PANCREAS CANCER

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

What you need to Know About Cancer of the Pancreas, NIH Publication No. 10-1560, 2010
RISK FACTORS FOR PANCREATIC CANCER

Risk for lung cancer in long term smokers is 8-15x

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>Smoking</td>
<td>2–3</td>
</tr>
<tr>
<td>Long-standing diabetes mellitus</td>
<td>2</td>
</tr>
<tr>
<td>Nonhereditary and chronic pancreatitis</td>
<td>2–6</td>
</tr>
<tr>
<td>Obesity, inactivity, or both</td>
<td>2</td>
</tr>
<tr>
<td>Non-O blood group</td>
<td>1–2</td>
</tr>
<tr>
<td>Genetic syndrome and associated gene or genes — %</td>
<td></td>
</tr>
<tr>
<td>Hereditary pancreatitis (PRSS1, SPINK1)</td>
<td>50</td>
</tr>
<tr>
<td>Familial atypical multiple mole and melanoma</td>
<td>10–20</td>
</tr>
<tr>
<td>syndrome (v16)</td>
<td></td>
</tr>
<tr>
<td>Hereditary breast and ovarian cancer syndromes</td>
<td>1–2</td>
</tr>
<tr>
<td>(BRCA1, BRCA2, PALB2)</td>
<td></td>
</tr>
<tr>
<td>Peutz–Jeghers syndrome (STK11 [LKB1])</td>
<td>30–40</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colon cancer (Lynch</td>
<td></td>
</tr>
<tr>
<td>syndrome) (MLH1, MSH2, MSH6)</td>
<td></td>
</tr>
<tr>
<td>Ataxia–telangiectasia (ATM)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Li–Fraumeni syndrome (P53)</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.

Ryan et al, NEJM, 2014
SYMPTOMS OF PANCREATIC CANCER

- Jaundice (yellow skin and eyes, dark urine)
- Upper abdominal pain
- Mid back pain
- Nausea and vomiting
- Weight loss
- Loss of appetite (“anorexia”)
- Feeling full quickly (“early satiety”)
- Lethargy

What you need to Know About Cancer of the Pancreas, NIH Publication No. 10-1560, 2010
DIAGNOSING PANCREAS CANCER

1. CT or MRI imaging

2. Biopsy:
   - Endoscopic ultrasound (EUS)
   - Percutaneous liver biopsy
   - Surgical

Kamisawa, Wood & Takaori, Lancet, 2016
American Cancer Society, Cancer Facts and Figures 2017
Most patients have metastatic disease at diagnosis.

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

American Cancer Society, Cancer Facts and Figures 2017
**BARRIERS TO EARLY DETECTION**

- Early symptoms are generic (“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

## Stage at Diagnosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor confined to the pancreas</td>
</tr>
<tr>
<td>II</td>
<td>Resectable but tumor extends beyond pancreas or lymph nodes involved</td>
</tr>
<tr>
<td>III</td>
<td>Tumor in the pancreas is not resectable but no spread to distant organs</td>
</tr>
<tr>
<td>IV</td>
<td>Spread to distant organs</td>
</tr>
</tbody>
</table>

**“Early” (Curable)**

**“Locally Advanced”**

**“Metastatic”**
5-YEAR SURVIVAL % BY STAGE

American Cancer Society, Cancer Facts and Figures 2017
EARLY STAGE DISEASE: **SURGERY + CHEMOTHERAPY**

Surgical resectability is defined by degree of vascular involvement
EARLY STAGE DISEASE: SURGERY + CHEMOTHERAPY

1. Whipple
   - For tumors in pancreatic head
   - Very complicated procedure
   - High morbidity and mortality rate
     - Delayed gastric emptying (21%)
     - Fistula (1.5%)
     - Wound infection (11%)
     - Bleeding (2%)
     - Chyle leak (1%)
     - Cardiac event (3%)
     - Pneumonia (2%)
   - Long recovery period
   - Long-term complications

2. Distal Pancreatectomy

3. Total Pancreatectomy
   - Results in insulin dependence

Images from www.mumbaicancer.com/surgery-pancreas.html

Cameron and He, J. Am. Coll. Surg., 2015
EARLY STAGE DISEASE: SURGERY + CHEMOTHERAPY

