TREATMENT APPROACHES FOR PANCREATIC CANCER

JANUARY 24, 2018

IF YOU EXPERIENCE TECHNICAL DIFFICULTY DURING THE PRESENTATION:
CONTACT WEBEX TECHNICAL SUPPORT DIRECTLY AT:
US TOLL FREE: 1-866-779-3239
TOLL ONLY: 1-408-435-7088
OR
SUBMIT A QUESTION TO THE EVENT PRODUCER VIA THE Q&A PANEL

Thank you to our webinar sponsor:
An Update On Treatment Approaches For Resectable Pancreas Cancer and Review of Current Clinical Trials

Syed A. Ahmad, MD
Professor of Surgery
Associate Director University of Cincinnati Cancer Institute
Head Gastrointestinal Comprehensive Center
Director of Pancreatic Disease Center
Format

- Background
- Current standard for resectable pancreas cancer
- Ongoing clinical studies for resectable pancreas cancer
- Future targeted therapies

Truths Regarding Pancreatic Cancer

- Eighth most common malignancy
- Fourth leading cause of cancer death among men and women
- Incidence rates and mortality rates are almost identical
- Risk of pancreatic cancer increases after the age of 50
- Surgery Remains only hope for long-term cure
Truth Regarding Pancreas Cancer

• 55,440 patients will be diagnosed with pancreas cancer in 2018
  • 44,330 patients will die of pancreas cancer
• The 5-year survival rate has slowly improved but is still around 5-10%
• The 5-year survival rate is better for patients who are able to undergo surgery
• Most patients are diagnosed late in their disease state after metastases have formed
• Very little progress has been made in improving survival in the last several decades

Cancer Rates

• Frequency increases with age
  • The mean onset of pancreatic cancer is 65 years
  • 80% of patients are older than 60
  • Patients at younger age usually have an undiagnosed genetic risk factor
• Higher rates in men compared to women
  • Most likely due to differences in smoking
  • As more women are smoking, these differences are disappearing
Cancer Rates

• Racial Differences
  • Rates in African Americans 50% greater than Whites
  • Rates in non-Whites, non-AA are similar to Whites

• Regional
  • Highest: North America, Europe
  • Lowest: Africa, Asia, South America
  • May be related to differences in cigarette smoking

Modifiable Risk Factors

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>RISK ESTIMATE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Cigarette Smoking</td>
<td>OR = 2.20 (1.71-2.83)</td>
</tr>
<tr>
<td>Past Cigarette Smoking</td>
<td></td>
</tr>
<tr>
<td>1-10 years since quitting</td>
<td>OR = 1.64 (1.36-1.97)</td>
</tr>
<tr>
<td>15-20 years since quitting</td>
<td>OR = 1.12 (0.86-1.44)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
</tr>
<tr>
<td>&lt;3 years</td>
<td>RR = 7.94 (4.70-12.55)</td>
</tr>
<tr>
<td>&gt;10 years duration</td>
<td>OR = 1.51 (1.16-1.96)</td>
</tr>
<tr>
<td>BMI (&gt;35 vs 18.9-24.9)</td>
<td>OR = 1.55 (1.16-2.07)</td>
</tr>
<tr>
<td>Heavy Alcohol (&gt;6 drinks/day)</td>
<td>OR = 1.46 (1.16-1.83)</td>
</tr>
<tr>
<td>Pancreatitis (&gt;2 years)</td>
<td>2.71-fold (1.96-3.74)</td>
</tr>
</tbody>
</table>
Inherited Risk Factors

