Improving the Outcome of Patients with Metastatic Pancreatic Cancer

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Median overall survival following standard frontline therapies in metastatic disease: 1997 -

- Gemcitabine
- Gemcitabine erlotinib
- Gemcitabine nabpaclitaxel
- FOLFIRINOX

How to improve on current gains with induction chemotherapy?

• Increasing cytotoxic power (and toxicity!) in the frontline and beyond
• Rational sequencing of tolerable therapies
• Maintenance after shorter induction therapy
• Ablative/surgical strategies to treat residual disease
PRODIGE 35: PANOPTIMUX study allows interruption of FOLFRINOX after 8 cycles without loss in survival

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS in mo</td>
<td>10.1</td>
<td>11.0</td>
<td>7.3</td>
</tr>
<tr>
<td>6 mo (%)</td>
<td>73.6</td>
<td>75.0</td>
<td>60.0</td>
</tr>
<tr>
<td>12 mo (%)</td>
<td>43.3</td>
<td>28.0</td>
<td>13.9</td>
</tr>
<tr>
<td>18 mo (%)</td>
<td>18.5</td>
<td>28.0</td>
<td>13.9</td>
</tr>
</tbody>
</table>

Dahan L, et al, ASCO 2018
Drugs and targets that failed in clinical trials involving pancreatic adenocarcinoma: December 2015 – May 2018

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target/Mechanism</th>
<th>Phase</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evofosfamide</td>
<td>Alkylator (Hypoxia)</td>
<td>3</td>
<td>694</td>
</tr>
<tr>
<td>Ruxolotinib</td>
<td>JAK1/2</td>
<td>3</td>
<td>Early termination</td>
</tr>
<tr>
<td>Necuparanib</td>
<td>Heparan mimetic</td>
<td>1/2</td>
<td>128</td>
</tr>
<tr>
<td>Masatinib</td>
<td>TKI (Kit, Lyn, Fyn)</td>
<td>3</td>
<td>353</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>TKI (VEGFR2, RET, EGFR)</td>
<td>2</td>
<td>142</td>
</tr>
<tr>
<td>Algenpantucel-L</td>
<td>Vaccine</td>
<td>3</td>
<td>722</td>
</tr>
<tr>
<td>CRS-207 + GVAX</td>
<td>Vaccine</td>
<td>2b</td>
<td>240</td>
</tr>
<tr>
<td>Tarextumab</td>
<td>Notch2/3</td>
<td>2</td>
<td>177</td>
</tr>
<tr>
<td>Demcizumab</td>
<td>DLL4</td>
<td>2</td>
<td>204</td>
</tr>
<tr>
<td>90Y-Clivatuzumab Tetraxetan</td>
<td>MUC1</td>
<td>3</td>
<td>334</td>
</tr>
<tr>
<td>Apatorsen</td>
<td>HSP27</td>
<td>2</td>
<td>132</td>
</tr>
<tr>
<td>Simutuzumab</td>
<td>LOX-2</td>
<td>2</td>
<td>240 (159)</td>
</tr>
</tbody>
</table>
A shifting paradigm in developing new therapies for pancreatic adenocarcinoma

Targeting isolated gene product and/or pathway

- No driver genes
- Complex biology
- No good correlation with clinical outcome

Modifying unique aspects of pancreas cancer biology

- Better correlation with clinical outcome
- Opportunities for rational drug combinations
- Benefiting from evolving molecular classifiers
Integrated genomic characterization of pancreatic cancer (TCGA)

Raphael et al, Cancer Cell, 32:185-203, 2017
Exploiting DNA repair defects in pancreatic cancer

PARP inhibitors and platinums in \textit{BRCA} mutated tumors: emerging prospective data

The pilot study
O’Reilly et al, Cancer 2018

The current RP2 study
N = 50, Primary EP = RR
POLO: Phase 3 international PARPi maintenance study in *gBRCA* mutated patients

Metastatic pancreas ca
Prior platinum therapy
Germline *BRCA* mut
ECOG 0-1

Primary EP = PFS
N = 145

Olaparib
300 mg po BID

Placebo
300 mg po BID

NCT02184195
Modulating the unique microenvironment of pancreatic adenocarcinoma

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

J Natl Cancer Inst. 2010;102(7):448-450;
Select stromal targeting

- 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
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

Hingorani et al, JCO 2018

<table>
<thead>
<tr>
<th>HALO-301</th>
<th>Phase</th>
<th>Sites</th>
<th>HA</th>
<th>N</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem/nab-paclitaxel +/- PEGPH20 NCT02715804</td>
<td>III</td>
<td>Global</td>
<td>High only</td>
<td>420</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
A Phase IB/II Randomized Study of mFOLFIRINOX (mFFX) + PEGPH20 versus mFFX in Patients with Metastatic Pancreatic Adenocarcinoma unselected for HA expression: SWOG- S1313

**Progression-Free Survival**
Data as of December 5, 2017

<table>
<thead>
<tr>
<th></th>
<th>mFOLFIRINOX</th>
<th>PEGPH20 + mFOLFIRINOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Risk</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Failed</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>Median in Months</td>
<td>6.2</td>
<td>4.3</td>
</tr>
</tbody>
</table>

HR 0.61
95% CI: 0.40-0.93, P=0.02

**Overall Survival**
Data as of December 5, 2017

<table>
<thead>
<tr>
<th></th>
<th>mFOLFIRINOX</th>
<th>PEGPH20 + mFOLFIRINOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Risk</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Deaths</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>Median in Months</td>
<td>14.4</td>
<td>7.7</td>
</tr>
</tbody>
</table>