CONKO-001

Disease-Free Survival in Patients With R0 Resection

Log-Rank $P < 0.001$

+Gem

observe

No. at Risk
Gemcitabine 145 78 33 21 14 9 6 1
Observation 148 49 23 9 6 6 2 0

Oettle et al, JAMA, 2007

ESPAC-4

G+C (R0)

Gem (R1) Gem (R0) G+C (R1)

Neoptolemos et al, Lancet, 2017
STANDARD TREATMENTS FOR ADVANCED DISEASE

Chemotherapy:
- FOLFIRINOX
- Gemcitabine + NAB-paclitaxel
- Gemcitabine + erlotinib
- Gemcitabine
- 5-FU or capecitabine
- Capecitabine + liposomal irinotecan

**FOLFIRINOX**

ORR = 31.6%
PFS = 6.6 m

Conroy et al, NEJM, 2011
PROMISE OF NEW TREATMENTS?

No efficacy of targeted therapies +/- gemcitabine.

No efficacy with immune checkpoint inhibitors


Topalian et al, Cancer Cell, 2015
PALLIATING SYMPTOMS OF PANCREATIC CANCER

Obstruction
- Biliary => jaundice
- Gastric or Duodenal => vomiting, poor nutrition

Pain

Weight loss and wasting syndrome

Nausea and vomiting

Poor appetite and feeling full quickly

Diabetes (“endocrine insufficiency”)

Fat soluble vitamin deficiency (“exocrine insufficiency”)

Blood clots

Fogel et al, J. Am. Gastroenterol., 2017
ON THE HORIZON

Stromal modulating agents
- PEGPH20
- FAK inhibitor

Immune therapy combinations
- Dual checkpoint inhibitor therapy
- +immune modulating agent
- +vaccine
- +oncolytic virus
- +radiation
- +drugs

Immune Cell Based Therapies

Current Phase III Treatment Studies

Advanced Dz
- Olaparib for germline BRCA mutant patients
- Gem + NAB-paclitaxel + PEGPH20
  - Pegylated hyaluronidase
- Gem + NAB-paclitaxel + napabucasin
  - STAT3 inhibitor
- Gem + Cape + GV1001
  - Telomerase peptide vaccine
- Gem + NC-6004
  - Micellar cisplatin formulation

Adjuvant
- FOLFIRINOX/ FOLFOXIRI
- Gem + NAB-paclitaxel
SUMMARY OF PANCREATIC CANCER

3rd leading cause of cancer death in United States because

- Many patients are diagnosed at a late stage
- Our treatments for early stage disease are not as effective as those available for other tumor types

Early diagnosis is difficult

Pancreatic cancer surgeries are very tough

Available drug treatments are relatively ineffective

Many new treatments are currently under investigation

Side effects of pancreatic cancer and its current treatments have significant impact on patient quality of life
MY RESEARCH: MESOTHELIN-TARGETED THERAPY FOR PANCREATIC CANCER

- Cancer-specific surface antigen expressed by many solid tumors
  - Mesothelioma
  - Pancreatic (95% have it)
  - Ovarian
  - Lung
  - Gastric
  - TNBC

- Normal expression limited to cells that line lung, heart and abdominal cavity
MSLN-TARGETED THERAPEUTICS IN THE CLINIC

Adapted from R. Hassan et al., in press J. Clin. Onc.
Pseudomonas Exotoxin A

RECOMBINANT IMMUNOTOXIN (RIT)

SS1(dsFv)PE38

Targeting Fv

Anti-MSLN dsFv

PE payload
RECOMBINANT IMMUNOTOXINS

eEF2

NAD+
Nicotinamide

PE

ADP-Ribose

eEF2 = Elongation Factor-2

Inhibits protein synthesis

LMB-100 (RG7787)

SS1P

Mechanism of Action
Inhibits protein synthesis
LMB-100 WORKS WITH NAB-PACLITAXEL TO ELIMINATE PDAC TUMORS

KLM1

Time since inoculation (Days)  L = LMB-100 (2.5 mg/kg)

Kolyvas, Alewine et al, Oncotarget, 2016
LMB-100 WORKS WITH NAB-PACLITAXEL TO ELIMINATE PDAC TUMORS