<table>
<thead>
<tr>
<th>GENERATION GROUP</th>
<th>RISK ESTIMATE (95% CI)</th>
<th>ESTIMATED LIFETIME PANCREATIC CANCER RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>1</td>
<td>0.9% by age 80 [23]</td>
</tr>
<tr>
<td>Familial Pancreatic Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall: 3 or more first-degree relatives with pancreatic cancer</td>
<td>BRCA1: 0.6 (4.54-9.75)</td>
<td>Varies with youngest age of onset</td>
</tr>
<tr>
<td>High Penetance</td>
<td>BRCA2</td>
<td>8.51 (1.07-6.58)</td>
</tr>
<tr>
<td>PALB2</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>BRCA1</td>
<td>OR = 2.26 (1.36-4.06)</td>
<td>2.10% (age 80)</td>
</tr>
<tr>
<td>Mismatch Repair (HNRC)</td>
<td>BRCA1: 6.6 (4.7-15.7)</td>
<td>3.68% (1.45-5.88% (age 70)</td>
</tr>
<tr>
<td>Hereditary Pancreatic (PSS)</td>
<td>BRCA1: 58 (23-105)</td>
<td>30-40% (age 70)</td>
</tr>
<tr>
<td>Peutz-Jeghers (STK11)</td>
<td>BRCA1: 132 (44-367)</td>
<td>11% (32% (2.32)</td>
</tr>
<tr>
<td>Familial Melanoma (CDKN2A)</td>
<td>BRCA1: 38 (10-97)</td>
<td>17% (age 75)</td>
</tr>
<tr>
<td>ATM</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Low Penetance</td>
<td>ABO blood group</td>
<td>OR = 1.10 (1.12-1.28)</td>
</tr>
<tr>
<td>1q21.20(578844 T/C)</td>
<td>OR = 0.77 (0.71-0.84)</td>
<td>0.73% (age 80)</td>
</tr>
<tr>
<td>19q12.11(950325 T/C)</td>
<td>OR = 1.26 (1.18-1.35)</td>
<td>1.2% (age 80)</td>
</tr>
<tr>
<td>5p15.33a(9416681 C/T)</td>
<td>OR = 1.59 (1.11-2.21)</td>
<td>1.10% (age 80)</td>
</tr>
</tbody>
</table>

Wolfgang CL et al. CA Cancer J Clin, 2013

Malignant Tumors of the Pancreas

- Ductal Adenocarcinoma
- Acinar Cell Carcinoma
- Serous Cystic Neoplasia
- Mucinous Cystic Neoplasia
- IPMN
- Solid-pseudopapillary
- Pancreatic Endocrine Neoplasms.

Atypical glandular cells
Desmoplastic stroma
IPMN
How Do Patients With Pancreas Cancer Present?

Clinical Presentation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss</td>
<td>90%</td>
</tr>
<tr>
<td>Pain</td>
<td>75%</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>75%</td>
</tr>
<tr>
<td>Jaundice</td>
<td>70%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>60%</td>
</tr>
<tr>
<td>Pruritis</td>
<td>40%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15%</td>
</tr>
</tbody>
</table>
Is Surgery An Option?

- Need to determine which category the tumor fits into:
  - Resectable (Not involving surrounding blood vessels)
    - Surgery followed by chemotherapy +/- radiation
    - Neoadjuvant therapy followed by Surgery
  - Borderline Resectable (Touching surrounding blood vessels)
    - Neoadjuvant therapy
  - Locally Advanced Unresectable (Encircling surrounding blood vessels)
    - Chemotherapy +/- XRT (small subset get to surgery)
  - Metastatic (Spread to a distant site such as liver, lung, peritoneum)
    - Chemotherapy only

Resectable Pancreatic Cancer

- No involvement of surrounding blood vessels
  - Mesenteric artery
  - Celiac artery
  - Hepatic Artery
  - Mesenteric/ Portal vein
- No blood clot in the portal vein
- No distant spread
- Strong enough to tolerate surgery
Resectable

Tumor

SMV

SMA

Head of Pancreas

Unresectable

Tumor growing around mesenteric artery and vein
Pre-operative Evaluation

- Performance Status
  - Cardiac
  - Pulmonary
  - Nutrition
- Blood Work
- CT scan
- Endoscopic Ultrasound
- ERCP
- MRI

