Evolving Treatments for Pancreas Cancer

Wells Messersmith, MD, FACP
Associate Professor
Director, GI Medical Oncology Program
Program co-Leader, Developmental Therapeutics
Pancreatic Cancer

- Epidemiology and risk factors
- Pathology
- Molecular Genetics
- Adjuvant Therapy
- Palliative Therapy
- Future Directions
Epidemiology
2011 Estimated US Cancer Deaths

<table>
<thead>
<tr>
<th>Site</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>300,430</td>
<td>271,520</td>
</tr>
<tr>
<td>Prostate</td>
<td>11%</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Liver/intrahepatic bile duct</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>All other sites</strong></td>
<td>22%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Lung & bronchus 29%
Prostate 11%
Colon & rectum 9%
**Pancreas** 6%
Non-Hodgkin’s lymphoma 4%
Leukemia 4%
Esophagus 4%
Liver/intrahepatic bile duct 3%
Urinary bladder 3%
Kidney 3%
**All other sites** 22%

American Cancer Society – Facts & Figures, 2011
Epidemiology
Demographics and Presentation

Annual US incidence (2008) ~ 37,680
Annual US mortality (2008) ~ 34,290

Survival is dismal.

- resectable stage I and II
- unresectable stage III and IV
Clinical Stage and Survival

- Resectable Stage I-II
- Unresectable Stage III
- Stage IV
- All Stages

1 Year and 5 Year survival rates.
## Surgical Stage and Survival

<table>
<thead>
<tr>
<th>AJCC</th>
<th>TNM</th>
<th>5 yr survival (%)</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis (PanIN-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>T1N0</td>
<td>24-28</td>
<td>21-23</td>
</tr>
<tr>
<td>1B</td>
<td>T2N0</td>
<td>15</td>
<td>15-20</td>
</tr>
<tr>
<td>IIA</td>
<td>T3N0</td>
<td>11-17</td>
<td>15-20</td>
</tr>
<tr>
<td>IIB</td>
<td>T1-3,N1</td>
<td>11-17</td>
<td>13-16</td>
</tr>
<tr>
<td>III</td>
<td>T4, any N</td>
<td>8</td>
<td>6-10</td>
</tr>
<tr>
<td>IV</td>
<td>Any T, any N</td>
<td>1</td>
<td>3-6</td>
</tr>
</tbody>
</table>

Notes: Margin (-) 5 yr survival 21%, median survival 19 mo; Margin (+) 5 yr survival 6%, MS 12 mo (J GI Surgery 4:567-79, 2000); [www.nomograms.org](http://www.nomograms.org)
Risk Factors

- **Age:** 90% >55 y.o.; 70% >65 y.o.
- **Sex:** M > F (possibly due to tobacco)
- **Race:** African Americans > caucasions
- **Smoking:** 2-3 fold higher risk (20-30% cases are due to cigarette smoking)
- **Obesity / sedentary lifestyle**
- **Diabetes:** also can be a symptom
- **Chronic Pancreatitis**
Most cases are sporadic (10% familial).
# Genetic Syndromes and Pancreatic Cancer

<table>
<thead>
<tr>
<th>Genetic Syndromes</th>
<th>Gene (location)</th>
<th>Inherited Risk of Panc Ca (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast/Ovarian CA</td>
<td>BRCA2 (13q12-q13)</td>
<td>3.5-10</td>
</tr>
<tr>
<td>Familial atypical multiple mole melanoma syndrome (FAMMM)</td>
<td>P16 (9p21)</td>
<td>12-20</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>STK11/LKB1 (19p13)</td>
<td>36</td>
</tr>
<tr>
<td>HNPCC (Lynch II variant)</td>
<td>hMSH2,hMLH1</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>PRSS1 (7q35)</td>
<td>50</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM (11q22-23)</td>
<td>Rare</td>
</tr>
<tr>
<td>Li-Fraumeni Syndrome</td>
<td>P53</td>
<td>Unknown</td>
</tr>
<tr>
<td>Family X</td>
<td>4q32-34</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Pancreatic Cancer

- Epidemiology and risk factors
- Pathology
- Molecular Genetics
- Adjuvant Therapy
- Palliative Therapy
- Future Directions
**Pathologic Classification**

