Metastatic Pancreatic Adenocarcinoma.. Current Stand And Future Directions

Laith Abushahin MD
Gastrointestinal Oncology
University of Iowa Hospitals and Clinics
Iowa Oncology Society Fall Conference 10/9/2015
Disclosures

Clinical Research Funding Through The Institution:

• OncoMed (Demzicumab)

• Merck (Pembrolizomab)
Pancreatic Adenocarcinoma

Estimated 48,960 new cases and 40,560 death in 2015 in USA.

5-y OS

Pancitic Cancer
Hepatobiliary Cancer
Lung Cancer
Esophageal Cancer

5-Y OS over the last 30 years

Cancer facts and figures 2015, American Cancer Society
Metastatic Pancreatic Adenocarcinoma

Timeline for development of cytotoxic therapy for pancreatic Adenocarcinoma

- **Gemcitabine**
  - 1996
- **G+ Erlotinib**
  - 2005
- **FOLFIRINOX**
  - 2010
- **G+ Nab-paclitaxel**
  - 2014
Metastatic Pancreatic Adenocarcinoma

**Gemcitabine:**

<table>
<thead>
<tr>
<th></th>
<th>Gem</th>
<th>5-FU</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt No.</td>
<td>63</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>5.4%</td>
<td>0%</td>
<td>0.0025</td>
</tr>
<tr>
<td>OS</td>
<td>5.65m</td>
<td>4.4m</td>
<td>0.0025</td>
</tr>
<tr>
<td>TTF</td>
<td>2.1m</td>
<td>0.9m</td>
<td>0.0025</td>
</tr>
<tr>
<td>1-y survival</td>
<td>18%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Clinical Benefit RR</td>
<td>24%</td>
<td>5%</td>
<td>0.0022</td>
</tr>
</tbody>
</table>

Burris, JCO 1997
Metastatic Pancreatic Adenocarcinoma

**Gemcitabine:**
- Gemcitabine monotherapy consistently reported OS ~6 months and 1-y s~20%

<table>
<thead>
<tr>
<th>Trial</th>
<th>No of pt</th>
<th>Gem OS</th>
<th>Gem 1-y s</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG2297 Gem vs Gem 5FU</td>
<td>327</td>
<td>5.4</td>
<td>~15-17%</td>
</tr>
<tr>
<td>Bramahl/UK Gem vs Gem + marimastat</td>
<td>239</td>
<td>5.5</td>
<td>17%</td>
</tr>
<tr>
<td>NCI-C Gem vs Bay 12-</td>
<td>277</td>
<td>6.7</td>
<td>25%</td>
</tr>
<tr>
<td>Van Custem/ Belgium Gem vs Gem + Tipifarinib</td>
<td>688</td>
<td>6.1</td>
<td>24%</td>
</tr>
</tbody>
</table>
### Metastatic Pancreatic Adenocarcinoma

<table>
<thead>
<tr>
<th>Gemcitabine vs</th>
<th>No.</th>
<th>OS&lt;sub&gt;gemcitabine&lt;/sub&gt;</th>
<th>OS&lt;sub&gt;combination&lt;/sub&gt;</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine + 5-FU (ECOG2297, 2002)</td>
<td>327</td>
<td>5.4</td>
<td>6.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Gemcitabine + Irinotecan (Caio, 2004)</td>
<td>360</td>
<td>6.6</td>
<td>6.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Gemcitabine + tipifarinip (Van Custem, 2004)</td>
<td>688</td>
<td>6.3</td>
<td>6.0</td>
<td>0.75</td>
</tr>
<tr>
<td>Gemcitabine + Oxaliplatin (GERCOR, 2005)</td>
<td>313</td>
<td>7.1</td>
<td>9.0</td>
<td>0.13</td>
</tr>
<tr>
<td>Gemcitabine + Pemetrexed (Oettle, 2005)</td>
<td>565</td>
<td>6.3</td>
<td>6.2</td>
<td>0.84</td>
</tr>
<tr>
<td>Gemcitabine + Cisplatin (Heinemann, 2006)</td>
<td>192</td>
<td>6.0</td>
<td>7.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Gemcitabine + Cetuximab (SWOG 0205, 2007)</td>
<td>760</td>
<td>6.0</td>
<td>6.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Gemcitabine + Capecitabine (Cunningham, 2009)</td>
<td>533</td>
<td>6.2</td>
<td>7.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Gemcitabine + Bevazicumab (CALGB80303, 2010)</td>
<td>602</td>
<td>5.9</td>
<td>5.8</td>
<td>0.95</td>
</tr>
<tr>
<td>Gemcitabine + axitinib (Kindler, 2011)</td>
<td>632</td>
<td>8.3</td>
<td>8.5</td>
<td>0.54</td>
</tr>
</tbody>
</table>
Metastatic Pancreatic Adenocarcinoma

