Venous Thromboembolism

**Nutritional**
- Cancer-Associated Cachexia

**Psychosocial**
- Depression

Surgery for Pancreas Cancer

Need high quality radiographic evidence of resectability

Most resectable cancers are limited to small tumors in the head of the pancreas

Pancreaticoduodenectomy (Whipple) 80%
Distal Pancreatectomy 20%

Even after resection, most patients have recurrent disease
Adjuvant Therapy

XRT is controversial
- GITSG 9173: benefit with XRT
- ESPAC 1: detriment with XRT

Modest benefit at best with adjuvant treatment (NCCN category 1)
- CONKO 1: gemcitabine vs surgery alone – 22.8 mo vs 20.2 mo (p=0.005)
- RTOG 9704: gemcitabine versus 5FU (both arms with XRT) – pancreas head tumors 20.5 mo versus 16.9 mo

RTOG 0848
- Phase 3 trial evaluating adjuvant chemotherapy with or with chemoradiation (slow to accrue)
ESPAC-4: A multicenter, international, open label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP), versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma

Treatment Received

- GEM 1,000mg/m² d1 @wk for 3/4 wks for 6 cycles
- Total protocol GEM=3,000mg/m² per cycle, overall=18,000mg/m²
- 1 (0.3%) of 366 patients received NO GEM
- 239 (65%) of 366 patients received 6 cycles GEM
- Median total GEM dose: 16,750mg/m² (Range: 1000-18,750)
- Median protocol GEM dose: 93% (Range: 5-104%)

- GEMCITABINE 1,000mg/m² d1 @wk for 3/4 wks for 6 cycles
- Total protocol GEM=3,000mg/m² per cycle, overall=18,000mg/m²
- CAPECITABINE 1,660mg/m2/day – 21/28d
- Total protocol CAP=34,860mg/m² per cycle, overall=209,160mg/m²
- 5 (1%) received no GEM and 6 (2%) of 364 patients received NO CAP
- 195 (54%) of 364 patients received 6 cycles GEMCAP
- Median total GEM dose: 15,000mg/m² (Range: 1,000-20,500)
- Median protocol GEM dose: 83% (Range: 5-114%)
- Median total CAP dose: 162,680mg/m² (Range: 1660-209,910)
- Median protocol CAP dose: 78% (Range: 0.8-100%)

Presented By John Neoptolemos at 2016 ASCO Annual Meeting
Survival by Treatment

HR = 0.82 (95% CI, 0.68-0.98)
\( \chi^2(1) = 4.61, p = 0.032 \)

Median S(t) = 25.5 months (95% CI: 22.7-27.9)
Median S(t) = 28.0 months (95% CI: 23.5-31.5)

Presented By John Neoptolimos at 2016 ASCO Annual Meeting
Conclusions

- Median survival for patients treated with GEMCAP was significantly better than GEM: 28.0 (95% CI, 23.5 - 31.5) vs 25.5 (22.7-27.9) months
- The estimated 5 years survival rate was superior with GEMCAP than GEM: 28.8 (22.9-35.2)% vs 16.3 (10.2-23.7)%
- As expected there was slightly more toxicity in the GEMCAP arm but overall this was manageable and not significant: 154 SAEs in 86 (24%) GEMCAP patients vs 151 SAEs in 94 (26%) GEM patients
- The 5 year survival rate with GEMCAP=28.8 (22.9-35.2)%, was superior to previous ESPAC trial arms including no chemotherapy=8.0 (3.8-14.1)%, chemoradiotherapy=10.8 (6.1-17.0)%, 5FU/FA=15.9 (12.7-19.4)%
- Marginal benefit of active agents in advanced pancreatic cancer can translate into a much bigger effect in the adjuvant setting
- All patients with pancreatic cancer should be offered entry into randomised trials: biomarkers must be evaluated (hENT1, etc)
- Adjuvant GEMCAP is the new standard of care for resected pancreatic cancer
NewLink Genetics Announces Results from Phase 3 IMPRESS Trial of Algenpantucel-L for Patients with Resected Pancreatic Cancer

