Pancreatic Cancer: From Bench to Bedside

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Incidence and mortality

Pancreatic Cancer Incidence and Mortality

- 3rd leading cause of cancer death in the United States
- Median 5 year survival is 9%
- Median overall survival is < 6 months
- Estimated 55,440 new diagnoses and 44,330 deaths in 2018
Deaths annually increasing

Pancreatic Cancer: Second Leading Cause of Cancer-related Deaths by 2030

Rahib, L., et. al., Cancer Res., 74, 2913-21, 2014
### Risk Factors

**Table 1. Risk Factors and Inherited Syndromes Associated with Pancreatic Cancer.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Approximate Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor</td>
<td></td>
</tr>
<tr>
<td>Smoking&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2–3</td>
</tr>
<tr>
<td>Long-standing diabetes mellitus&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>Nonhereditary and chronic pancreatitis&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2–6</td>
</tr>
<tr>
<td>Obesity, inactivity, or both&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>Non-O blood group&lt;sup&gt;7&lt;/sup&gt;</td>
<td>1–2</td>
</tr>
<tr>
<td>Genetic syndrome and associated gene or genes — %</td>
<td></td>
</tr>
<tr>
<td>Hereditary pancreatitis (&lt;i&gt;PRSS1, SPINK1&lt;/i&gt;)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>50</td>
</tr>
<tr>
<td>Familial atypical multiple mole and melanoma syndrome (&lt;i&gt;p16&lt;/i&gt;)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>10–20</td>
</tr>
<tr>
<td>Hereditary breast and ovarian cancer syndromes (&lt;i&gt;BRCA1, BRCA2, PALB2&lt;/i&gt;)&lt;sup&gt;10,11&lt;/sup&gt;</td>
<td>1–2</td>
</tr>
<tr>
<td>Peutz–Jeghers syndrome (&lt;i&gt;STK11&lt;/i&gt; [&lt;i&gt;LKBI1&lt;/i&gt;])&lt;sup&gt;12&lt;/sup&gt;</td>
<td>30–40</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colon cancer (Lynch syndrome) (&lt;i&gt;MLH1, MSH2, MSH6&lt;/i&gt;)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>Ataxia–telangiectasia (&lt;i&gt;ATM&lt;/i&gt;)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Unknown</td>
</tr>
<tr>
<td>Li–Fraumeni syndrome (&lt;i&gt;PS3&lt;/i&gt;)&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

* Values associated with risk factors are expressed as relative risks, and values associated with genetic syndromes are expressed as lifetime risks, as compared with the risk in the general population.
Types and stage

Pancreatic Cancer: Types and Stage at Diagnosis

- Adenocarcinoma (~90%)
- Neuroendocrine (<5%)
- Adenosquamous
- Acinar Cell Carcinoma
- Mucinous cystadenocarcinoma

American Cancer Society, Cancer Facts and Figures 2017

- Early 9%
- Metastatic 52%
- Regional 39%
Early detection

**Why can’t we detect pancreatic cancer earlier?**

- Early symptoms are non-specific
- Current imaging methods rarely detect small lesions
- Difficulty in identifying specific biomarkers
  - Pancreatic Cancer is relatively rare (12.1/100,000 persons)
  - Test with 100% sensitivity and 99% specificity => 83 false positive for every real case
- Retroperitoneal positioning of the pancreas makes biopsy difficult
- Risk vs. benefit of removing suspicious pre-cursor lesions
Carbohydrate antigen 19-9

**Carbohydrate Antigen 19-9 (CA19-9)**

- Serum CA19-9 >37 U/ml

**Pancreatic Cancer vs Healthy Individual**

- Sensitivity: 80.3% (95% CI 77.2-82.6)
- Specificity: 80.2% (95% CI 78-82.3)

**Malignant vs Benign Pancreatic Disease**

- Sensitivity: 78.2%
- Specificity: 82.2%
Glypican-1 positive exosomes
Carcinogenesis

Progression Model of Pancreatic Carcinogenesis

Pancreatic Intraepithelial Neoplasia

Low grade

Normal

PanIN-1

PanIN-2

PanIN-3

High grade

Cancer

Telomere Shortening

KRAS2

CDKN2A

TP53

SMAD4

Iacobuzio-Donahue, C.A., Gut, 61, 2012
Early stage disease
Neoantigen qualities

Letter

Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer


Balachandran et. al., Nature 551, Nov 2017

- Highest neoantigen number
- Abundant CD8+ T Cell Infiltrate
- Neoantigen quality promotes T Cell Activity in Long-term survivor
Cancer treatment

