Terminology

- Pancreatic cancers:
  - majority are pancreatic adenocarcinomas
  - few are pancreatic neuroendocrine cancers
  - Lymphoma, sarcomas, others are rare
Pancreatic Cancer - Some simple statistics

- About 53,000 patients diagnosed this year in the U.S.
- Cure is rare: this is a systemic disease at presentation
- 100 Patients
  - 15-20 patients will have operable tumors
  - Almost 80 will have inoperable, advanced cancers

Why does it present late?

- ‘Nonspecific’ symptoms which can mimic other common conditions
- ‘Tucked away’: no early symptoms or signs
- No good screening test
Molecular Progression Model
Pancreatic Intraepithelial Neoplasia (PanINs)

Staging of Pancreatic Cancer

- **Stage 1**: Isolated to the Pancreas, no lymph nodes or blood vessels involved
- **Stage II**: Extends beyond the pancreas. No blood vessels involved
- **Stage III**: Blood vessels involved
- **Stage IV**: Spread to distant organs
Staging of Pancreatic Cancer

Resectable (Stages I and II)
- **Stage 1**: Isolated to the Pancreas, no lymph nodes or blood vessels involved
- **Stage II**: Extends beyond the pancreas. No blood vessels involved

Unresectable (Stages III and IV)
- **Stage III**: Blood vessels involved
- **Stage IV**: Spread to distant organs

Clinical Staging for Pancreatic Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>(10-15%)</td>
</tr>
<tr>
<td>Borderline Resectable</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>(50%)</td>
</tr>
<tr>
<td>III. Metastatic</td>
<td>(35-40%)</td>
</tr>
</tbody>
</table>
Borderline Resectable Pancreatic Cancer

Metastatic pancreatic cancer: Patterns of Spread

- Liver
- Lung
- Lymph Nodes
- Peritoneum
- Other
Treatment options for Pancreatic Cancer

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Radiation</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Borderline Resectable</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Locally Advanced</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Metastatic</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Resectable Pancreatic Cancer

- Surgery first followed by chemotherapy is standard
- 15-20% of all patients – and can lead to cure in a small group of patients
- Most patients still relapse
  » In the surgical bed.
  » In the liver, lung, lymph nodes, or peritoneum.
- Significant morbidity and mortality (inversely correlated with experience)
  » Length of hospital stay 1-2 weeks
  » Recovery period 2 months
Hospital Volume and Surgical Mortality in the U.S.

Birkmeyer et al, NEJM 2005

“Margin” and surgery

RP margin
Options after surgery

- **Chemotherapy**
  - To kill any microscopic amounts of tumor floating around in the liver, lung, lymph nodes....

- **Radiation (select group of patients)**
  - To prevent tumor from coming back in the surgical bed.

### Randomized Trials of Adjuvant Therapy

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Number of Patients</th>
<th>Pts with R1 Resection (%)</th>
<th>Treatment Median Survival Months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG (1985)</td>
<td>49</td>
<td>0</td>
<td>5-FU + XRT 21.0</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Observation 10.9</td>
<td></td>
</tr>
<tr>
<td>EORTC 40891 (1999)</td>
<td>114</td>
<td>21</td>
<td>5-FU + XRT 17.1</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Observation 12.6</td>
<td></td>
</tr>
<tr>
<td>ESPAC-1 (2004)</td>
<td>289</td>
<td>18</td>
<td>5-FU Chemotherapy 20.1</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No Chemotherapy 15.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-FU- XRT 15.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No XRT 17.9</td>
<td>0.05</td>
</tr>
<tr>
<td>RTOG 9704 (2006)</td>
<td>380 (Head lesions)</td>
<td>&gt; 35</td>
<td>GEM then 5-FU/XRT then GEM 20.0</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-FU then 5-FU/XRT then 5-FU 10.0</td>
<td></td>
</tr>
<tr>
<td>CONKO 001 (2007-08)</td>
<td>368</td>
<td>19</td>
<td>Gemcitabine 22.8</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Observation 20.2</td>
<td></td>
</tr>
<tr>
<td>ESPAC 3 (2009)</td>
<td>1088</td>
<td>35</td>
<td>5FU 23 months</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td></td>
</tr>
<tr>
<td>CapRI (2010)</td>
<td>110</td>
<td>39</td>
<td>5FU 28.5 months</td>
<td>Not signif</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5FU/CCDPP/3N/F + XRT (+5FU x 2) 32 months</td>
<td></td>
</tr>
</tbody>
</table>
### Role of Postoperative Chemo alone in Resected PC

