Improving the Outcome of Pancreatic Cancer

Philip Agop Philip, MD, PhD, FRCP
Karmanos Cancer Institute
Wayne State University
Detroit, USA
Incremental improvement in systemic therapies that are largely based on cytotoxic drugs

Metastatic mOS in months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>6 mon</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nab-Paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POLO</td>
<td>54.4</td>
<td></td>
</tr>
</tbody>
</table>

Localized/Resectable mOS in months

<table>
<thead>
<tr>
<th>Study</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observe</td>
<td>19.0</td>
</tr>
<tr>
<td>RTOG</td>
<td>20.5</td>
</tr>
<tr>
<td>ESPAC1</td>
<td>21.6</td>
</tr>
<tr>
<td>CONKO1</td>
<td>22.8</td>
</tr>
<tr>
<td>ESPAC4</td>
<td>28.0</td>
</tr>
<tr>
<td>CONKO5</td>
<td>28.0</td>
</tr>
<tr>
<td>APACT</td>
<td>40.5</td>
</tr>
<tr>
<td>JASPAC1</td>
<td>46.5</td>
</tr>
<tr>
<td>PRODGE</td>
<td>54.4</td>
</tr>
</tbody>
</table>

# Drugs and Targets That Failed in Clinical Trials Involving Pancreatic Adenocarcinoma: December 2015 – July 2019

<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>III</td>
<td>694</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>JAK1/2</td>
<td>III</td>
<td>Early termination</td>
</tr>
<tr>
<td>Necuparanib</td>
<td>Heparan mimetic</td>
<td>I/II</td>
<td>128</td>
</tr>
<tr>
<td>Masitinib</td>
<td>TKI (Kit, Lyn, Fyn)</td>
<td>III</td>
<td>353</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>TKI (VEGFR2, RET, EGFR)</td>
<td>II</td>
<td>142</td>
</tr>
<tr>
<td>Algenpantucel-L</td>
<td>Vaccine</td>
<td>III</td>
<td>722</td>
</tr>
<tr>
<td>CRS-207 + GVAX</td>
<td>Vaccine</td>
<td>IIb</td>
<td>240</td>
</tr>
<tr>
<td>Tarextumab</td>
<td>Notch2/3</td>
<td>II</td>
<td>177</td>
</tr>
<tr>
<td>Demcizumab</td>
<td>DLL4</td>
<td>II</td>
<td>204</td>
</tr>
<tr>
<td><strong>Y-Clivatuzumab Tetrazetan</strong></td>
<td>MUC1</td>
<td>III</td>
<td>334</td>
</tr>
<tr>
<td>Apatorsen</td>
<td>HSP27</td>
<td>II</td>
<td>132</td>
</tr>
<tr>
<td>Z-360</td>
<td>CCK2</td>
<td>II</td>
<td>167</td>
</tr>
<tr>
<td>Simtuzumab</td>
<td>LOX-2</td>
<td>II</td>
<td>240 (159)</td>
</tr>
<tr>
<td>MM-141</td>
<td>IGF-1R/ErbB-3</td>
<td>II</td>
<td>88</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>BTK</td>
<td>III</td>
<td>424</td>
</tr>
<tr>
<td>Napabucasin</td>
<td>STAT3</td>
<td>III</td>
<td>&gt;1,100</td>
</tr>
</tbody>
</table>
A Shifting Paradigm in Developing New Therapies for Pancreatic Adenocarcinoma

**Targeting isolated gene product and/or pathway**
- No druggable oncogenes
- Complex biology
- No good correlation with clinical outcome

**Modifying unique aspects of pancreas cancer biology**
- Correlation with clinical behavior (phenotype)
- Rational drug combinations
- Molecular classifiers to personalize therapy
Bulk of gene mutations in pancreatic cancer: **KRAS (>90%),** **p53, SMAD4, and CDKN2A**

KRAS protein is hard to target!

