New agents/strategies on the horizon in pancreatic cancer

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Disclosures

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  – Celgene, Halozyme, Merck, Momenta, Incyte, Novartis, Bayer,

• Honoraria:
  – Celgene, Halozyme, Merrimack, BMS, Lilly, Amgen, Bayer
Small incremental benefits with frontline cytotoxic therapies over the last 2 decades

Earlier anti-signaling studies in pancreatic cancer in molecularly unselected cohorts were unsuccessful.
## Drugs that failed in clinical trials:
December 2015 – June 2017

<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>Cytotoxic/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>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>Vandetanib</td>
<td>VEGFR2, RET, and EGFR</td>
<td>2</td>
<td>142</td>
</tr>
<tr>
<td>$^{90}$Y-Clivatuzumab Tetraxetan</td>
<td>MUC1</td>
<td>3</td>
<td>334</td>
</tr>
</tbody>
</table>
Is genomic stratification feasible in designing targeted therapies in pancreatic cancer?

- Oncogenic mutations
  - KRAS 90-100%
  - Others: < 2%

- Tumor suppressor gene mutations
  - p53, p16, SMAD4

- DNA repair
  - BRCA, PALB2, ATM < 10%
  - MSI-high ≤1%

- There is need for identification of molecular subsets
  - Examples: Immune profile, stroma score, DNA repair defects, etc.
New drug development in pancreatic cancer: potential targets

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

### Studies

<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/2</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>Accruing</td>
</tr>
</tbody>
</table>
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

N = 47

Ongoing trials of modulating tumor associated macrophages in advanced pancreatic cancer: enhancing cytotoxicity and/or enhancing antitumor immunity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Combined with</th>
<th>Phase</th>
<th>N</th>
<th>NCT</th>
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</thead>
<tbody>
<tr>
<td>PF-04136309</td>
<td>CCR2</td>
<td>Gemcitabine/nabpaclitaxel</td>
<td>1b/II</td>
<td>02732938</td>
<td></td>
</tr>
<tr>
<td>CCX872-B</td>
<td>CCR2</td>
<td>FOLFIRINOX</td>
<td>1b</td>
<td>54</td>
<td>02345408</td>
</tr>
<tr>
<td>BMS-813160</td>
<td>CCR2/CCR5</td>
<td>nivolumab</td>
<td>1/2</td>
<td>260*</td>
<td>03184870</td>
</tr>
<tr>
<td>AMG 820</td>
<td>CSF-1R</td>
<td>pembrolizumab</td>
<td>1/2</td>
<td>197*</td>
<td>02713529</td>
</tr>
<tr>
<td>Pexidartinib</td>
<td>CSF-1R</td>
<td>durvalumab</td>
<td>1</td>
<td>58*</td>
<td>02777710</td>
</tr>
</tbody>
</table>

* Includes other cancers also
DNA repair defects form a molecular subset that is targetable

Exploiting DNA repair defects in pancreas cancer: platinum compounds and/or PARP inhibitors

Golan T et al, Br J Cancer 111:1132–1138, 2014

Kaufman B et al, J Clin Oncol 33:244-250, 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 platins</td>
<td>III</td>
<td>145</td>
<td>02184195</td>
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<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>
NQO1: enzyme that is overexpressed in pancreatic cancer relative to normal cells and provides a selective target

- Beta-lapachone (ARQ761) is activated by NQO1 –
- Selective to the cancer cells that also have low catalase

Slide and information courtesy of Drs Beg and Boothman
Translating the pre-clinical data into a Phase I/Ib multi-center trial of ARQ-761 plus gemcitabine/nab-paclitaxel in advanced pancreatic cancer (NCT02514031)

Information and slides courtesy of Dr Shaalan Beg and David Boothman
Targeting abnormal metabolism in pancreatic cancer cells

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
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
EECOG 0/1

CPI-613 500 mg/m²
Lower dose FOLFIRIONX

“Full dose” FOLFIRIONX

Sponsored by Rafael
Mesothelin-based Immunotherapy is rational based on the high expression in 85% of pancreatic cancers

Hassan R et al J Clin Oncol 34:4171-4179,
Zhao et al, Clinical Cancer Drugs, 2016, 3:76-86
## Targeting mesothelin by multiple strategies: Phase 1-2 of drug development

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Phase</th>
<th>N</th>
<th>NCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anetumab ravtansine</td>
<td>mAb + tubulin inhibitor</td>
<td>2</td>
<td>30</td>
<td>03023722</td>
</tr>
<tr>
<td>Anetumab ravtansine</td>
<td>mAb + tubulin inhibitor</td>
<td>1</td>
<td>348*</td>
<td>03102320</td>
</tr>
<tr>
<td>CAR T cells</td>
<td>Autologous T cells</td>
<td>1</td>
<td>30</td>
<td>02706782</td>
</tr>
<tr>
<td>CAR T cells</td>
<td>Autologous T cells</td>
<td>1/2</td>
<td>136</td>
<td>01583686</td>
</tr>
<tr>
<td>Antibody/LMB-100</td>
<td>Immunotoxin</td>
<td>1/2</td>
<td>100</td>
<td>02810418</td>
</tr>
</tbody>
</table>