NCI-C Trial:

- **PFS:** 3.75 VS. 3.55 (P=0.004)
- **RR:** 8.6% VS 8.0% (P=NS)
- 1-Y survival: 23% vs 17% (p=0.023)
- QOL better on placebo
- Cost increase ~500 k$/YLG

**Meta-analysis:** Heinemann et al, BMC Cancer 2008

- Pooled 4465 patients from 15 randomized trials.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem + X</td>
<td>0.91</td>
<td>0.004</td>
</tr>
<tr>
<td>Gem + platinum</td>
<td>0.85</td>
<td>0.01</td>
</tr>
<tr>
<td>Gem + Fluorouracil</td>
<td>0.9</td>
<td>0.03</td>
</tr>
</tbody>
</table>

- Pooled 1682 patients with documented PS:

<table>
<thead>
<tr>
<th>PS Level</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good PS (E 0-1, KPS90-100%)</td>
<td>0.76</td>
<td>0.0001</td>
</tr>
<tr>
<td>Poor PS (E2, KPS 60-80%)</td>
<td>1.08</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Metastatic Pancreatic Adenocarcinoma

**PRODIGE4-ACCORD11 trial:**

- Randomize
- 342 Pts
- FOLFIRINOX
- Gemcitabine
- No Prior Chemo
- Ps0-1
- <76 Y
- Measurable Metastatic Disease
- Normal Organ Function

Statistics: 80% power to detect an increase from 7-10 months (HR:0.7)

Metastatic Pancreatic Adenocarcinoma

**PRODIGE4-ACCORD11 trial:**

<table>
<thead>
<tr>
<th></th>
<th>FOLFOIRNOX</th>
<th>Gemcitabine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>31.6%</td>
<td>9.4%</td>
<td>0.0001</td>
</tr>
<tr>
<td>DCR</td>
<td>70.2%</td>
<td>50.9%</td>
<td>0.0003</td>
</tr>
<tr>
<td>OS</td>
<td>11.1m</td>
<td>6.8m</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-y s</td>
<td>48.4%</td>
<td>20.6%</td>
<td></td>
</tr>
<tr>
<td>18 m s</td>
<td>18.6%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>6.4</td>
<td>3.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Metastatic Pancreatic Adenocarcinoma

MPACT Trial:

- 861 patients
- 151 sites
- 3 continents

- Stage IV
- KPS>70%
- No Prior Treatment

Gemcitabine 1g/m² IV QW 3/4
+ Nab-paclitaxel 125mg/m² IV QW 3/4

## Metastatic Pancreatic Adenocarcinoma

<table>
<thead>
<tr>
<th></th>
<th>Nab-G</th>
<th>Gemcitabine</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>23%</td>
<td>7%</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DCR</td>
<td>48%</td>
<td>33%</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M OS</td>
<td>8.5</td>
<td>6.7</td>
<td><strong>0.72</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-Y S</td>
<td>35%</td>
<td>22%</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>18-M S</td>
<td>16%</td>
<td>9%</td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>24-M S</td>
<td>9%</td>
<td>4%</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>PFS</td>
<td>5.5</td>
<td>3.7</td>
<td><strong>0.69</strong></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade ¾ toxicity</th>
<th>Nab-G</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>38%</td>
<td>27%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17%</td>
<td>7%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>17%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>G-CSF</td>
<td>26%</td>
<td>15%</td>
</tr>
</tbody>
</table>

