New agents/strategies on the horizon in pancreatic cancer

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Outline of this Talk

• Cytotoxics
• Microenvironment
• DNA repair
• Novel agents
Pancreatic cancer is a **Systemic** disease from the outset

- High frequency of systemic failures of disease even after curative resections
- Subclinical metastases present at the outset
- *KRAS* mutations in > 90%
- *TP53, SMAD4, CDKN2A inactivations* in > 50%
Liposomal irinotecan has second line activity in combination with 5FU/LCV: NAPOLI Phase III

<table>
<thead>
<tr>
<th></th>
<th>MM-398/5FU/LCV</th>
<th>5FU/LCV</th>
<th>Hazard ratio, $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mon</td>
<td>6.1</td>
<td>4.2</td>
<td>0.67, 0.012</td>
</tr>
<tr>
<td>Median PFS, mon</td>
<td>3.1</td>
<td>1.5</td>
<td>0.56, &lt; 0.001</td>
</tr>
</tbody>
</table>

Single agent MM-398 did not improve over 5FU/LCV

von Hoff, et al, World GI Symposium, Barcelona, 2014
Projected cancer deaths in 2030 (thousands)

Rahib et al (PanCan), Cancer Research, 2014
Expanding range of targets!
Pancreatic Cancer: A Very Challenging Biology

- Frequent *de novo* drug resistance
- Stroma as a barrier to drug delivery
- Complex and poorly understood microenvironment
- Multiple gene mutations
- “Nondruggable” tumor suppressor genes
- No biomarkers
Complexity of genetic mutations in pancreatic tumors

- 20,661 genes
- Average 63 alterations per patient
- Mostly point mutations

Jones et al, Science, September, 2008
Targeting the Microenvironment

Targeting Angiogenesis in Pancreatic Cancer Has Been Ineffective; possibly related to hypovascularirty

Failed phase 3 trials

- Bevacizumab
- Afiblercept
- Axitinib

Hypoperfusion of pancreatic cancer on CAT scan and MRI

Von Hoff, Korn and Mousses, Cancer Cell July 7, 161: 7-8, 2009
Hypoxia activated alkylating agent TH302

Phase III trial (MAESTRO) of gemcitabine plus TH 302 completed and results pending

Glycocalyx as a barrier to therapeutic delivery

• Hyaluronan overexpression in >80% of pancreatic cancers

• Tumors that overexpress hyaluronan develop high interstitial fluid pressure and drug resistance

• Hyaluronan is associated with disease progression & poor prognosis

Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer

Michael A Jacobetz, Derek S Chan, Albrecht Neesse, Tashina E Bapiro, Natalie Cook, Kristopher K Frese, Christine Feig, Tomoaki Nakagawa, Meredith E Caldwell, Heather I Zecchini, Martijn P Lolkema, Ping Jiang, Anne Kultti, Curtis B Thompson, Daniel C Maneal, Duncan I Jodrell, Gregory I Frost, H M Shepard, Jeremy N Skepper, David A Tuveson

Median survival (days) n
- Vehicle: 10.5, 7
- Gemcitabine: 15.0, 11
- PEGPH20: 9.0, 10
- Gemcitabine/PEGPH20: 28.5, 11
Ongoing randomized studies with pegylated hyaluronidase (PEGPH20) in pancreatic cancer

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Platform</th>
<th>Phase</th>
<th>Stage</th>
<th>Status</th>
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<tbody>
<tr>
<td>SWOG</td>
<td>mFOLFIRINOX</td>
<td>I/II</td>
<td>IV</td>
<td>ongoing</td>
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<tr>
<td>Halozyme</td>
<td>Gem/nab-paclitaxel</td>
<td>II</td>
<td>IV</td>
<td>ongoing</td>
</tr>
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</table>
Preliminary data from randomized Phase 2 Gem/Nab-paclitaxel +/- PEGH20