Disappointing Progress in the Treatment of Pancreatic Cancer

  - Gemcitabine
  - Survival time: 5.6 months vs. 4.1 months for 5-FU

- **Moore et al., J. Clin. Oncol. 25, 2007**
  - Gemcitabine + Erlotinib
  - Survival time: 100% vs. 85% at 1 year

- **Conroy et al., NEJM, 36, 2011**
  - Folfirinox
  - Survival time: 11.1 months

- **Von Hoff, D.D. et al., NEJM, 369, 2013**
  - Gemcitabine + nab-Paclitaxel
  - Overall survival: HR = 0.72 (95% CI, 0.62–0.83)

  - Nanoliposomal irinotecan + fluorouracil + folinic acid
  - Survival time: 4.2 months vs. 6.1 months
Immune checkpoint blockade

The disappointment of immune checkpoint blockade in pancreatic cancer

Anti-CTLA4

Anti-PD1

<table>
<thead>
<tr>
<th>Cohort-Tumor Type</th>
<th>N</th>
<th>ORR</th>
<th>mPFS (mo)</th>
<th>mOS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>471</td>
<td>14%</td>
<td>2.2</td>
<td>11.3</td>
</tr>
<tr>
<td>Mesothelioma (MPM)</td>
<td>25</td>
<td>20%</td>
<td>5.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Nasopharyngeal Carcinoma</td>
<td>27</td>
<td>26%</td>
<td>6.5</td>
<td>16.6</td>
</tr>
<tr>
<td>Neuroendocrine Carcinomas</td>
<td>16</td>
<td>6%</td>
<td>4.5</td>
<td>21</td>
</tr>
<tr>
<td>Ovarian Epithelial FTC/PPC</td>
<td>26</td>
<td>12%</td>
<td>1.9</td>
<td>13.8</td>
</tr>
<tr>
<td>Pancreatic ACA</td>
<td>24</td>
<td>0%</td>
<td>1.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Prostate ACA</td>
<td>23</td>
<td>17%</td>
<td>3.5</td>
<td>7.9</td>
</tr>
<tr>
<td>Salivary Gland Carcinoma</td>
<td>26</td>
<td>12%</td>
<td>3.8</td>
<td>13.2</td>
</tr>
<tr>
<td>SCLC</td>
<td>24</td>
<td>33%</td>
<td>1.9</td>
<td>9.7</td>
</tr>
</tbody>
</table>


% Change from Baseline SD

Anti-PD1 in Mismatch repair deficient
Novel immune therapies

Novel immunotherapies - an active area of investigation

- Make “cold” tumor hot by combining with agents that stimulate immune response
  - Radiation
  - Tumor vaccine
  - Oncolytic virus
  - Chemotherapy
- CSF-1R inhibitor: block cytokine signaling to relocate immunosuppressive macrophages
- CD40 agonist: reprogram poorly functioning ADC’s
- Block other checkpoints
Genetic alterations

Gene Alterations in Pancreatic Cancer

TP53  SMAD4  KRAS  CDKN2A

Know Your Tumor: Precision Medicine for PDAC

- N = 640 patients accrued
- Adequate samples for sequencing in >90%
- “50% with actionable mutations (27% highly actionable)"
  - DNA repair genes (BRCA, ~8%)
  - Cell cycle genes (CCND1/2/3, CDK4/6, ~8%)
- Effect of matched therapy
  - N = 18
  - PFS 4.1 vs. 1.9 m (HR 0.47, p = 0.03)
iExosomes for delivery of siRNA targeting mutant KRAS

- Package anti-KRAS\textsuperscript{G12D} siRNA into artificial iExosomes
- Exosomes are more resistant to ingestion by macrophages in circulation than liposomes
- iExosomes preferentially accumulate in liver, pancreas and lungs
- Increased macropinocytosis in KRAS mutant cells $\Rightarrow$ increased uptake of iExosomes
- No toxicity seen; no effect on KRAS WT cells
The complex microenvironment of pancreatic cancer