- Press release May 9, 2016
- IMmunotherapy for Pancreatic RESectable cancer Study (IMPRESS)
- Whole-cell immunotherapy consisting of irradiated allogeneic pancreatic cancer cells genetically engineered to express the murine enzyme α-GT, which results in hyperacute rejection of the tumor cells with complement-and antibody-dependent cytotoxicity
- Median survival was 30.4 months and 27.3 months for the control and study groups, respectively
APACT: Phase 3 Trial Adjuvant Nab-paclitaxel plus Gemcitabine versus Gemcitabine Alone in pts with Surgically Resected Pancreatic Cancer

Completed accrual in March
What is the optimal therapy for locally advanced pancreas cancer?

To give radiation therapy or not to give radiation therapy, that is the question.

Conflicting results

- ECOG 4201 – A randomized phase III study of gemcitabine with or without radiation therapy (Only 74 of a planned 316 patients accrued)
- Primary objective – overall survival
- OS survival benefit 11 vs 9 months p=0.017
- More grade 4/5 toxicities
Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib (LAP–07)

LAPC ECOG 0-2 (442 Pts)

- Gemcitabine
  - 4 months
  - CT Eval for progression
  - ChemoXRT
  - Chemo 2 months

Gemcitabine + erlotinib

Results: LAP–07 trial

Median overall survival
16.4 vs 15.2 months (CT vs CRT group) (hazard ratio [HR] 1.03, 95% CI [0.79, 1.34], p = 0.8295)

After formal RT quality assessment
- 32% chemoradiotherapy arm were treated per protocol
- 50% had minor deviations
- 18% had major deviations
Clinical Trials for Locally Advanced or Borderline Resectable Pancreatic Cancer

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>NCCN Recommendations</th>
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<tbody>
<tr>
<td>FOLFIRINOX for Unresectable Locally Advanced and Borderline Resectable Pancreatic Cancer (NCT01688336)</td>
<td>1) Clinical trial preferred</td>
</tr>
<tr>
<td>Phase 2 LAPACT Gemcitabine + nab-paclitaxel (NCT02301143)</td>
<td>2) FOLFIRINOX or Gemcitabine + nab-paclitaxel</td>
</tr>
<tr>
<td>Phase III FOLFIRINOX (mFFX) +/- SBRT in Locally Advanced Pancreatic Cancer (NCT01926197)</td>
<td>3) Chemoradiation in selected patients</td>
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<td></td>
<td>4) Gemcitabine or 5FU alone for poor performance status patients</td>
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Pancreatic Cancer Is Typically Diagnosed at a Late Stage

Worst survival of any solid tumor
2016 US estimation
• 53,070 new cases
• 41,780 deaths


Improvements in Survival and Clinical Benefit as First-Line Therapy for Patients with Advanced Pancreas Cancer

Primary endpoint – clinical benefit response (CBR)

Composite of measurements of pain (analgesic consumption and pain intensity), KPS and weight

Clinical benefit required a sustained >= 4 weeks improvement in at least one parameter without worsening in others

CBR 24% vs 5% p=0.0022
OS 5.65 mo vs 4.4 mo p=0.0025

Gemcitabine approved by the FDA for pancreas cancer in 1996

Gemcitabine 1000 mg/m²

Fluorouracil 600 mg/m²

Advanced symptomatic pancreas cancer

Burris, et al. JCO 1997
FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer (Accord 11)

- Majority of patients had body and tail lesions
- Over 80% of patients did not have a biliary stent

**Primary endpoint:** overall survival

11.1 vs 6.8 months

HR 0.57

p<0.001

**Conroy, et al. NEJM 2011.**
Gemcitabine plus nab-paclitaxel versus Gemcitabine in Patients with Metastatic Pancreatic Cancer (MPACT)