<table>
<thead>
<tr>
<th></th>
<th>Gem+Nab-paclitaxel (61)</th>
<th>Gem+Nab-paclitaxel+PEGH20 (45)</th>
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</thead>
<tbody>
<tr>
<td><strong>Objective responses (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Hyaluronan</td>
<td>52</td>
<td>24</td>
</tr>
<tr>
<td>Low Hyaluronan</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td><strong>mPFS (months)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Hyaluronan</td>
<td>9.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Low Hyaluronan</td>
<td>5.3</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Presented By Sunil Hingorani at 2015 ASCO Annual Meeting
JAK/STAT Kinase Inhibitors

IL-6 JAK-STAT axis upregulated in GI cancers

Ruxolitinib JAK 1/2 inhibitor FDA approved for myelofibrosis, polycythemia vera

A randomized phase 2 study of ruxolitinib or placebo with capecitabine as second-line therapy in patients with metastatic pancreatic cancer

Patient Eligibility
- Histologically confirmed metastatic PDAC
- Karnofsky PS ≥60
- Failed gemcitabine

RANOMIZED

1:1

Ruxolitinib
(15 mg BID, days 1–21)
Capecitabine
(1000 mg/m² BID, days 1–14)

Placebo
(BID, days 1–21)
Capecitabine
(1000 mg/m² BID, days 1–14)

Hurwitz et al, #4000, ASCO, 2014
Survival benefit when selected for CRP $\geq$ 13

- Improved clinical benefit response, ORR, and weight gain in combination therapy
- Ruxolitinib in combination with capecitabine was generally well tolerated
- Phase III trials are ongoing (CRP $\geq$ 10)
Necuparanib as a multi-targeted agent: Encouraging pilot data

Multitargeted agent:
- P-selectin
- CXCR4/SDF1
- VEGF/fgf2
- Heparanase

Ongoing randomized phase II study of gemcitabine/nab-paclitaxel +/- necuparanib

O’Reilly et al, Abstract 4114, ASCO 2015
Immunotherapy in the setting of a complex microenvironment
Cyclophosphamide/GVAX ± Listeria monocytogenes-expressing mesothelin boost CRS-207

Randomized Phase 2

- N = 93 previously treated
- Metastatic PC
- ECOG 0-1

R
2:1

Cy/GVAX followed by CRS-207

Arm A
OS: 6.1 months

Arm B
OS: 3.9 months; HR: 0.54, \( P = .011 \)

Primary endpoint: OS

Increased benefit in 3rd-line patients?

Le D. et al, JCO, 2015
ECLIPSE Trial: Randomized Phase 2B

- N = 240 previously treated
- Metastatic PC
- ECOG 0-1

- Primary endpoint: OS

aGemcitabine/capecitabine/erlotinib/irinotecan.
What about PD-1 inhibitors?

- GVAX + CRS-207 +/- nivolumab
  - Randomized phase 2

- Ipilumab +/- nivolumab
  - Phase I/2, randomized
Targeting BTK

- Randomized phase 2 trials with gemcitabine/nab-paclitaxel
  - ACP-196
  - Ibrutinib
- ACP-196 [second gene BTKi] +/- pembrolizumab
  - Phase 2 (KEYNOTE144)

Cell surface expression change when activated

↑ CD69
Early marker of lymphocyte activation

↑ CD86
Provides costimulatory signals for T cells
Whole genome sequencing and target identification

DNA repair defects

BRCA mutations may predict survival in patients treated with platinum compounds or PARP inhibitors

Golan et al, BJC 2014

Kaufman et al, JCO, 2014
## Selected studies in *BRCA* mutated pancreatic cancers

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Stage</th>
<th>Phase</th>
<th>No.</th>
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</thead>
<tbody>
<tr>
<td>GemCis +/- veliparib, vs. valiparib</td>
<td>Advanced</td>
<td>II</td>
<td>NCT01585805</td>
</tr>
<tr>
<td>FOLFOX + veliparib</td>
<td>Advanced</td>
<td>I/II</td>
<td>NCT01489865</td>
</tr>
<tr>
<td>Olaparib VS Placebo</td>
<td>No progression on frontline platins</td>
<td>III</td>
<td>NCT02184195</td>
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</tbody>
</table>