- **Ductal Adenocarcinoma** (85 - 90%)
  - Desmoplastic reaction, associated pancreatitis
  - CK7+, CK19+, CA19-9 +, MUC (1,3,4,5)+. CK20-, 55% DPC4 loss
  - Mucinous (colloid), signet ring cell type, clear cell, adenosquamous

- **Acinar cell carcinoma** (1%)
  - Mixed acinar-endocrine, acinar-ductal, zymogen Granules

- **Serous Cystic Neoplasms**

- **Mucinous Cystic Neoplasms**
  - Young/middle aged women, commonly in tail, ovarian-like stroma

- **Intraductal Papillary Mucinous Neoplasm** – IPMN –
  - Multifocal dilation of ductules

- **Solid Pseudopapillary** (F >>M, age ~26)

- **Pancreatic endocrine (“islet cell tumors”)**

- **High grade neuroendocrine carcinoma**
  - Small cell, large cell neuroendocrine
IPMN’s and MCN’s can transform into carcinomas, but PanIN is riskiest.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Normal</th>
<th>PanIN-1A</th>
<th>PanIN-1B</th>
<th>PanIN-2</th>
<th>PanIN-3</th>
<th>Infiltrating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Her2/neu</td>
<td>5%</td>
<td>82%</td>
<td>86%</td>
<td>92%</td>
<td>100%</td>
<td>69%</td>
</tr>
<tr>
<td>K-ras</td>
<td>0-15%</td>
<td>35%</td>
<td>43%</td>
<td>86%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>P16</td>
<td>0%</td>
<td>24%</td>
<td>19%</td>
<td>55%</td>
<td>71%</td>
<td>95%</td>
</tr>
<tr>
<td>P53</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>21%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Dpc4</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>31%</td>
<td>55%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
<td>7%</td>
</tr>
</tbody>
</table>
PanIN = pancreatic intraepithelial neoplasm.
Cancers arising from PanIN are 30-100 fold more common than IPMN’s or MCN (which are visible on scan and diagnosed earlier).
Pancreas Cancer Sequencing Project

- 24 pancreas cancers were subjected to full exomic gene sequencing
  - 20,661 protein coding genes
  - 99.6% of known coding genome
  - 220,844,033 base pairs sequenced in 7 samples

- “Rapid Autopsy Protocol” at Hopkins where patients consented early in disease; donated tissue within hours of death. Matched primaries, metastases

- 1562 somatic mutations were identified; 148 genes had two or more mutations; 198 homozygous deletions; 144 amplifications
Rapid Autopsy Protocol
“founder mutations” (blue, present in the primary tumor and all metastases) outnumber progressor mutations (orange).
Primary tumors are heterogeneous
Yachida.
Nature 2010
Chromosomal abnormalities are common.

“Circle plots” show chromosomes around the outer ring; copy # plots on inner ring; individual rearrangements shown as arcs joining the two loci.

Campell, C. Nature 2010
Inter-patient heterogeneity is daunting; highly variable rearrangements from patient to patient.

Campell, C. *Nature* 2010
What about metastases?

Commonalities between primary tumor and metastases (green) outweigh differences (tan). Metasases in a single organ are more similar than those in other organs.

Campell, C. *Nature* 2010
Key Lessons From Sequencing

Clonal evolution and expansion within the developing primary tumor leads to a subclone which can metastasize. Different metastases can develop from different subclones, which themselves can seed tertiary metastases.

Campell, C. Nature 2010
The complexity of pancreas cancer can be simplified by recognizing that these genetic changes affect a limited number (n=12) of pathways. Instead of targeting 1300 genes, we can target 12 pathways.
Key Lessons From Sequencing

Conservative estimates show that we have 18 years to detect and intervene. Major implications for screening strategies. Blood test to detect mutated DNA (such as KRAS?)