Targeting KRAS driven tumors by dual inhibition of downstream signaling and autophagy

Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer


Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers

DNA repair defects in pancreatic cancer: emerging opportunities in a very complex system


Pilie et al, Nature Reviews, 2019
POLO: unanswered questions and future opportunities

- Reliability of somatic *BRCA* profiling in patient selection?
- Olaparib maintenance after gemcitabine and nabpaclitaxel?
- PARP inhibitors in earlier stage?
  - Maintenance in resected disease (proposed)
- Lack of survival benefit in POLO?
Future of DNA repair defect (DDR) targeted research in pancreatic adenocarcinoma

- Better identification of patients with DNA repair defects
  - Expanding beyond germline *BRCA*
  - Homologous Repair Defect: phenotype *versus* genotype reliable tests to identify true HRD

- Combinatorial treatment strategies
  - Targeting the DDR signaling in multiple points
  - Adding immunotherapy to PARP inhibition (proposed)
Exploring the Unique Microenvironment in Pancreatic Adenocarcinoma: Stroma, Cells, etc.

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

Select Stromal Targeting

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

Targeting hyaluronan using pegylated recombinant human hyaluronidase (PEGPH20)

Phase III trial HALO301

Randomize

PEGPH20
Gem + Nabpaclitaxel

Gem + Nabpaclitaxel

Primary endpoint = overall survival
N = 500

SWOG- S1313: A Phase IB/II Study of mFOLFIRINOX + PEGPH20 vs mFFOX in Metastatic Pancreatic Cancer Unselected for HA Expression

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

- At Risk: 56
- Failed: 42
- Median in Months: 6.2

- At Risk: 55
- Failed: 47
- Median in Months: 4.3

HR 0.61
95% CI: 0.40-0.93, P = .02

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

- At Risk: 56
- Deaths: 50
- Median in Months: 14.4

- At Risk: 55
- Deaths: 50
- Median in Months: 7.7

HR 0.50
95% CI: 0.31-0.81, P<.01

**Table**

<table>
<thead>
<tr>
<th></th>
<th>PEGPH20 + mFFOX</th>
<th>mFFOX</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>

Targeting Metabolism in Pancreatic Cancer

The Warburg effect metabolism with pathways

Interaction of signaling

CPI-613: Selectively Blocks PDH and KGDH Triggering Cell Death That Is Highly Selective to Tumor Cells

Lipids
Proteins
Nucleic Acids

glucose
\downarrow
gluconeogenic pathway

pyruvate
\downarrow

acetyl-CoA
\downarrow

CPI-613
\uparrow

PDH

KGDH

oxaloacetate
malate
fumarate
succinate

\uparrow
\uparrow
\uparrow
\uparrow

citrate
isocitrate
α-ketoglutarate

\downarrow
\downarrow
\downarrow

succinyl-CoA

\downarrow

\downarrow

glutamate

\downarrow

\downarrow

glutamine

Pilot clinical trial

CPI-613 + lower-dose FOLFIRINOX

Oxaliplatin 65 mg/m²
Irinotecan 140 mg/m²
5FU 2400 mg/m²

Change in tumor size from baseline (%)

Patient number

AVENGER 500: Phase III trial of CPI-613 plus lower dose FOLFIRINOX

Previously untreated metastatic pancreatic cancer
EECOG 0/1
N = 500

Randomize

CPI-613 500 mg/m2
Lower dose FOLFIRINOX

"Full dose" FOLFIRINOX

Primary endpoint: Overall response rate & PFS

NCT03504423
L-asparaginase prolongs survival in a pilot trial in patients after failure of frontline therapy

Hammel et al, ESMO 2017
TRYbeCA1: study of eryaspase with chemotherapy vs chemotherapy alone as 2nd-line treatment in metastatic pancreatic cancer

- Previously treated (one line)
- Metastatic disease
- ECOG 0/1

RANDOMIZE

Eryaspase 100 units/Kg
Gem + nab-paclitaxel, or
Irinotecan/5FU

Gem + nab-paclitaxel, or
Irinotecan/5FU

Primary endpoint = overall survival
N = 500 patients

Pl: Drs. Hidalgo and Hammel

National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/show/NCT03665441
Immunotherapy for Pancreatic Cancer

- Pancreatic cancer is nonimmunogenic 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

PD-1 inhibitor (durvalumab) with or without CTLA4 inhibitor (tremelimumab): did not work!