* Includes other cancers
**KRAS remains at large and not druggable**

70-100% of pancreatic adenocarcinomas have *RAS* mutations

- Blocking downstream signaling
- Engineered exosome delivery of *KRAS* siRNA (Kamerkar/Kalluri, MDACC)
- T cell transfer therapy (Tran/Rosenberg, NCI)

Targeting CDK4/6: a rational strategy in pancreatic cancer because of universal KRAS mutations and frequent p16 mutilations
Targeting CDK4/6: a rational strategy in pancreatic cancer because of universal \textit{KRAS} mutations and frequent \textit{p16} mutilations
Targeting CDK4/6: a rational strategy in pancreatic cancer because of universal \textit{KRAS} mutations and frequent \textit{p16} mutilations.

- **Rb**
- **E2F**
- **Cyclin D1**
- **CDK4/6**
- **MEK**
- **AKT**

**Clinical Trials:***

- **NCT02703571**: Ribociclib plus trametinib
  - P1/2, N = 124

- **NCT03065062**: Palbociclib plus gedatolisib
  - P1, N = 96

- **NCT02981342**: Abemaciclib +/- other
  - P2, N = 256
Napabucasin targets STAT3 signaling in cancer stem cells

- Oral inhibitor of STAT3
- Blocks CSC self renewal
- Kills CSC and cancer cells


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

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

N = 66

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

NCT02231723, Dr. Bekaai-Saab
Immunotherapy for pancreatic cancer

• Pancreas cancer is non-immunogenic secondary to immunosuppressive elements, low mutational burden, and paucity of T cells

• Single agent therapeutics approaches focusing on overcoming T-cell immunologic endpoints with immune checkpoint inhibitors or vaccines have not been encouraging

Royal Re et al. J Immunother 210;33:828-833
Select immune checkpoint inhibitor combination studies in pancreatic cancer

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Study Phase</th>
<th>Estimated Numbers</th>
<th>NCT number</th>
</tr>
</thead>
<tbody>
<tr>
<td>GVAX + CRS-207 +/- nivolumab</td>
<td>2</td>
<td>108</td>
<td>02243371</td>
</tr>
<tr>
<td>ACP-196 +/- Pembrolizumab</td>
<td>2</td>
<td>76</td>
<td>02362048</td>
</tr>
<tr>
<td>Gem/Nabpacli +/- durvalumab/teremlimumab</td>
<td>2</td>
<td>180</td>
<td>02879318</td>
</tr>
<tr>
<td>Durvalumab + pexidartinib</td>
<td>1</td>
<td>58</td>
<td>02777710</td>
</tr>
<tr>
<td>Tremelimumumab, durvalumab, SBRT (in 3 combos/arms)</td>
<td>1</td>
<td>60</td>
<td>02311361</td>
</tr>
<tr>
<td>Epacadostat, Pembro, CRS-207</td>
<td>2</td>
<td>70</td>
<td>03006302</td>
</tr>
</tbody>
</table>
Too many possibilities of combinations with the immune checkpoint inhibitors

Co-stimulatory mAbs targeting:
- CD137
- OX40
- CD40
- GITR

Conventional agents inducing immunogenic cell death:
- Chemotherapy
- Radiotherapy
- Anti-angiogenics
- Targeted therapies

TReg cell targeting or inhibition

Cancer vaccines considering individual neoantigens

Other checkpoint inhibitory molecules:
- CTLA4
- LAG3
- TIM3
- BTLA
- TIGIT

Functional modification of immunosuppressive enzymes such as:
- IDO1
- iNOS

Adoptive cell therapy

Myeloid cell modulation

Conventional agents inducing immunogenic cell death:
- Chemotherapy
- Radiotherapy
- Anti-angiogenics
- Targeted therapies

Other checkpoint inhibitory molecules:
- CTLA4
- LAG3
- TIM3
- BTLA
- TIGIT
Pancreas cancer: the big picture!

1. Tumor and host profiling

2. Big Data profile versus outcome

3. Consensus on molecular & metabolic classifiers

4. Personalized combination therapies

Clinical trials interrogating different aspects of the biology
Pancreas cancer: the big picture!

1. Tumor and host profiling
2. Big Data profile versus outcome
3. Consensus on molecular & metabolic classifiers
4. Personalized combination therapies

Clinical trials interrogating different aspects of the biology

We are here!
Conclusions

• Several areas of interest and promise that include DNA repair, hyaluronan, mesothelin, cancer cell stemness, metabolism, and others
• Still too early for immunotherapy but we have many opportunities using rational combinations
• Promising agents must be advanced to biomarker based testing and into rational combinations
• Smart clinical trial designs are needed!!
Thank you!

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