Types of Surgery

Distal Pancreatectomy
The Whipple Operation (Pancreaticoduodenectomy)

Step 1: exposure of SMV

Slide Courtesy D. Evans
Step 2: Kocher maneuver

Slide Courtesy D. Evans

Step 3: portal dissection

Slide Courtesy D. Evans
Step 4: gastric transection

Step 5: mobilization of the duodenum/jejunum
Step 6: division of pancreas and the retroperitoneal dissection

Retroperitoneal Margin

Slide Courtesy D. Evans
Unfortunately, After Surgery The Cancer Can Return. This Is Why We Give Adjuvant Therapy.

Where Does the Cancer Return?

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemoradiation</th>
<th>Local</th>
<th>Incidence of Metastases (%)</th>
<th>Peritoneal</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tepper et al.</td>
<td>No</td>
<td>50%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GITSG</td>
<td>No</td>
<td>33%</td>
<td>-</td>
<td>52%</td>
<td>-</td>
</tr>
<tr>
<td>Whittington et al.</td>
<td>No</td>
<td>85%</td>
<td>23%</td>
<td>23%</td>
<td>-</td>
</tr>
<tr>
<td>Ozaki et al.</td>
<td>No</td>
<td>86%</td>
<td>36%</td>
<td>79%</td>
<td>-</td>
</tr>
<tr>
<td>GITSG</td>
<td>Yes</td>
<td>51%</td>
<td>-</td>
<td>43%</td>
<td>-</td>
</tr>
<tr>
<td>Foo et al.</td>
<td>Yes</td>
<td>7%</td>
<td>43%</td>
<td>43%</td>
<td>-</td>
</tr>
<tr>
<td>Staley et al.</td>
<td>Yes</td>
<td>11%</td>
<td>11%</td>
<td>53%</td>
<td>-</td>
</tr>
<tr>
<td>Pisters et al.</td>
<td>Yes</td>
<td>5%</td>
<td>5%</td>
<td>50%</td>
<td>-</td>
</tr>
</tbody>
</table>
# Rationale for Combined Modality Therapy

## Median Survival - Surgery vs Surgery + CR

<table>
<thead>
<tr>
<th>Institution/Group</th>
<th>First Author (Yr)</th>
<th>No. Resected</th>
<th>Postoperative Treatment</th>
<th>Median Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG</td>
<td>GITSG ('87)</td>
<td>22</td>
<td>5-FU + 40 Gy</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21</td>
<td>5-FU + 40 Gy</td>
<td>20*</td>
</tr>
<tr>
<td>Hopkins</td>
<td>Yeo ('97)</td>
<td>53</td>
<td>5-FU + &gt; 45 Gy</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>5-FU + &gt; 45 Gy</td>
<td>20*</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>Demeure ('98)</td>
<td>15</td>
<td>5-FU + &gt; 50.4 Gy</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>5-FU + &gt; 50.4 Gy</td>
<td>25*</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Conlon ('96)</td>
<td>118</td>
<td>5-FU + 50.4 Gy</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Davis ('96)†</td>
<td>34</td>
<td>5-FU + 50.4 Gy</td>
<td>16</td>
</tr>
</tbody>
</table>

† T3, 85%; N1, 79%; positive margins, 50%

*P < 0.05

---

**ESPAC-1**

- **289 Patients** with histologically proven adenocarcinoma of the pancreas who had undergone potentially curative resection
- **69 Assigned to Observation**
- **73 Assigned to Chemotherapy**
- **79 Assigned to Chemotherapy and Chemotherapy**