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Pts</th>
<th>R1 Resection (%)</th>
<th>Treatment</th>
<th>Median Survival Months</th>
<th>Treatment</th>
<th>Median Survival Months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONKO 001</td>
<td>368</td>
<td>19</td>
<td>Gemcitabine 22.8 (DFS=13.9)</td>
<td>Observation 20.2 (DFS=6.9)</td>
<td>0.05</td>
<td>&lt;0.001</td>
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<tr>
<td>ESPAC 3 (V2)</td>
<td>1088</td>
<td>35</td>
<td>5FU 23</td>
<td>Gemcitabine 23.6</td>
<td>0.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPAC 4</td>
<td>730</td>
<td>60</td>
<td>GEMCAP 28</td>
<td>Gemcitabine 25.5</td>
<td>0.032</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After upfront surgery some therapy better than no therapy
Usually 6 months of Gemcitabine

ESPAC 3 Neoptolemos JP et al. JAMA 2010
ESPAC 4 Neoptolemos JP et al. ASCO 2016

### Sequencing Therapies for Resectable cancers

#### Traditional approach in patients

Operable Pancreatic Cancer → Surgery → Post-Operative Therapy (Adjuvant Therapy)

#### Preoperative Approach in select patients

Operable Pancreatic Cancer → Preoperative Therapy (Neo-adjuvant Therapy) → Surgery
Preoperative therapy

- Average time between start of preoperative therapy and surgery is about 3 - 4 months.
- Isolated local progression during therapy is rare.
- Patients deemed unresectable after preoperative therapy are those with distant metastasis seen on restaging scans or at the time of surgery.
- Newer multiagent therapies used (folfirinox and gem+nab-paclitaxel)

Treatment options for Pancreatic Cancer

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<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Locally Advanced</td>
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<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Metastatic</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Borderline Resectable Pancreatic Cancer

Tumor

Positive Surgical Margin

Staging CT

Systemic Therapy

Gemcitabine-based 2-4 months

(restaging CT scan)

Classified as borderline resectable types A, B, C

Restaging CT

No Progression

Regression

4 to 6 Weeks Break

Change Therapy

Restaging CT

No Progression

Regression

Surgery

*Consider adjuvant therapy based on duration of preoperative treatment and pathology.

Treatment Schema-Borderline Resectable
Borderline Resectable Pancreatic Cancer

After Preoperative Chemotherapy and ChemoRT

Non-viable rim

Negative Surgical Margin!

Viable Tumor

Fine line between BRPC and LAPC: easier in retrospect
Locally Advanced Pancreatic Cancer

Sequencing Therapies for locally advanced Pancreatic Cancer

**Previous approach**

Locally advanced Pancreatic Cancer → ChemoRADIATION → Chemotherapy

**Changed paradigm**

Locally advanced Pancreatic Cancer → Chemotherapy for several months if no progression (and no urgent need for radiation e.g. uncontrollable pain, bleeding) → ChemoRADIATION in Select patients (not common in UK/Europe)
Metastatic Pancreatic Cancer
## Pancreatic cancer - Approved Drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-1996</td>
<td>The dark ages. Nothing worked</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td><strong>Gemcitabine</strong> improves survival compared with 5-FU. Gemcitabine is approved for PC</td>
<td></td>
</tr>
<tr>
<td>1996-2005</td>
<td>Many agents tested. No drug or drug combination is better than Gemcitabine</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td><strong>Erlotinib + Gemcitabine</strong> modestly improves survival compared with Gemcitabine. Erlotinib is approved for PC</td>
<td></td>
</tr>
<tr>
<td>2005-2009</td>
<td>More drugs tested. Many more negative trials</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>Gemcitabine + Capecitabine superior to Gemcitabine in a pooled analysis of 3 trials</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td><strong>FOLFIRINOX</strong> improves survival compared with Gemcitabine</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td><strong>nab-Paclitaxel + Gemcitabine</strong> improves survival compared with Gemcitabine</td>
<td></td>
</tr>
<tr>
<td>Oct 2015</td>
<td><strong>Nal-iri</strong> approved for Gem treated PDAC</td>
<td></td>
</tr>
</tbody>
</table>