Complex microenvironment

Kleeff, J. et al. (2016) Pancreatic cancer
Desmoplastic stroma
Cancer associated fibroblasts

Cancer associated fibroblast (CAF) heterogeneity and stromal targeting in PDAC

Tumor Promoting

Tumor Restraining

Tumor secreted Ligands TGF-β and IL-1 promotes CAF heterogeneity

Targeting distinct Fibroblast niche- Tumor Promoting Inflammatory CAF

From: Biffi, G., et. al., Cancer Discov., Oct 2018
Tumor heterogeneity

Tumor Heterogeneity and Molecular Subtypes
PDAC subtypes
Classical subtype responds better to chemotherapy

Swimmer plot: how durable?
“durable” = the tx works a long time

Waterfall plot: how deep is the response?
“Deep” = the tx shrinks the tumor a lot

Chromosome structure
Stroma specific subtypes
Metabolic reprogramming
Stellate cells

Pancreatic stellate cells support tumor metabolism

- Stellate cells
  - Amino acids (Ala)
- Cancer cells
  - Fuels TCA cycle
  - Supports lipid and NEAAs biosynthesis
  - Shunts glucose to Ser/Gly biosynthesis

- Supports proliferation (in low-nutrient environment)
- Increases autophagy

Co-targeting of RAS/MAPK pathway and autophagy

Symbols:
- KRAS
- RAF
- MEK
- ERK
- LKB1
- AMPK
- ULK-1
- HCLK
- Hydroxychloroquine (HCQ)

Drugs:
- Trametinib
- Hydroxychloroquine (HCQ)

Reference:
Trametinib plus HCQ

Trametinib (MEK inhibitor) + HCQ (autophagy inhibition)
Drug delivery

Treatment Strategies to Improve Disease Outcome

Drug Delivery and Effectiveness of Systemic Therapy

Targeting Stroma
Mouse model

**Pancreatic Cancer Mouse Model (KPC)**

*LSL-Kras-G12D X p53 LSL R172H X Pdx-Cre 1*

\[ \text{Pancreatic Ductal Adenocarcinoma (PDAC)} \]

(Median Survival = 4-5 months)

*Hingorani, S. et. al., Cancer Cell, 2005*
Stroma targeting

Enzymatic Targeting of Stroma Enhances Therapeutic Response

Provenzano et. al., Cancer Cell, 21, 2012
Therapeutic response

Enzymatic Targeting of Stroma Enhances Therapeutic Response

A. Baseline

B. PEGPH20

C. Gem+PEGPH20

P_i > P_e and diffusion and convection limited

P_i < P_e and diffusion and convection favorable

↑ Hyaluronic Acid

Provenzano et. al., Cancer Cell, 21, 2012
Phase II trial

PEGPH20 in Clinic (Phase II)

- Patients with advanced pancreatic cancer
- Arms:
  - Gem + nab-p
  - Gem + nab-p + PEGPH20
- No difference in PFS in the whole study population (negative)
- Pre-specified subgroup analysis:
  - Hyaluronin(HA) high patients

Phase 3 study was just reported negative in press release

Hedgehog signaling

Inhibition of Hedgehog Signaling Depleted Stroma, Enhanced Drug Delivery and Improved Survival in Mice

Olive KP et. al., Science, 324, 2009

V=Vehicle
G=Gemcitabine
I= IPI-926 (Hedgehog Inhibitor)
I/G= IPI-926/Gem
Tumor suppressor

Sonic Hedgehog as a Tumor Suppressor in PDAC

Genetically Engineered Mouse Model

C

Percent survival

PKCY (n=26)
Shh-PKCY (n=23)
p = 0.0049, Log Rank

D

Survival from Repletion of Tumor
(implant)

PKCY
ShhPKCY

E

Malignant lesions
(Percent)

PKCY
ShhPKCY

F

Number (40 total)

PKCY (8 weeks)
ShhPKCY (8 weeks)

A = Acinar to Ductal Metaplasia
1 = PanIN1
2 = PanIN2
3 = PanIN3

Rhim AD et al., Cancer Cell, 25, 2014
Myoblast depletion

Myofibroblast depletion enhances PDAC

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Ozdemir, BC et. al., Cancer Cell, 25, 2014
Overall survival