Based on this study, Europeans only use chemotherapy after surgery. In North America, the role of radiation after surgery remains unanswered. Our standard in Cincinnati is to use **Both Radiation and Chemotherapy** after surgery.
Based on the results of this study, many consider the standard chemotherapy regimen after surgery to be a combination of Gemcitabine and Capecitabine.
So the current standard is surgery followed by chemotherapy (Gem/Capecitabine) plus/minus radiation.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>n</th>
<th>Treatment arm</th>
<th>Control arm</th>
<th>Median OS (mos) (treatment v. control)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG</td>
<td>1985</td>
<td>43</td>
<td>5-FU-based chemoradiation followed by</td>
<td>Observation</td>
<td>21.0 v. 10.9</td>
<td>0.03</td>
</tr>
<tr>
<td>EORTC</td>
<td>1999</td>
<td>114</td>
<td>5-FU-based chemoradiation</td>
<td>Observation</td>
<td>17.1 v. 12.6</td>
<td>NS</td>
</tr>
<tr>
<td>ESPAC-1</td>
<td>2001</td>
<td>541</td>
<td>Chemotherapy</td>
<td>No chemotherapy</td>
<td>19.7 v. 14.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemoradiation</td>
<td>No chemoradiation</td>
<td>15.5 v. 16.1</td>
<td>NS</td>
</tr>
<tr>
<td>ESPAC-1</td>
<td>2004</td>
<td>289</td>
<td>Chemotherapy</td>
<td>No chemotherapy</td>
<td>20.1 v. 15.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemoradiation</td>
<td>No chemoradiation</td>
<td>15.9 v. 17.9</td>
<td>0.05</td>
</tr>
<tr>
<td>CONKO-001</td>
<td>2008</td>
<td>368</td>
<td>Gemcitabine</td>
<td>Observation</td>
<td>22.8 v. 20.2</td>
<td>0.005</td>
</tr>
<tr>
<td>RTDG 97-04</td>
<td>2008</td>
<td>388</td>
<td>Gemcitabine, 5-FU-based chemoradiation</td>
<td>Gemcitabine</td>
<td>20.5 v. 16.9</td>
<td>NS</td>
</tr>
<tr>
<td>ESPAC-3</td>
<td>2010</td>
<td>1088</td>
<td>5-FU</td>
<td>Gemcitabine</td>
<td>23 v. 23.6</td>
<td></td>
</tr>
<tr>
<td>JASPAC-01</td>
<td>2013</td>
<td>378</td>
<td>5-1</td>
<td>Gemcitabine</td>
<td>46.3 v. 23.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESPAC-4</td>
<td>2017</td>
<td>732</td>
<td>Gem + Cape</td>
<td>Gemcitabine</td>
<td>28 v. 25.5</td>
<td>0.002</td>
</tr>
<tr>
<td>CONKO-005</td>
<td>2017</td>
<td>436</td>
<td>Gem + Erlotinib</td>
<td>Gemcitabine</td>
<td>24.5 v. 26.5</td>
<td>NS</td>
</tr>
</tbody>
</table>
But We Are Making **Progress**: Two Positive Clinical Trials?

These studies were done in patients with advanced pancreas cancer.

Based on these studies, we are now trying to determine if these regimens can be utilized for patients with potentially resectable tumors.
Which Trials Should We Be Aware Of?

- Adjuvant Studies For Resectable Tumors
- Neoadjuvant Studies
  - Resectable
  - Borderline Resectable
- Studies for Locally Advanced Tumors

Phase III adjuvant studies in resected pancreatic cancer

- Shift to combination therapies
- Role of adjuvant radiotherapy still needs to be defined

<table>
<thead>
<tr>
<th>Study</th>
<th>Question</th>
<th>Treatment</th>
<th>Projected number</th>
<th>NCT number</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACT</td>
<td>Gem/nab- paclitaxel</td>
<td>Gemcitabine vs. Gem/nab- paclitaxel</td>
<td>800</td>
<td>02301143</td>
</tr>
<tr>
<td>ACCORD24</td>
<td>FOLFIRINOX</td>
<td>mFOLFIRINOX vs. gemcitabine</td>
<td>490</td>
<td>01526135</td>
</tr>
<tr>
<td>RTOG-0848</td>
<td>C-RT role</td>
<td>Any chemo x 6 months +/- C-RT</td>
<td>950</td>
<td>01013649</td>
</tr>
</tbody>
</table>
Take home message: This study is trying to determine if Gem plus nab-Paclitaxel is better than Gem alone after surgery.