<table>
<thead>
<tr>
<th></th>
<th>D + T (n=32)</th>
<th>D (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>3.1 (2.2–6.1)</td>
<td>3.6 (2.7–6.1)</td>
</tr>
<tr>
<td>Survival at 6 months, % (95% CI)</td>
<td>36.2 (20.0–52.7)</td>
<td>34.9 (19.2–51.1)</td>
</tr>
<tr>
<td>Survival at 12 months, % (95% CI)</td>
<td>8.8 (1.8–22.8)</td>
<td>6.3 (1.1–18.4)</td>
</tr>
</tbody>
</table>

O’Reilly et al, ASCO GI, 2018
Select Major Ongoing Immunotherapy Combination Studies in Advanced Pancreatic Cancer

- CD40 agonist
- Anti-CXCR4
- XRT
- Anti-PD-1/Anti-PD-L1
- Chemo
- Vaccines
- Anti-CSF1R
SEQUOIA: Randomized phase III study of FOLFOX +/- Pegilodekan (pegylated IL-10) in second line metastatic pancreatic cancer

- IL-10
  - Enhances CD8+ cytotoxicity
  - Suppresses inflammatory cytokines
  - Induces phagocytosis and antigen presentation
  - Induces antigen antigen-specific immunity

Primary endpoint = Overall survival

Oft M, Cancer Immunology Research, 2:194-199, 2013
https://clinicaltrials.gov/ct2/show/NCT02923921
APX005M (CD40 agonist) mAb together with gemcitabine/nabpaclitaxel +/- nivolumab

O’Hara, et al, Parker Institute, AACR 2019
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 blocks myeloid monocyte/macrophage recruitment to tumor microenvironment
Targeting the tumor associated macrophages (TAMs) with anti-CSF-1R antibody

CONTROL
Chemo alone

Cabiralizumab
Nivolumab

Cabiralizumab
Nivolumab
AG

Cabiralizumab
Nivolumab
mFOLFOX

N = 160
Primary endpoint = PFS
CD40 and anti-CSF-1R in reprogramming tumor macrophages to induce an inflammatory response

Hoves et al, JEM, 2018
Better control of systemic disease may offer a “selective” role for local regional treatment modalities.

**Systemic**
- 5FU
- Gemcitabine
- Combination chemotherapy

**Local-regional**
- TTF
- Ablative XRT
- Protons
- HIFU
- IRE
- SBRT
- Conventional Cobalt
- Conformal RT
- Intensity modulated RT

- Debulking/ablative
- Immune-modulation
- Palliation
- ? Curative
Molecular subtyping of pancreatic cancer: awaiting clinic applications
Supportive care is often forgotten but is an invaluable component of patient care

- Slows down deterioration of quality of life
- Allows safer delivery of therapies
- Prevents early discontinuation of therapy
- Facilitates subsequent lines of therapy
CONCLUSIONS

- Cytotoxic therapy is the mainstay of systemic therapy resulting in modest benefit in pancreatic cancer
- Single molecule/pathway targeting is unlikely to result in significant clinical benefit
- DNA damage repair response (DDR) system is an emerging biological target for therapy in advanced pancreatic cancer
- Emerging strategies include tumor metabolism and tumor microenvironment
- Combination therapy is the likelier strategy to succeed. But we need,
  - Rational combinations with strong science base
  - Tumor classifiers for personalized therapy strategies
Thank You!

philipp@Karmanos.org
Save the Date

Expert Practice in Pancreatic Cancer

Friday and Saturday
25 – 26 October 2019
Prague, Czech Republic

Chairs
Philip Agop Philip, MD, PhD, FRCP
Wayne State University and Karmanos Cancer Institute
Detroit, Michigan, United States

Thomas Seufferlein, MD, PhD
University of Ulm
Ulm, Germany

Eric Van Cutsem, MD, PhD
University Hospitals Leuven
Leuven, Belgium

TRAVEL GRANTS AVAILABLE—APPLY NOW!
primebymedscape.org/expert-practice-pancreatic-cancer-2019