### Randomized phase III trial comparing FOLFIRINOX (F) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma: PRODIGE 4/ACCORD 11 trial.

**F**
- O 85 mg/m² d1 + I 180 mg/m² d1 + LV 400 mg/m² d1 followed by 5FU 400 mg/m² bolus d1 and 2,400 mg/m² 46h continuous infusion biweekly
- PS 0-1
- Stratified by: PS, Center, Tumor location
- **R 360**
- **R, Ph II**
- F>G

**G**
- Gemcitabine 1000 mg/m²,
- 70 min IV
- wkly 7 on 1 off, then 3 on 1 off
Randomized phase III trial comparing FOLFIRINOX versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA)

<table>
<thead>
<tr>
<th></th>
<th>F Grade ¾ (%)</th>
<th>G Grade ¾ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>12.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>15.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24</td>
<td>14.3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>47.9</td>
<td>19.2</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>5.7</td>
<td>0</td>
</tr>
</tbody>
</table>

T Conroy et al. ASCO 2010
NEJM, May 2011

PRODIGE 4/ACCORD 11 trial – FOLFIRINOX
SURVIVAL AND RESPONSE DATA

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRINOX (n=171)</th>
<th>GEM (n=171)</th>
<th>Overall Survival mo</th>
<th>Response Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival mo</td>
<td>11.1 mo</td>
<td>6.8 mo</td>
<td>HR 0.57 P &lt;0.001</td>
<td>32 %</td>
</tr>
<tr>
<td>Response Rate %</td>
<td>32 %</td>
<td>9%</td>
<td>HR 0.57 P &lt;0.001</td>
<td>32 %</td>
</tr>
</tbody>
</table>
Randomized Phase III Study of Weekly nab-Paclitaxel plus Gemcitabine vs Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas (MPACT)

**Planned N = 842**
- Stage IV
- Untreated
- KPS ≥70

**Primary Endpoint: OS**
Treat until progression
CT scans every 8 weeks

**nab-Paclitaxel plus Gemcitabine (MPACT)**

**SAFETY**

<table>
<thead>
<tr>
<th></th>
<th>nabP + GEM (n=421)</th>
<th>GEM (n=402)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Neutropenia</td>
<td>3 %</td>
<td>1 %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>17 %</td>
<td>&lt; 1 %</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 %</td>
<td>1 %</td>
</tr>
</tbody>
</table>

44% patients with peripheral neuropathy resumed nab-P after improvement (median to improvement to grade ≤1 = 29 days)

Von Hoff et al., ASCO GI 2013 LBA148
**SURVIVAL AND RESPONSE DATA**

<table>
<thead>
<tr>
<th></th>
<th>nabP + GEM (n=431)</th>
<th>GEM (n=430)</th>
<th>HR 0.72 P &lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Survival mo</strong></td>
<td>8.5 mo</td>
<td>6.7 mo</td>
<td></td>
</tr>
<tr>
<td><strong>Response Rate %</strong></td>
<td>23%</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

*Mr. T  
Pastor from Georgia  
Pancreatic cancer for 2 + years, clinical trial for 9 months*

"Dum spiro, spero "While I breath, I hope” - Latin Proverb

Von Hoff et al., ASCO GI 2013 LBA148
FOLFIRINOX vs. Gemcitabine and Abraxane

- No head to head comparison
- Patient preference is important which both options seem equally reasonable
- Presence of diarrhea, weight loss.. does go into the planning
- Biliary stent issues
- Family history of pancreas cancer
- Burden of disease
- Performance status : sense of well being, functional

We must accept finite disappointment, but never lose infinite hope – Martin Luther King Jr.