**PRODIGE24/ ACCORD24**

- **Surgery**: Gemcitabine 1000 mg/m²
  - 6 Cycles

- **mFOLFIRINOX**: 12 Cycles

**Primary Endpoints:**
- 3-year DFS

**Secondary Endpoints**
- OS and DSS

Take home message: This study is trying to determine if FOLFIRINOX is better than Gem alone after surgery.

Slide Courtesy P. Philip MD
This study was designed to determine, once and for all, if radiation therapy was necessary after surgery— but it has had a difficult time accruing.

**Primary Endpoints:**
- 3-year DFS

**Secondary Endpoints:**
- OS and DSS

The Design was simplified to improve accrual. This study is important with regards to informing us on the role of radiation after surgery.
Evolution of neoadjuvant therapy in resectable and borderline resectable

- Development of optimal neoadjuvant/perioperative combination chemotherapy platforms
  - SWOG 1505
  - ESPAC-5
- Role of radiotherapy in borderline resectable disease
  - Alliance A021501
  - ESPAC-5

**SWOG 1505- Treatment/Schema**

- FOLFIRINOX
  - Every 2 weeks, 6 doses
- Gemcitabine/nab-Paclitaxel
  - D 1, 8, 15, qD22, 9 doses
- Rx: 12 weeks
- Restaging (CT/AIB)
- Surgery (if no PD on restaging)
- Gemcitabine/nab-Paclitaxel
  - D 1, 8, 15, qD22, 9 doses

This study compares FOLFIRINOX to Gemcitabine/ nab-Paclitaxel head to head to determine which is better after surgery.

Accrued

104/150

Ahmad, Sohal et al.
Clinical spectrum of resectability

Resectable  Borderline Resectable  Unresectable

R0 likely
Surgery/adjvant tx standard

R1 likely
Surgery possible but results suboptimal

R2 likely
Surgery not a technical option

Patient with BLR PDAC
(Intergroup Definition)

Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer
Alliance for Clinical Trials in Oncology Trial A021101

- Centralized radiographic review of pretreatment and restaging studies
- Prospective QC of all modalities

PI: Katz MH, Ahmad SA, Marsh R, Hermann, J
Baseline profile

Baseline clinical profile of 22 patients who received any therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>64 (50-76)</td>
</tr>
<tr>
<td>White race</td>
<td>21 (96)</td>
</tr>
<tr>
<td>Female gender</td>
<td>12 (55)</td>
</tr>
<tr>
<td>ECOG 0</td>
<td>14 (64)</td>
</tr>
<tr>
<td>Tumor diameter, median (range)</td>
<td>30 (16 – 49) mm</td>
</tr>
</tbody>
</table>

Vessel, n (%)^* Total TVI < 180° TVI ≥ 180°

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Total</th>
<th>TVI &lt; 180°</th>
<th>TVI ≥ 180°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior mesenteric artery</td>
<td>13 (59)</td>
<td>13 (59)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Celiac trunk</td>
<td>2 (9)</td>
<td>2 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Common Hepatic Artery</td>
<td>6 (27)</td>
<td>5 (23)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Portal Vein</td>
<td>16 (73)</td>
<td>7 (32)</td>
<td>9 (41)</td>
</tr>
<tr>
<td>Superior Mesenteric Vein</td>
<td>16 (73)</td>
<td>10 (46)</td>
<td>6 (27)</td>
</tr>
</tbody>
</table>