Choosing a biomarker for selection?
- Germline *BRCA* mutations
- Somatic *BRCA* mutations
- Homologous recombination deficiency (HRD) score
Targeting the old *KRAS*: Mutated in > 90%
Targeting HER and IGF-1R–Related Pathways

- **EGFR**
  - Erlotinib = marginal benefit
  - Cetuximab = no benefit
  - Afatinib (EGFR/Her2,4) = pending

- **IGF-1R**
  - Ganitumab (AMG479) = no benefit
  - AMC102 = no benefit

- **MEK**
  - GSK1120212 = no benefit
Challenges of feedback and cross-talk in targeting MEK
Worse outcome with combined Akt and MEK blockade!

Chung et al, ASCO 2015
PAK as choke point downstream of KRAS
PAK4 Inhibitors Induce Pancreatic Cancer Cell Specific Apoptosis

Azmi et al. GI ASCO 2014 (Abstract 233)
Challenges of targeting tumor suppressor gene aberrations in pancreatic cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency of mutations (%)</th>
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<tbody>
<tr>
<td>p16</td>
<td>&gt;90</td>
</tr>
<tr>
<td>p53</td>
<td>50-70</td>
</tr>
<tr>
<td>SMAD4</td>
<td>55</td>
</tr>
</tbody>
</table>

Selinexor (KPT-330)

• Small molecule oral allosteric inhibitor of XPO1/CRM1
• First in class of SINE (Selective Inhibitor of Nuclear Transport)
• Forces retention of tumor suppressor gene proteins in the nucleus and their re-activation
• Clinical activity in hematological malignancies
Preclinical data for selinexor in pancreatic cancer

Azmi et al., Gastroenterology 2013 44(2)
Selinexor, Gemcitabine Hydrochloride, and Paclitaxel Albumin-Stabilized Nanoparticle Formulation in Treating Patients With Metastatic Pancreatic Cancer

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2015 by Barbara Ann Karmanos Cancer Institute

Sponsor:
Barbara Ann Karmanos Cancer Institute

Collaborator:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
Philip Philip, Barbara Ann Karmanos Cancer Institute

ClinicalTrials.gov Identifier:
NCT02178436

First received: June 23, 2014
Last updated: March 30, 2015
Last verified: March 2015
History of Changes
Select randomized trials in advanced pancreatic cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Chemo Backbone</th>
<th>Trial number</th>
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<tbody>
<tr>
<td>MM-141</td>
<td>Her-3 &amp; IGF-1R</td>
<td>Gem/Nab-pacli</td>
<td>NCT02399137</td>
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<tr>
<td>NPC-1C</td>
<td>Antigen</td>
<td>Gem/Nab-pacli</td>
<td>NCT01834235</td>
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<tr>
<td>FG-3019</td>
<td>Connective tissue GF</td>
<td>Gem/Nab-pacli</td>
<td>NCT02210559</td>
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<tr>
<td>OMP-59R5</td>
<td>Notch 3</td>
<td>Gem/Nab-pacli</td>
<td>NCT01647828</td>
</tr>
<tr>
<td>L-asparaginase</td>
<td>asparagine</td>
<td>Gem or FOLFOX</td>
<td>NCT02195180</td>
</tr>
<tr>
<td>Glufosfamide</td>
<td>DNA</td>
<td>5-FU</td>
<td>NCT01954992</td>
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</table>
Pancreas cancer remains a major unmet need

- Advances have been in cytotoxic therapies but benefits have been marginal to very modest
- Promising therapies include stroma-directed strategies, targeting DNA repair deficiencies, and immune modulation
- Ongoing needs
  - Discovery of biomarkers for patient selection
  - Focus on *frontline* therapies
  - *Don’t forget* unfavorable performance status pts
  - Consideration of clinical trials for *all* newly diagnosed patients and those failing frontline therapies
  - Optimize tissue acquisition
Thank you!

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