Mr. L. 54 year old
Completed FOLFIRINOX 10 cycles
Works full time
Decline in marker, improvement in scans, handling chemotherapy well
Enjoys getting out of town and time with family
Clinical trials: Definitions

• PHASE I TRIALS: Experimental drug is tested in a small group of patients, with different cancers for the **first time**- to determine safety, identify side effects and get some early signal of benefit

• PHASE II TRIALS: Experimental drug is given to a larger group of patients (with same cancer) to determine effectiveness, monitor side effects, compare it to commonly used drugs

• PHASE III TRIALS: Experimental treatment given to large groups of patients to confirm effectiveness, compare it to commonly used drugs (standard of care) – if positive, may establish change in standard of care.

Thrust of ongoing efforts : Broad Categories

• BRCA, BRCAness and Familial Pancreatic Cancer
  Platinum agents;  PARPi

• Stroma targeting agents
  PEGPH20; Heparin analogs; Vit D receptor analogs

• Specific pathways targeting agents
  MM-141; Ruxolitinib

• Metabolic pathways targeting agents
  Hydroquinone, Oxphos inhibitors

• Enhancing immune destruction of Pancreatic Cancer
  Vaccines; Anti-CTLA 4 antibodies, Anti PD-1/PD-L1 antibodies
  CD40 agonists Ab,  OX40, IDO and others
BRCA, BRCAness and Familial Pancreatic Cancer

<table>
<thead>
<tr>
<th>Hereditary breast and ovarian cancer</th>
<th>BRCA1, BRCA2</th>
<th>3.5-10</th>
<th>Ductal adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peutz Jegher</td>
<td>STK11/LKB1</td>
<td>132</td>
<td>IPMN</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>PRSS1, SPINK1</td>
<td>53</td>
<td>Ductal adenocarcinoma</td>
</tr>
<tr>
<td>HNPCC</td>
<td>MMR genes</td>
<td>?</td>
<td>Medullary carcinoma</td>
</tr>
<tr>
<td>FAMMM</td>
<td>CDKN2</td>
<td>13-22</td>
<td>Ductal adenocarcinoma</td>
</tr>
</tbody>
</table>

| Familial pancreatic cancer | ? | 9-32 | |

Family history is crucial: those with hereditary cancers are more responsive to ‘platinum therapies’ and may respond to (new) PARP inhibitors class of agents

Ashworth, A. J Clin Oncol; 26:3785-3790 2008

Targeting Stroma in Pancreatic Cancer

PEGPH20 temporarily degrades hyaluronan (HA) that accumulate around pancreatic cancers. Preclinical studies have shown that removal of HA from tumors improves the ability of chemotherapies or immunotherapies to penetrate the tumor, inhibiting its growth. Trials with this agent are ongoing.
Pancreatic cancer and Immunotherapy

We have not seen the progress with immunotherapy in pancreas cancer as in some other cancers.

Pancreatic cancers restrictive microenvironment makes it difficult for immunotherapy to work.

Several trials are underway with combination therapies that allow infiltration of activated T cells into the tumor and then 'remove the brakes'.

Immunotherapy is treatment that uses certain parts of a person's immune system to fight cancer. These treatments that work in different ways. Some boost the body's immune system in a very general way. Others help train the immune system to attack cancer cells specifically.

It is important to tackle all symptoms – they feed on each other - domino effect.

- Open communication with the health care team
- Is it a side effect of treatment or symptom of cancer
- Many options for supportive care to improve quality of life
Summary: Pancreatic Cancer

- Pancreatic cancer is a local disease and a systemic disease.

- Do not make treatment decision in haste (especially surgery)

- The research teams are working toward personalizing therapies and trials to match the patient

- We have a long way to go but we are definitely making progress