Pl: Katz MH, Ahmad SA, Marsh R, Hermann, J

Surgery and pathology

<table>
<thead>
<tr>
<th>Operation</th>
<th>N*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD/PPPD</td>
<td>14</td>
<td>93</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1</td>
<td>6.7</td>
</tr>
<tr>
<td>Vein resection</td>
<td>12</td>
<td>80</td>
</tr>
<tr>
<td>Hepatic artery</td>
<td>4</td>
<td>27</td>
</tr>
</tbody>
</table>

Pathologic variable | N | %* | %**

<table>
<thead>
<tr>
<th>Pathologic variable</th>
<th>N</th>
<th>%*</th>
<th>%**</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>14</td>
<td>64</td>
<td>93</td>
</tr>
<tr>
<td>N0</td>
<td>10</td>
<td>46</td>
<td>67</td>
</tr>
<tr>
<td>&lt; 5% residual cells</td>
<td>7</td>
<td>32</td>
<td>47</td>
</tr>
<tr>
<td>pCR</td>
<td>2</td>
<td>9.1</td>
<td>13</td>
</tr>
</tbody>
</table>

* Among patients who underwent surgical resection
** Among patients who underwent surgical resection (n = 15)

Pl: Katz MH, Ahmad SA, Marsh R, Hermann, J
Follow-up Study: Alliance 021501

This study is trying to determine if radiation is necessary for patients with tumors involving blood vessels (Borderline Resectable Tumors).

PI: Katz MH, Ahmad SA, Marsh R, Hermann, J

Opened, Accrual=72

ESPAC 5

This is a European Study similar to the the Alliance study trying to determine which chemotherapy, if any, and/or radiation is necessary for tumors involving blood vessels (Borderline Resectable)

Borderline Resectable Pancreas Cancer

Additional Chemotherapy
Locally advanced pancreatic cancer

Treatments are evolving as improvements in systemic and loco-regional therapies improve

- Conventional Cobalt
- Conformal RT
- Intensity modulated RT
- SBRT
- SFU
- Gemcitabine single agent
- Combination chemotherapy

Major studies and questions being asked in locally advanced pancreatic cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Question(s)</th>
<th>Treatment</th>
<th>Projected number</th>
<th>NCT number</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONKO-07</td>
<td>C-RT role</td>
<td>Gem or FOLFIRINOX +/- C-RT</td>
<td>830</td>
<td>01827553</td>
</tr>
<tr>
<td>SCALOP-2</td>
<td>1. RT dose 2. Naftinavir</td>
<td>Induction AG then C-RT +/- Nafti</td>
<td>289</td>
<td>02024009</td>
</tr>
<tr>
<td>PRODIGE29/NEOPAN</td>
<td>FOLFIRINOX</td>
<td>Versus gemcitabine</td>
<td>170</td>
<td>02539537</td>
</tr>
<tr>
<td>LAPACT (ESMO 2017)</td>
<td>Gem/nab-paclitaxel</td>
<td>Single arm, C-RT physician’s choice</td>
<td>110</td>
<td>02301143</td>
</tr>
</tbody>
</table>

Slide Courtesy P. Philip MD
LAPACT phase II study of gemcitabine/Nab-paclitaxel: Efficacy during Induction Phase

Median percent change = 17.9%
Partial Responses = 33.6%

Philip P et al, ESMO, 2017

This study demonstrated that Gemcitabine and nab-paclitaxel can keep the disease stable without progressing for a prolonged period of time.