861 patients randomized
Median OS 8.5 vs 6.7 mo HR 0.72
p=0.000015
Median PFS 5.5 vs 3.7 mo HR 0.69
p=0.000024

Von Hoff, et al. ASCO GI 2013
## Differences Between the Accord and MPACT Trials

<table>
<thead>
<tr>
<th>Accord 11</th>
<th>MPACT</th>
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<tbody>
<tr>
<td>48 centers in France</td>
<td>International trial</td>
</tr>
<tr>
<td>ECOG 0-1</td>
<td>ECOG 0-2</td>
</tr>
<tr>
<td>Pancreatic head tumors 39.2% (stent 16%)</td>
<td>Pancreatic head tumors 44% (stent 19%)</td>
</tr>
<tr>
<td>Grade &gt;=3 neutropenia 46%</td>
<td>Grade &gt;=3 neutropenia 38%</td>
</tr>
<tr>
<td>Febrile neutropenia 5%</td>
<td>Febrile neutropenia 3%</td>
</tr>
<tr>
<td>Grade &gt;=3 thrombocytopenia 9%</td>
<td>Grade &gt;=3 thrombocytopenia 13%</td>
</tr>
<tr>
<td>Excluded patients 76 years old and older</td>
<td>Oldest patient on trial 88 y/o</td>
</tr>
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</table>
Phase III MAESTRO Study: Evofosfamide (TH-302) + Gemcitabine

Pancreatic cancer, hypoxia, and novel therapy

- The tumor microenvironment in pancreatic cancer is characterized by hypoxia, which modulates many of the key features of cancer\(^1\)\(^–\)\(^3\)
- Evofosfamide is a hypoxia-activated prodrug that preferentially releases the cytotoxic bromo-isophosphoramide mustard (Br-IPM) in areas of severe hypoxia\(^4\)\(^,\)\(^5\)
- Combining evofosfamide with conventional chemotherapy has the potential to induce cell death in hypoxic and normoxic tumor cells

1. Neuzillet, et al. 2015
2. Stewart, et al. 2010
4. Liang, et al. 2015
Results of the Phase III MAESTRO Study

Despite encouraging phase 2 results, the phase 3 trial did not meet its primary endpoint

Slightly more hematologic toxicity

Signal seen for antitumor activity

Presented By Eric Van Cutsem at 2016 ASCO Annual Meeting
Current On-going Pancreatic Cancer Trials

Phase II/III Study of BTK inhibitor Ibrutinib (Imbruvica®) in Combination with Nab-paclitaxel and Gemcitabine Versus Placebo in Combination with Nab-paclitaxel and Gemcitabine in Patients with Metastatic Pancreatic Adenocarcinoma (RESOLVE)

Phase III Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) in Combination with nab-Paclitaxel Plus Gemcitabine Compared with Placebo Plus nab-Paclitaxel and Gemcitabine in Patients with Hyaluronan-High Stage IV Previously Untreated Pancreatic Ductal Adenocarcinoma
Treatment of Refractory Metastatic Pancreatic Cancer

mFOLFOX
- CONKO-003 trial - improved OS with OFF
- PANCREOX (ASCO 2014 J Clin Oncol 32:5s, 2014 (suppl; abstr 4022)
- Randomized phase 3 (108 patients)
  - Primary objective was PFS
  - 20% of patients on the mFOLFOX6 arm withdrew due to toxicities
  - PFS was similar between the arms but overall survival was worse in the oxaliplatin arm (6.1 vs 9.9 months)
  - Post-progression therapy was higher in the 5FU arm (25 vs 6.8%)

FOLFIRI
- Observation study (63 patients) Disease control rate (39.7%) ; OS 6.6 months
- S1513 FOLFIRI +/- veliparib (opening soon)
NAPOLI-1