Iacobuzio-Donahue, C. *Gut* 2011
Pancreatic Cancer

- Epidemiology and risk factors
- Pathology
- Molecular Genetics
- Adjuvant Therapy
- Palliative Therapy
- Future Directions
Case #1

- 56 y/o white male previously healthy with new onset painless jaundice.
- CT scan demonstrates mass in head of pancreas, with no clear vascular involvement or extra-pancreatic disease.
- Pancreaticoduodenectomy
- Pathology c/w moderately differentiated adenocarcinoma (3 cm), 6/23 LN (+), uncinate margin (+) (T3N1M0, stage IIIB)
Case #1

• What would you recommend next?
  – No Further Therapy
  – Radiation therapy alone
  – Chemotherapy alone
  – Chemoradiation
  – Clinical Trial
Practical Definitions of Resectable Pancreatic Cancer

- Absence of extra-pancreatic cancer
- No radiographic evidence of vascular encasement of celiac trunk or SMA
- Patency of SMV-PV confluence (or at least able to reconstruct)
- No other significant co-morbidities that would preclude surgery or significantly complicate recovery
Practical Definitions of Resectable Pancreatic Cancer
Practical Definitions of Resectable Pancreatic Cancer

Borderline Resectable

?Resectable: may need venous resection

WARNING: CT image interpretation by a medical oncologist should be reviewed by someone who is actually qualified ("courage of the noncombatant")
<table>
<thead>
<tr>
<th>Study</th>
<th>Tx</th>
<th>2 yr (%)</th>
<th>5 yr (%)</th>
<th>Median survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG (1985) N=43</td>
<td>Obs. V chemorad</td>
<td>15 v. 42</td>
<td>NR</td>
<td>11 v. 20 (p=.01)</td>
</tr>
<tr>
<td>Sohn (2000) N=452</td>
<td>Obs. V. chemorad</td>
<td>22 v. 38</td>
<td>9 v. 20</td>
<td>11 v. 19 (p&lt;.001)</td>
</tr>
<tr>
<td>CONKO-1 (2007) N=354</td>
<td>Obs v. gem</td>
<td>42 v. 47</td>
<td>11 v. 22</td>
<td>20 v. 22 (p=.06)</td>
</tr>
<tr>
<td>RTOG-9704 (2008) N=538</td>
<td>Gem- 5FU/XRT v. 5-FU-5FU/XRT</td>
<td>35 v.39</td>
<td>~ 20 v. ~20</td>
<td>20.6 v. 16.9 (p=.03)</td>
</tr>
<tr>
<td>ESPAC-3 (2009) N=1030</td>
<td>Gem v. 5FU</td>
<td>~40 v. 40</td>
<td>NR</td>
<td>23.6 v. 23 (NS)</td>
</tr>
<tr>
<td>Study</td>
<td>Tx</td>
<td>R0 v. R1 (%)</td>
<td>Lymph Node status (%)</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------------------</td>
<td>------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>EORTC (1999)</td>
<td>Obs. V. chemorad</td>
<td>R1: 24 v. 19</td>
<td>54 v. 47</td>
<td></td>
</tr>
<tr>
<td>N=228</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sohn (2000)</td>
<td>Obs. V. chemorad</td>
<td>R1: 30</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>N=452</td>
<td></td>
<td>All pts</td>
<td>All pts</td>
<td></td>
</tr>
<tr>
<td>Japan (2002)</td>
<td>Obs. V. chemo</td>
<td>NR</td>
<td>75 v. 84</td>
<td></td>
</tr>
<tr>
<td>N=158</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=289</td>
<td>(Obs v chemo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONKO-1 (2007)</td>
<td>Obs v. chemo</td>
<td>R0- 85 v.81</td>
<td>73 v.71</td>
<td></td>
</tr>
<tr>
<td>N=354</td>
<td></td>
<td>R1- 15 v.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG-9704 (2008)</td>
<td>Gem- 5FU/XRT v. 5-FU-5FU/XRT</td>
<td>R1: 35 v. 33</td>
<td>68 v. 65</td>
<td></td>
</tr>
<tr>
<td>N=538</td>
<td></td>
<td>unknown 26 v. 23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Resected pancreas adenocarcinoma
- PS 0-2
- Primary endpoint OS

N=538

RTOG 9704: Design

- 5FU (CI) X 1, 5-FU CI + XRT, 5-FU CI X 3 (n=270)
- Gem X 1, 5-FU CI + XRT, Gem X 2 (n=268)
### RTOG 9704
Efficacy and Safety

<table>
<thead>
<tr>
<th></th>
<th>5-FU CI N=270</th>
<th>Gem N=268</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (mo)</td>
<td>16.9</td>
<td>20.6 (P=.03)</td>
</tr>
<tr>
<td>3 yr survival</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Gr 3/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>10</td>
<td>58</td>
</tr>
</tbody>
</table>
RTOG 9704
Efficacy and Safety

Missed the overall survival endpoint, even with pancreas head tumors only.