The Future: Understanding Biology!!
Phases of clinical trials

- **PHASE 0**: From the work bench to humans. Is the agent hitting its target?
- **PHASE 1**: Deciding on a dose, considering DLT and MTD
- **PHASE 2**: Drug activity, safety and feasibility evaluation
- **PHASE 3**: Clinical outcomes compared to a control arm
- **PHASE 4**: Post marketing surveillance – long-term safety

Drug Review Steps

1. Preclinical (animal) testing.
3. Phase 1 studies
4. Phase 2 studies
5. Phase 3 studies
6. Submission of New Drug Application (NDA) is the formal step asking the FDA to consider a drug for marketing approval.
7. FDA reviewers will approve the application or find it either "approvable" or "not approvable."
8. Phase 4 studies
New drug development in pancreatic cancer: potential targets

- Targets linked to pancreatic cancer biology
- Targets less specific to pancreatic cancer
- Immuno-therapies

New Strategy: Look “Outside” The Cancer Cell
The unique microenvironment in pancreatic adenocarcinoma

- Promotes/sustains cancer progression and drug resistance
- Very desmoplastic
  - Limits drug delivery
- An “Immune desert”
Select stromal targeting agents

- Hedgehog inhibitors
- Recombinant human hyaluronidase: PEGylated-rHuPH20 (PEGPH20)
- CD40 agonists
- Vitamin D analogues
- Focal adhesion kinase (FAK) inhibitors

Olive, Science 2009; 324:1457-61
Provenzano, Cancer Cell 2012; 21:418-29
Beatty, Science 2011; 331:1612-6
Sherman, Cell 2014;159:80-93
Alvarez, Br J Cancer 2013, 109:926-33
Sherman, Cell 2014;159:80-93

Targeting the stroma: hyaluronan (HA) targeting with pegylated recombinant human hyaluronidase (PEGPH20)

- Study 202: PEGPH20 improved PFS with manageable thrombotic events
- Hyaluronan (HA) IHC as a companion diagnostic and predictive biomarker

<table>
<thead>
<tr>
<th>Studies</th>
<th>Phase</th>
<th>Sites</th>
<th>HA</th>
<th>N</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFOLFIRINOX +/- PEGPH20</td>
<td>I/II</td>
<td>US intergroup</td>
<td>Any</td>
<td>&lt; 170</td>
<td>Terminated</td>
</tr>
<tr>
<td>Gem/nab-paclitaxel +/- PEGPH20</td>
<td>III</td>
<td>Global</td>
<td>High only</td>
<td>420</td>
<td>Accrueing</td>
</tr>
</tbody>
</table>

Slide Courtesy P. Philip MD
Exploiting DNA repair defects in pancreas cancer: platinum compounds and/or PARP inhibitors

Kaufman B et al, J Clin Oncol 33:244-250, 2014
Golan T et al, Br J Cancer 111:1132-1138, 2014

Select ongoing studies of PARP inhibitors in advanced pancreatic cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Phase</th>
<th>N</th>
<th>NCT number</th>
</tr>
</thead>
<tbody>
<tr>
<td>GemCis +/- veliparib, vs. veliparib</td>
<td>First and subsequent</td>
<td>II</td>
<td>107</td>
<td>01585805</td>
</tr>
<tr>
<td>FOLFOX + veliparib</td>
<td>First and subsequent</td>
<td>I/II</td>
<td>79</td>
<td>01489865</td>
</tr>
<tr>
<td>Olaparib vs. Placebo</td>
<td>No progression on frontline platinums</td>
<td>III</td>
<td>145</td>
<td>02184195</td>
</tr>
<tr>
<td>FOLFIRI +/- Veliparib</td>
<td>Second-line</td>
<td>II</td>
<td>143</td>
<td>02890355</td>
</tr>
<tr>
<td>Cediranib + olaparib</td>
<td>Multiple tumors</td>
<td>2</td>
<td>126</td>
<td>02498613</td>
</tr>
</tbody>
</table>

Slide Courtesy P. Philip MD
Targeting How Pancreas Cancers Metabolize Glucose

The Warburg Effect

Interaction of metabolism with signaling pathways


CPI-613: selectively blocks PDH and KGDH triggering cell death that is highly selective to tumor Cells

Slide Courtesy P. Philip MD
Phase 1b study of CPI-613 in 20 patients with metastatic pancreatic cancer

CPI-613 + lower dose FOLFIRINOX

Oxaliplatin 65 mg/m²
Irinotecan 140 mg/m²
5FU 2,400 mg/m²

Alistar et al, Lancet Oncology, Vol 18, June 2017

Phase III trial in preparation: CPI-613 plus low dose FOLFIRINOX

Previously untreated metastatic pancreatic cancer
ECOG 0/1

Sponsored by Rafael

Slide Courtesy P. Philip MD
Role of Pancreas Stem Cells?