Phase 3 trial of MM-398 alone, MM-398 + 5FU or 5FU/LV alone in patients refractory to prior gemcitabine based chemotherapy

MM-398 nanoliposomal encapsulation of irinotecan

- Allows for longer drug exposure and more accumulation of drug at the tumor site

OS (4.9 vs 6.1 vs 4.2 months respectively)
### Summary: NCCN Guidelines

**Always consider clinical trials**

**Adjuvant Treatment**
- Gemcitabine (CONKO-1)
- Gemcitabine and 5FU/XRT (RTOG 9704)
- Gemcitabine and capecitabine (ESPAC-4)

**Locally Advanced**
- FOLFIRINOX
- Gemcitabine + nab-paclitaxel
- ChemoXRT

**Metastatic Treatment**
- Gemcitabine
- Gemcitabine + erlotinib
- Gemcitabine + nab-paclitaxel
- FOLFIRINOX – Good KPS patient

**Second-line Treatment**
- Gemcitabine +/- nab-paclitaxel
- FOLFOX
- FOLFIRI
- Nano-liposomal irinotecan + 5FU
Pancreatic cancer is characterized by a dense, poorly vascularized stroma.
Phase I/IIb Trial of Saridegib (IPI-926) plus Gemcitabine in Patients with Pancreatic Cancer

Accumulation of hyaluronan along with other matrix components

- Increases tumor interstitial fluid pressure
- Constricting tumor vasculature
- Creates a unique microenvironment for the growth of tumor cells compared to normal cells

Using hedgehog inhibitors deplete the stroma to improve chemotherapy delivery

Interim analysis showed a difference in survival favoring the placebo plus gemcitabine arm due to a higher rate of progressive disease in the saridegib plus gemcitabine arm

Infinity voluntarily stopped the trial
Targeting the Extracellular Matrix

Raises several questions:

1) Does large amounts of stroma surrounding pancreatic cancer actually have protective properties?

2) Would combinations with more aggressive chemotherapy be better?

Phase III randomized, double-blind, placebo controlled study using Gemcitabine + nab-paclitaxel +/- PEGPH20 in HA high patients

SWOG: Phase Ib/ randomized phase II trial of FOLFIRINOX +/- PEGPH20
GVAX Pancreas Vaccine +/- CRS-207 in Adults With Metastatic Pancreatic Cancer

**GVAX**
- Genetically-modified cancer cells to secrete GM-CSF
- Irradiated to prevent further cell division.

**CRS-207**
- Weakened form of Listeria monocytogenes
- Elicit an immune response against the tumor-associated antigen mesothelin

90 patients (2:1)
- Arm A - two doses of CY/GVAX followed by four doses of CRS-207 three weeks apart
- Arm B - six doses of CY/GVAX every three weeks

**Primary endpoint**
- Overall survival

Le, et al. JCO 2015
Results

Attenuated cytotoxicity

- pts receiving ≥ 1 dose:
  - OS 6.1 vs 3.9 mo

- patients receiving ≥ three doses:
  - OS 9.7 vs 4.6 mo
Immunotherapy for Pancreatic Cancer
Randomized Phase 2 Study Acalabrutinib alone or with Pembrolizumab for Metastatic Pancreatic Cancer

Key Inclusion Criteria
- Histologically or cytologically confirmed advanced pancreatic ductal adenocarcinoma that is unresectable or metastatic
- ECOG PS ≤1
- Men and women ≥18 years of age
- Prior therapy with ≥1 systemic chemotherapy regimen for unresectable or metastatic pancreatic cancer or unwilling/unable to receive systemic chemotherapy

Key Exclusion Criteria
- Patients with CNS metastases or significant cardiovascular disease were excluded
- Prior treatment with a BTK or anti-PD-1/PD-L1 inhibitor was not allowed