Regine et al. JAMA, 2008
Adjuvant Gemcitabine

- Resected pancreas adenocarcinoma
- PS 0-2
- Primary endpoint DFS
- 80% R0 resection

N=368

Randomize

n=179

Gem x 6 cycles (6 months)

n=175

Observation

Oettle et al. JAMA, 2007
Adjuvant Gemcitabine

Disease-Free Survival

Log-Rank $P < .001$

Cumulative Percentage

No. at Risk
- Gemcitabine: 179, 96, 43, 25, 17, 11, 8, 1
- Observation: 175, 52, 24, 10, 6, 6, 2, 0

Months

### Adjuvant Gemcitabine

Benefit seen across subgroups for disease-free survival.

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Disease-Free Survival, Median (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gemcitabine</td>
<td>Observation</td>
</tr>
<tr>
<td>All patients</td>
<td>179</td>
<td>175</td>
</tr>
<tr>
<td>R0</td>
<td>145</td>
<td>148</td>
</tr>
<tr>
<td>R1</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>N−</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>N+</td>
<td>127</td>
<td>127</td>
</tr>
<tr>
<td>T1-2</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>T3-4</td>
<td>154</td>
<td>151</td>
</tr>
</tbody>
</table>

Oettle et al. JAMA, 2007
Conclusions for Resectable Dz

• 5FU/XRT is better than surgery alone (GITSG and multiple registry datasets)

• 5FU is better than 5FU/XRT? (ESPAC1)

• Gemcitabine is better than surgery alone (CONKO-001)

• Gem + 5FU/XRT is better than 5FU + 5FU/XRT (RTOG 9704)

• 5FU appears to be just as good as Gem (ESPAC3)

• Something is better than nothing for patients with adequate recovery from surgery

• Nothing is very effective

• The role of radiation is not clearly defined
## Selected Neoadjuvant ChemoRT Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Tx</th>
<th>Screened pts (unresectable v. borderline v. resectable (%))</th>
<th>% pts completing pre-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC (2008) retrospective</td>
<td>Chemorads (50.4 or 30 Gy) or various chemo 5FU/taxol/gem/xeloda; Chemo (gem or gem combinations)</td>
<td>160 borderline resectable (A, n=84), findings suggestive of but no diagnostic of mets (B, n=44), marginal PS (C, n=32)</td>
<td>125 (78%)</td>
</tr>
<tr>
<td>Small (2008) NW, U Mich, Karmanos, others</td>
<td>C1 and 3: gem 1000 mg/m2 day1,8 q 21 d C2: gem 1000 mg/m2 day 1,8,15 with 3D-CRT 36 Gy/15 fx</td>
<td>39 Resectable: 41% Borderline: 23% Unresectable 38%</td>
<td>33 (85%)</td>
</tr>
<tr>
<td>U Michigan (2007)</td>
<td>Gem 1000 mg/m2 d1,8,15, Oxali 85 mg/m2 da,15 X 2 cycles, XRT 27 Gy/1.8 Gy fx during C1</td>
<td>44 Resectable: 27% Unresectable: 65% Mets: 7%</td>
<td>38/44 (86%)</td>
</tr>
<tr>
<td>Study</td>
<td>Resected patients</td>
<td>Node + status (%)</td>
<td>R0 v. R1 (%)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>--------------</td>
</tr>
</tbody>
</table>
Pancreatic Cancer

- Epidemiology and risk factors
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- Future Directions
Case #2

- 62 y/o male with h/o type 2 DM presented in 1/2003 with progressive abdominal pain
- CT scan with pancreas tail mass with numerous liver lesions
- Biopsy of representative liver met c/w adenocarcinoma
What would you recommend next?