Myofibroblast depletion reduces overall survival

GCV = genciclovir (Depletes Myofibroblasts in PKT;αSMA-tk+ Mice)
Anti-stromal therapy

Two Faces of Anti-Stromal Therapy

Stromal-targeting may not (always) have beneficial therapeutic response

Tumor-Stromal interaction is complex and caution is required for therapeutic approaches targeting stroma
Mesothelin

My Research: Mesothelin-Targeted Therapy for Pancreatic Cancer

- Cancer-specific surface antigen expressed by many solid tumors
  - Mesothelioma
  - Pancreatic
  - Ovarian
  - NSCLC
  - Gastric

  Endometrial
  Cervical
  Thymic carcinoma
  Cholangiocarcinoma

- Normal expression limited to mesothelial cells
- No expression parenchyma of vital organs
- No phenotype in MSLN KO mice

Ma et al, J. Biol. Chem., 2012
### MSLN expression in pancreas ductal adenocarcinoma (PDA)

<table>
<thead>
<tr>
<th>Expression</th>
<th>Negative</th>
<th>1+ (1-25% cells)</th>
<th>2+ (26-50% cells)</th>
<th>3+ (&gt;50% cells)</th>
<th>Total</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/60</td>
<td>10/60</td>
<td>50/60</td>
<td>60/60 (100%)</td>
<td>Argani et al. (5)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/14</td>
<td>3/14</td>
<td>5/14</td>
<td>14/14 (100%)</td>
<td>Frierson et al. (2)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/11</td>
<td>0/11</td>
<td>2/11</td>
<td>10/11 (91%)</td>
<td>Ordonez (6)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/14</td>
<td>0/14</td>
<td>3/14</td>
<td>12/14 (86%)</td>
<td>Ordonez (1)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/68</td>
<td>22/68</td>
<td>39/68</td>
<td>61/68 (90%)</td>
<td>Swierczynski et al. (7)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/18</td>
<td>2/18</td>
<td>1/18</td>
<td>18/18 (100%)</td>
<td>Hassan et al. (8)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/185</td>
<td>37/185</td>
<td>138/185</td>
<td>175/185 (95%)</td>
<td>Total prevalence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:**
- 5% Neg
- 20% Low
- 75% Strong

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Scales et al., Mol. Cancer Ther, 2014
MSLN therapeutics

MSLN-targeted therapeutics in the clinic

Recombinant immunotoxin
Mechanism of action
LMB-100 plus paclitaxel

LMB-100 works with nab-paclitaxel to eliminate PDAC tumors

L = LMB-100 (2.5 mg/kg)
Active regimen

LMB-100 + NAB-paclitaxel is an active regimen

Better response is associated with higher MSLN expression in archival tissue
Anti-drug antibody

Peak serum levels of LMB-100 are limited by anti-drug antibody formation beginning with Cycle 2.
Decreasing ADA formation with tofacitinib

- Janus kinase (JAK) inhibitor
- Inhibits lymphocyte signaling
- FDA approved for treatment of autoimmune diseases
- Limits formation of ADAs against iTox in mice

Onda…Fitzgerald, J. Immunol., 2014
**Tofacitinib**

**Additional effect of tofacitinib: increased anti-tumor efficacy through stromal modulation**

**Tofacitinib treatment**

- Reduces macrophage population in tumors
  - Less non-specific uptake of iTox in tumor by macrophages
  - => Increases iTox serum half-life
  - => Increases iTox delivery to tumor

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Simon et al, *JCI Insight*, 2019
Tocacitinib + LMB-100

Phase I: tofacitinib + LMB-100

1. **Dose escalation** to determine maximum tolerated dose
   - MSLN(+) solid tumors

2. **Expansion phase** to assess impact on ADA formation
   - Pancreatic adenocarcinoma
   - Extrahepatic cholangiocarcinoma

Cycle 1 (21 days) | Cycle 2 | Cycle 3
--- | --- | ---
LMB-100 | LMB-100 | LMB-100

**Maintenance Therapy Arm**

- **BX** = optional tumor biopsy
- **CT** = imaging
- **ADA** = anti-drug antibody titer
- **10 mg PO, BID as per dose escalation**

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*Now accruing!*
Questions?