N = 76

ORR was 0% in the monotherapy arm and 7.1% in the combination arm, with no CRs

Acalabrutinib
100 mg BID PO
days 1 – 21 on
21-day schedule
n = 38

Acalabrutinib
100 mg BID PO
days 1 – 21
+ Pembrolizumab
200 mg Q3W IV
n = 38

CT scans (A) before and (B) after treatment with acalabrutinib plus pembrolizumab show partial response in a patient with familial pancreatic cancer and a BRCA2 variation of uncertain significance (VUS)

All 3 investigator-assessed PRs were in patients with strong family history of pancreatic or breast cancer
Examples of Ongoing Immunotherapy Trials

Phase Ib/II Study of Ibrutinib + durvalumab (MEDI4736) in pts with relapsed or refractory pancreatic adenocarcinoma (NCT02403271)

Neoadjuvant/Adjuvant GVAX Pancreas Vaccine (With CY) With or Without Nivolumab Trial for Surgically Resectable Pancreatic Cancer (NCT02451982)

Study With CY, Pembrolizumab, GVAX, and SBRT in Patients With Locally Advanced Pancreatic Cancer (NCT02648282)
Vaccination with high-dose p53MVA transiently increases the frequency of p53-reactive T cells in the peripheral blood of patients with gastrointestinal cancer.

Frequency of PD1⁺ T cells in patients' PBMC was significantly higher than in healthy controls. Frequency of PD1⁺CD8⁺ T cells showed an inverse correlation with the peak CD8⁺ p53 response (P = 0.02).
A Phase I Study Combining p53MVA Vaccine with Pembrolizumab

A p53MVA vaccine is injected and taken up by antigen presenting cells e.g. dendritic cells (DC) in the skin.

B DC process and present p53 epitopes, traffic to draining lymph nodes and prime a T cell response.

Case Study

HPI: 55 y/o female presented with abdominal pain and nausea.

Her symptoms initially improved but returned 1 month later.

Thought this was due to food poisoning but symptoms persisted.

She was diagnosed with gallstones and pancreatitis.

Urgent care diagnosed her with diverticulitis and she was treated with antibiotics.

Underwent a cholecystectomy but her symptoms returned soon after the surgery.
Case Study continued

PMH: None

All: NKDA

Medications:
  • Vicodin
  • Prilosec

SH: No tobacco, occasional alcohol

FH: breast cancer, NHL

Physical Exam

• T 36.7; P70; BP 147/85; 90 kg
• ECOG 0
• Gen – WNWD
• HEENT – no jaundice
• Abd – tender to deep palpation in the midepigastic region
• Extr – no edema
Case Study continued

CT showed mass in the pancreas

EUS and biopsy confirmed pancreatic adenocarcinoma

CA19-9 169

Exploratory laparotomy
  • Involvement of SMV and unable to resect
Treatment

Initially started FOLFIRINOX. After the first cycle, she developed persistent neutropenia despite pegfilgrastim and also had thrombocytopenia

- Cold related neuropathy lasting 1 week
- N/V for 3 days
- Anorexia and fatigue

Due to her intolerance to FOLFIRINOX, she received chemoradiation therapy followed by Gemcitabine + nab-paclitaxel
Pancreas Cancer Clinical Trials at COH

Adjuvant:
No Trials

Locally advanced:

Metastatic 1st line:
- IRB #14122 Gemcitabine, nab-paclitaxel, metformin and a combination dietary supplement
- IRB #13464 Modified FOLFIRINOX + pegylated recombinant human hyaluronidase (PEGPH20)
- IRB #15037 Yosemite: Gemcitabine, nab-paclitaxel +/- demcizumab (completed accrual 8/16)

Metastatic 2nd line:

Metastatic 3rd - 4th line:
- IRB #16215 RX-3117: Phase 2 expansion for pancreas and bladder cancer
- IRB #14152 90Y-Clivatuzumab Tetraxetan plus Low-Dose Gemcitabine
Questions

“I go home today. They cured me using this new miracle drug. I’m afraid it’ll be years before it’s approved for humans.”