- Gemcitabine
- Gemcitabine + Erlotinib
- Other Gemcitabine combination
- FOLFIRINOX
- Clinical Trial
Previously untreated pancreatic cancer (N=126)

Randomization

Gemcitabine (1000 mg/m2 weekly X 7 and 1 week rest; weekly X 3 every 4 weeks (n=63)

5-Fluorouracil (600 mg/m2 once weekly) (n=63)

Primary end point: Clinical Benefit response (analgesic consumption and pain intensity, KPS, weight ≥4 weeks improvement

Gemcitabine Registration Study

**Graph A**

- **% patients surviving**
- **Median survival (months)**
- **Survival duration**

**Log-Rank Test**

- **GEM**
  - n=63, 12.7% censored
  - 5.65
  - 6 months: 46%
  - 9 months: 24%
  - 12 months: 18%

- **5-FU**
  - n=63, 4.8% censored
  - 4.41
  - 6 months: 31%
  - 9 months: 6%
  - 12 months: 2%

**Survival time (months)**

- **Log-Rank Test**
  - p = 0.0025
Gemcitabine + Erlotinib

Overall Survival

HR = 0.82
95% CI (0.69 to 0.99)
*P* = .038

Erlotinib (n = 285)
Median = 6.24 months
1-year survival = 23%

Placebo (n = 284)
Median = 5.91 months
1-year survival = 17%

Moore – JCO 2007
Gemcitabine + Erlotinib

OS – Grade of Rash

Moore – JCO 2007
### Recent Phase II/III Cytotoxic Studies in Metastatic Pancreatic Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Pt #</th>
<th>Chemo</th>
<th>RR</th>
<th>MS (mo)</th>
<th>1 yr survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocha Lima (2003)</td>
<td>342</td>
<td>Gem +/- Irinotecan</td>
<td>4.4 v. 16</td>
<td>6.6 v. 6.3</td>
<td>22 v. 21</td>
</tr>
<tr>
<td>Heinemann (2003)</td>
<td>195</td>
<td>Gem +/- cisplatin</td>
<td>8 v. 10.2</td>
<td>6 v. 7.6</td>
<td>~22 v. ~26</td>
</tr>
<tr>
<td>(p=.12)</td>
<td></td>
<td></td>
<td></td>
<td>(p=.12)</td>
<td></td>
</tr>
<tr>
<td>O'Reilly (2004)</td>
<td>340</td>
<td>Gem +/- Exatecan</td>
<td>6.3 v. 8.2</td>
<td>6.2 v. 6.7</td>
<td>21 v. 23</td>
</tr>
<tr>
<td>(p=.52)</td>
<td></td>
<td></td>
<td></td>
<td>(p=.52)</td>
<td></td>
</tr>
<tr>
<td>Richards (2004)</td>
<td>565</td>
<td>Gem +/- Pemetrexed</td>
<td>9.1 v. 18.3</td>
<td>6.3 v. 6.2</td>
<td>21 v. 20</td>
</tr>
<tr>
<td>(p=.85)</td>
<td></td>
<td></td>
<td></td>
<td>(p=.72)</td>
<td></td>
</tr>
<tr>
<td>(p=.04)</td>
<td></td>
<td></td>
<td></td>
<td>(p=.13)</td>
<td></td>
</tr>
<tr>
<td>Cunningham (2005)</td>
<td>533</td>
<td>Gem +/- Capecitabine</td>
<td>14 v. 7 (p=.008)</td>
<td>7.4 v. 6</td>
<td>26 v. 19</td>
</tr>
<tr>
<td>(p=.008)</td>
<td></td>
<td></td>
<td></td>
<td>(p=&lt;.05)</td>
<td></td>
</tr>
<tr>
<td>Hermann (2007)</td>
<td>319</td>
<td>Gem +/- Capecitabine</td>
<td>10 v. 9</td>
<td>10.1 v. 7.4 (p = .014)</td>
<td>28 v. 35</td>
</tr>
</tbody>
</table>
Recent studies with **Biologics + Chemotherapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Pt #</th>
<th>Chemo</th>
<th>RR</th>
<th>MS</th>
<th>1 yr survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kindler (2004)</td>
<td>33</td>
<td>Gem + bevacizumab</td>
<td>24</td>
<td>12.4</td>
<td>54</td>
</tr>
<tr>
<td>Moore (2005)</td>
<td>569</td>
<td>Gem +/- erlotinib</td>
<td>8.7 v 7.9 (p=.8)</td>
<td>6.4 v. 5.9 (p=.025)</td>
<td>26 v. 20</td>
</tr>
</tbody>
</table>
FOLFIRINOX

- Resected pancreas adenocarcinoma
- PS 0-1 (not 2)
- Primary endpoint OS

N=342

RANDOMIZE

n=171

Gemcitabine

n=171

FOLFIRINOX

Conroy et al. NEJM, 2011
What is FOLFIRINOX?