- When Cancer Cells regress completely
- Minor population of tumor infiltrating cells survive
- These cells have stem cell property
- Stem cells are a population of cells within tumors that are not cancer cells but have the potential to become cancer cells when stimulated
- NEED TO TARGET BOTH TUMOR CELLS AND STEM CELLS

Lin W. et al, Cancer Res 2013

A Phase Ib/II Study of Cancer Stemness Inhibitor Napabucasin in Combination with Gemcitabine & Nab-paclitaxel in Metastatic Pancreatic Adenocarcinoma

N = 66

Median PFS = 7.1 months
Median OS = 10.7 months
Mainly added GI toxicity

Courtesy of Dr Bekaii-Saab, ASCO 2017
CanStem111P Trial: A Phase III Study of Napabucasin (BBI-608) plus nab-Paclitaxel with Gemcitabine in Patients with Metastatic Pancreatic Adenocarcinoma

Treatment naïve mPDAC patients (N = 1132)

- Primary endpoint = overall survival
- N = 1,132 patients
- Futility analysis after 200+ events

NCT02231723, Dr. Bekaii-Saab

Immunotherapy for pancreatic cancer: What is different about the Pancreatic tumor microenvironment?
Targeting tumor infiltrating macrophages (TAMs) and myeloid derived suppressor cells

- Myeloid-derived suppressor cells promote disease progression, metastasis, and immune suppression
- Targeting macrophages can improve cytotoxic efficacy and increases antitumor T-cell response in animals
- Targeting macrophage signaling (e.g., CCR2) will block myeloid monocyte/macrophage recruitment to tumor microenvironment

Lesokhin et al, Cancer Res; 72(4); 876–86. 2011; Mitchem JB et al, Cancer Res; 73(3) February 1, 2013

FOLFIRINOX + anti-CCR2 PF-04136309 in borderline resectable or locally advanced pancreatic cancer

Tissue Factor isoforms: full-length TF (flTF), alternatively spliced TF (asTF)

flTF

asTF

Bogdanov et al, Cincinnati

Pt45.P1 cells orthotopically co-implanted with inhibitory anti-asTF monoclonal antibody RabMab1 ("Rb1")

Unruh et al. Oncotarget '16
Summary

• Improvements in survival have occurred over the last 30 years
• Newer multi-agent combination chemotherapy
  • Improved survival in metastatic setting
  • Role in adjuvant and neoadjuvant have to be determined
  • Role in locally advanced has to be determined
• Role of radiation has to be clarified
• Newer biologic agents continue to be investigated in the metastatic setting
  • These agents may make their way into the algorithm for resectable tumors (but not yet)

The Future is Bright

• Awareness for this disease is at an all time high
  • Clinicians
  • Researchers
  • Funding agencies
  • Patients/ Care givers
• More research being done on pancreas cancer than ever before
• Visible progress is being made
• Newer drugs are on the horizon
Randy Pausch: The Last Lecture

“The brick walls are there for a reason. The brick walls are not there to keep us out. The brick walls are there to give us a chance to show how badly we want something. Because the brick walls are there to stop the people who don’t want it badly enough. They’re there to stop the other people.”
— Randy Pausch, *The Last Lecture*

Thank you for your participation.

If you have questions, please contact Patient Central at 877-2-PANCAN or e-mail patientcentral@pancan.org.

www.pancan.org