HR 0.50
95% CI: 0.31-0.81, P<0.01

<table>
<thead>
<tr>
<th></th>
<th>PEGPH20 + mFFX</th>
<th>mFFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median # of cycles</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Response (%)</td>
<td>29</td>
<td>45</td>
</tr>
</tbody>
</table>

Ramanathan et al, ASCO GI, 2018
Targeting metabolism in pancreatic cancer

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

Pilot clinical trial

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: CPI-613 plus mFOLFIRINOX to be launched Q3/2018

Previously untreated metastatic pancreatic cancer
EECOG 0/1

N = 500
Primary EP = RR/PFS

CPI-613 500 mg/m²
Oxaliplatin 65 mg/m²
Irinotecan 140 mg/m²
5FU 2,400 mg/m²

“Full dose” FOLFIRIONX

Sponsored by Rafael
L-asparaginase prolongs survival in a pilot trial in patients after failure of frontline therapy

<table>
<thead>
<tr>
<th>Time (Weeks)</th>
<th>Chemotherapy plus eryaspase</th>
<th>Chemotherapy alone</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Events n (%)</th>
<th>Censored n (%)</th>
<th>OS HR (95% CI)</th>
<th>P-value</th>
<th>Median OS (weeks)</th>
<th>OS rate at 24 weeks</th>
<th>OS rate at 52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>79 (83%)</td>
<td>16 (17%)</td>
<td>0.60 (0.40, 0.88)</td>
<td>0.009</td>
<td>26.1</td>
<td>46%</td>
<td>15%</td>
</tr>
<tr>
<td>40 (87%)</td>
<td>6 (13%)</td>
<td></td>
<td></td>
<td>19.0</td>
<td>37%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Hammel et al, ESMO 2017
Immunotherapy for pancreatic cancer

- Pancreas cancer is non-immunogenic because:
  - immunosuppressive cells and cytokines
  - low tumor mutational burden
  - paucity of T cells in tumor (number and function)

- Single agent therapeutic approaches focusing on overcoming T-cell immunologic endpoints with immune checkpoint inhibitors or vaccines are not encouraging

Royal Re et al. J Immonother 210;33:828-833
PD-1 inhibitor (durvalumab) with or without CTLA4 inhibitor (tremelimimumab): did not work!

O’Reilly et al, ASCO GI, 2018
MSI-high pancreatic cancers (1-2%) may respond to PD-1 inhibitors
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


Select major ongoing immunotherapy combination studies in advanced pancreatic cancer

- CD40 agonist
- Anti-CXCR4
- XRT
- PD-1i/PD-L1i
- Chemo
- Vaccines
- Anti-CSF1R
Stay tuned to these randomized trials!

<table>
<thead>
<tr>
<th>Study</th>
<th>Target(s)</th>
<th>Drug</th>
<th>Biology</th>
<th>Chemo platform</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESOLVE</td>
<td>Bruton’s tyrosine</td>
<td>Ibrutinib</td>
<td>mast-cells, inflammation, activity of T cells</td>
<td>Gem/Nab-paclitaxel</td>
<td>II/III</td>
</tr>
<tr>
<td></td>
<td>kinase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEQUOIA</td>
<td>IL-10 receptor</td>
<td>pegilodecakin</td>
<td>Enhance T cells</td>
<td>FOLFOX*</td>
<td>III</td>
</tr>
<tr>
<td>CanStem111P</td>
<td>STAT3</td>
<td>napabucassin</td>
<td>Cancer stem cells</td>
<td>Gem/Nab-paclitaxel</td>
<td>III**</td>
</tr>
<tr>
<td>CARRIE</td>
<td>IGF-1R/</td>
<td>MM-141</td>
<td>signaling</td>
<td>Gem/Nab-paclitaxel</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Erb-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Second line
** N > 1,00

NCT02436668, NCT02923921, NCT02993731, NCT02399137
Systemic therapy landscape for metastatic pancreatic cancer in 2018: outside of a clinical trial

Relapse/progression < 6 months of adjuvant therapy

- Got mFFX
  - Gem NAP
  - mFFX NAL/FU OFF FOLFOX
  - OFF NAL/FU

- Got Gem-based
  - Gem NAP
  - mFFX
  - NAP OFF FOLFOX

Metastatic de novo

- PS 0-2
  - mFFX
  - Gem NAP

- PS 3
  - mFFX
  - NAL/FU FOLFOX
  - OFF FOLFOX NAL/FU

BRCA mutated

- Platinum based
  - PARPi
  - OFF FOLFOX NAL/FU

MSI-High

- Chemo
- PD-1i

mFFX = modified FOLFIRINOX
NAP = nabpaclitaxel
NAL = naliri
OFF = oxaliplatin/5FU
Molecular subtyping of pancreatic cancer: limited relevance to the clinic at this time, but room for improvement!

Le Large, TY et al, Seminars in Cancer Biology (2017), http://dx.doi.org/10.1016/j.semcancer.2017.03.008
Conclusions

• Conventional cytotoxic drug combinations produced modest incremental improvements in survival of metastatic pancreatic cancer

• Treatment strategies to improve patient tolerance and allow prolonged exposure may improve outcome

• Radiational targeted therapies failed in the clinic and a shift of paradigm to targeting key biological events is under way

• Promising areas of progress are in DNA repair, stromal targeting and tumor metabolism

• Immunotherapy failed in its traditional single agent approach but combinations may hold promise
Thank you!

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