Kolyvas, Alewine et al, Oncotarget, 2016
PHASE IB/II: LMB-100 WITH NAB-PAACLITAXEL FOR PREVIOUSLY TREATED ADVANCED PANCREATIC CANCER

Primary Goals:
- Assess safety of the combination
- Determine whether the combination can shrink tumors better than nab-paclitaxel alone

Additional Goals:
- Assess immunogenicity of LMB-100
- Monitor how fast the body processes LMB-100
- Identify a mechanism for the major toxicity of immunotoxins (vascular leak syndrome)

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**Cycle 1-4**
(21 days)

L = LMB-100; Nab-P = NAB-paclitaxel

[Diagram showing the cycle with LMB-100 and Nab-P injections at specific days: 1, 3, 5, 7, 8, 15, and 21]
ACKNOWLEDGEMENTS

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  - Tim Greten
QUESTIONS?
BIOLOGICAL ROLE OF MSLN IN PANC CA

High expression prognostic for short survival in resectable patients

T. Einama et al, Pancreas, 2011

Table 3. Multivariate predictors of short-term survival. (<1yr)

<table>
<thead>
<tr>
<th>Prognostic marker</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSLN negative</td>
<td>Ref</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>MSLN 1+</td>
<td>1.65</td>
<td>(0.48, 5.72)</td>
<td></td>
</tr>
<tr>
<td>MSLN 2+</td>
<td>2.64</td>
<td>(0.85, 8.22)</td>
<td></td>
</tr>
<tr>
<td>MSLN 3+</td>
<td>12.47</td>
<td>(2.43, 64.14)</td>
<td></td>
</tr>
</tbody>
</table>

J. Winter et al, PLoSOne, 2012
### MSLN Expression in Pancreas Cancer

<table>
<thead>
<tr>
<th></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></td>
<td>60/60 (100%)</td>
<td>Argani et al. (5)*</td>
<td></td>
</tr>
<tr>
<td>0/14</td>
<td>3/14</td>
<td>5/14</td>
<td>6/14</td>
<td>14/14 (100%)</td>
<td>Frierson et al. (2),†</td>
<td></td>
</tr>
<tr>
<td>1/11</td>
<td>0/11</td>
<td>2/11</td>
<td>8/11</td>
<td>10/11 (91%)</td>
<td>Ordonez (6)*</td>
<td></td>
</tr>
<tr>
<td>2/14</td>
<td>0/14</td>
<td>3/14</td>
<td>9/14</td>
<td>12/14 (86%)</td>
<td>Ordonez (1)*</td>
<td></td>
</tr>
<tr>
<td>7/68</td>
<td>22/68</td>
<td>39/68</td>
<td></td>
<td>61/68 (90%)</td>
<td>Swierczynski et al. (7),*</td>
<td></td>
</tr>
<tr>
<td>0/18</td>
<td>2/18</td>
<td>1/18</td>
<td>15/18</td>
<td>18/18 (100%)</td>
<td>Hassan et al. (8)*</td>
<td></td>
</tr>
<tr>
<td>10/185 (5.4%)</td>
<td>37/185 (20%)</td>
<td>138/185 (75%)</td>
<td>175/185 (95%)</td>
<td>Total prevalence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 1% cutoff. †1+ was instead defined as focal (1-10% cells only) by Frierson et al. (2).

Swierczynski et al. (7) demonstrated 10% of positive PDAC tumors could be missed in TMAs versus whole sections due to focal mesothelin staining.

5% Neg 20% Low 75% Good to High
ADDITION OF LMB-100 ENHANCES TAXANE ACTIVITY PRIMES TUMOR CELLS FOR APOPTOSIS

KLM-1

Day 0 1 2 3
Plate LMB-100 Harvest Cells

Tax LMB-100 0 10 0 100 10

Acet Tub
Total α – Tub
γ – H2AX
GAPDH

Tax LMB-100 0 10 100 0 10

Mcl-1 37kD
Actin

E. Kolyvas et al, submitted Oncotarget
Survival 5 Years From Diagnosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>29%</td>
</tr>
<tr>
<td>Regional</td>
<td>11%</td>
</tr>
<tr>
<td>Metastatic</td>
<td>3%</td>
</tr>
<tr>
<td>All</td>
<td>8%</td>
</tr>
</tbody>
</table>