- Oxaliplatin
- Irinotecan
- Leucovorin 5-Fluorouracil bolus

Infusion center (1/2 day)

5-Fluorouracil Infusion for 46 hours

Home (2 days)

Neulasta (white cell growth factor)

Note: this is repeated every 14 days (12 days off between cycles)
**A Overall Survival**

Hazard ratio, 0.57 (95% CI, 0.45–0.73)
P<0.001 by stratified log-rank test

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>FOLFIRINOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>171</td>
<td>134</td>
<td>116</td>
</tr>
<tr>
<td>146</td>
<td>89</td>
<td>116</td>
</tr>
<tr>
<td>48</td>
<td>48</td>
<td>81</td>
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<tr>
<td>28</td>
<td>28</td>
<td>62</td>
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<tr>
<td>14</td>
<td>14</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>20</td>
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<td>6</td>
<td>6</td>
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</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Conroy et al. NEJM, 2011
### Table 2. Objective Responses in the Intention-to-Treat Population.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>FOLFIRINOX (N=171)</th>
<th>Gemcitabine (N=171)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (0.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>53 (31.0)</td>
<td>16 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>66 (38.6)</td>
<td>71 (41.5)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>26 (15.2)</td>
<td>59 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>25 (14.6)</td>
<td>25 (14.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Conroy et al. NEJM, 2011*
### Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

<table>
<thead>
<tr>
<th>Event</th>
<th>FOLFIRINOX (N=171)</th>
<th>Gemcitabine (N=171)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients/total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>75/164 (45.7)</td>
<td>35/167 (21.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9/166 (5.4)</td>
<td>2/169 (1.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15/165 (9.1)</td>
<td>6/168 (3.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Anemia</td>
<td>13/166 (7.8)</td>
<td>10/168 (6.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39/165 (23.6)</td>
<td>30/169 (17.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24/166 (14.5)</td>
<td>14/169 (8.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21/165 (12.7)</td>
<td>3/169 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>15/166 (9.0)</td>
<td>0/169</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated level of alanine aminotransferase</td>
<td>12/165 (7.3)</td>
<td>35/168 (20.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conroy et al. NEJM, 2011
Pancreatic Cancer

- Epidemiology and risk factors
- Pathology
- Molecular Genetics
- Adjuvant Therapy
- Palliative Therapy
- Future Directions
Stromal SPARC (secreted protein acidic and rich in cysteine; matrix protein) expression carries a poor prognosis.
SPARC and Abraxane

Infante, JCO 2007
Paclitaxel (Taxol) is highly **insoluble**. Prepared in chremophor; often allergic reactions.

Paclitaxel was **bound to albumin** (Abraxane) “nanoparticle” which mostly solves allergic reactions.

**Albumin binds to SPARC**, thereby providing potential selective targeting to tumor stroma and therefore tumor cells.
At the maximum tolerated dose, response rate was 48% (versus 10% with gemcitabine alone), median OS 12.2 (versus 5.5 in most studies).
Elevated expression of SPARC was associated with improved survival (despite carrying a poor prognosis).

However, this regimen is fairly toxic.

49% grade 4 neutropenia
20% grade 3 neuropathy
27% grade 3 fatigue

Von Hoff, JCO 2011
Hedgehog Inhibitors

• Hedgehog is a **developmental pathway**; discovered in drosophila in 1980 in segmentation studies

• Loss-of-function mutations in negative regulator PTCH1 leads to **Gorlin Syndrome**: basal cell carcinomas (BCC), medulloblastoma, sarcomas.

• Sporadic BCC has high frequency of PTCH1 inactivating mutations, or SMO activating mutations (constitutive activation of HH pathway)

• Crosstalk with Ras, Wnt, Notch, TGF-beta, etc
Hedgehog Pathway

Hedgehog (Sonic, Indian, or Desert)

- Overexpression
  - Patched
- Mutation
  - Inactive SMO
- Mutation
  - SMO
  - Gli
  - Activated Gli
  - SuFu

Pathway Mechanism: Unknown

Nuclear Membrane

Hedgehog Gene Targets: GLI1, BCL2, SNAIL, etc

- Proliferation and survival
- Stem Cell Maintenance
- Angiogenesis
Pancreas tumors are known to be poorly vascularized. CD31 stain (endothelial cells) from:
A: transplanted tumors (tumor contacts vessel)
B: KPC mouse (KRAS and p53 mutation)
C: Human tumor (shows stroma interposed between tumor/vessel)
Preclinical Study Supporting Hedgehog in Pancreas Cancer

Higher microvessel density (panel A) and chemotherapy concentrations (B) when a hedgehog inhibitor IPI-926 was used either alone (green) or with chemotherapy (purple).
Hedgehog inhibitors in development

- **GDC-0449** (Vismodegib; Phase I, NEJM\(^1\); 33 BCC patients, RR=50-60%; also medulloblastoma patient\(^2\))
- **IPI-926** (cyclopamine derivative)
- **XL139 / BMS-833923, LDE225**
- Monoclonal antibodies (mAb’s) being developed

Pancreas Cancer Trial: Randomized Ph II of gemcitabine +/- **IPI-926** (ASCO 2011; impressive early results)

\(^1\)Von Hoff, NEJM 2009
\(^2\)Rudin, NEJM 2009
Phase I/II Study of Gem + IPI-926

Target Lesion Change

Patients (N = 16)

-30%
-20%
-10%
0%
+10%
+20%
+30%

IPI-926 110 mg
IPI-926 130 mg
IPI-926 160 mg
PR Partial Response

5/16 (31%) patients with partial response

Abdominal CT: Pre-Treatment

Abdominal CT: 4 Months of Treatment

Stephenson, ASCO 2011
Summary for Pancreas Cancer

- Remarkable advances in molecular understanding of the disease based on DNA sequencing. Heterogeneity is daunting, although # of pathways is not.
- Rapid changes in standard of care:
  - Advanced disease first-line (FOLFIRINOX, 2011; gemcitabine/erlotinib 2007)
  - Advanced disease 2\textsuperscript{nd} line (FOLFOX phase II’s, 2007)
  - Adjuvant setting, chemo (CONKO, gemcitabine, 2007)
  - Adjuvant setting, chemoRT (RTOG 9704)
- Total failure of targeted agents such as cetuximab and bevacizumab.
Clinical Trials at UCCC/UCH

- **Adjuvant setting:**
  - HyperAcute Vaccine pIII (non-mammalian protein)

- **Locally Advanced**
  - Gemcitabine/dasatinib pII (Src inhibitor)
  - Developing gem/HH/SBRT study internally

- **Advanced 1st line**
  - Gemcitabine/abraxane pIII wrapping up
  - Gemcitabine/ON1910 pIII (PI3K/PLK inhibitor)
  - Gemcitabine/BAY86-9766 (MEK) pl/II

- **Advanced 2nd line**
  - Notch inhibitor plI trial (with Hopkins)

- **GI human explant tumor bank**
Surg Onc / Med Onc Collaboration

Human tumor *explant model* (patients are consented prior to surgery)
Excess tumor tissue is harvested; blood collected
We have >140 GI cancer patients consented.
Searching for Src Biomarkers in pancreas cancer

Human tumor explant model

Using xenografts at the extremes of sensitivity, search for expression profiles. Reduce expression profile to assay that can be implemented in the clinic with limited samples.
Development of Predictive Biomarkers

Effect of AZD0530 on the growth pattern of human pancreatic tumors

% Growth (Mean ± SEM)

Patient Pancreatic Tumors Xenografted in Mice

PIK3CA
Thank You!

Wells Messersmith, MD, FACP
Associate Professor
Director, GI Medical Oncology Program
Program co-Leader, Developmental Therapeutics