# Metastatic Pancreatic Adenocarcinoma

## Cross Trials Comparison?

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRINOX</th>
<th>NAB-3/4 toxicity</th>
<th>NEUTROPIA</th>
<th>NF</th>
<th>G-CSF</th>
<th>Thrombocytopenia</th>
<th>Diarrhea</th>
<th>Fatigue</th>
<th>Neuropathy</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Center</strong></td>
<td>1 country</td>
<td>3 continents / 151 centers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>342</td>
<td>861</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age&lt;=75</strong></td>
<td>100%</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PS</strong></td>
<td>0</td>
<td>37%</td>
<td>100</td>
<td>16%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>62%</td>
<td>90</td>
<td>42%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatic head</strong></td>
<td>39%</td>
<td>44%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stent</strong></td>
<td>16%</td>
<td>19%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Liver metastases</strong></td>
<td>88%</td>
<td>85%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SELECTION?**

- **SEQUENCE?**
- **ADJUVANT?**

**Grade 3/4 toxicity**

- Neutropenia: 46% vs. 38%
- NF: 5% vs. 3%
- G-CSF: 43% vs. 26%
- Thrombocytopenia: 9% vs. 13%
- Diarrhea: 13% vs. 6%
- Fatigue: 24% vs. 17%
- Neuropathy: 9% vs. 17%

**Cost**

- High cost of supportive care vs. High cost of drug
Metastatic Pancreatic Adenocarcinoma

- Performance status and age.
- Patient preference for schedule.
- Cost?
- Biomarker?
  - SPARC (Secreted Protein acidic and rich in cysteine)
  - Matricellular glycoprotein, binds to albumin
Metastatic Pancreatic Adenocarcinoma

Second Line Therapy:

- Limited data, mostly following Gemcitabine failure:
  - CONKO-003 v1: OFF > BSC
    - 46 patients, (4.8m vs 2.3m)
  - CONKO-003 v3: OFF > FF
    - 168 pts, (5.9m vs 3.3m)
  - PANCREOX: 5FU/LV > FOLFOX
    - 108 patients, (9.9 m vs 6.1m)
Metastatic Pancreatic Adenocarcinoma

**1st Line**
- Gemcitabine/ nab-paclitaxel

**2nd Line**
- FU-based regimen

**3rd Line**
- PS0-1: Irinotecan or platinum based regimen if no previous exposure

**2nd Line (Right)**
- FOLFIRINOX

**3rd Line (Right)**
- Gemcitabine+/- nab-paclitaxel
**Metastatic Pancreatic Adenocarcinoma**

Where to go from here?

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic cancer cells resistance to therapies</td>
</tr>
<tr>
<td>Microenvironment</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Pancreatic Cancer Stem Cells</td>
</tr>
<tr>
<td>Recurrent genetic and epigenetic aberrancies</td>
</tr>
</tbody>
</table>
Metastatic Pancreatic Adenocarcinoma

Novel Cytotoxic agents:

• **MM-398**: Nano liposomal formulation of Irinotecan

Metastatic Pancreatic Adenocarcinoma

- FDA review by 10/25 for first agent in 2nd line.
- Is MM-398 better than Irinotecan?
- Can it replace Irinotecan in FOLFIRINOX
- Cost?
Metastatic Pancreatic Adenocarcinoma

Novel Cytotoxic agents:

**Evofusfamide (TH 302)**

- Prodrug for Bromo-isophosphoramid mustard
- Selective activation in hypoxic microenvironment

Weiss, Clin Cancer Res. 2011;17:2997-3004
Metastatic Pancreatic Adenocarcinoma

Randomized Phase II of Gemcitabine+ TH302 (214pts)

- Median PFS 5.6 VS 3.6 (P:0.005)
- OS 9.2 vs 6.9 (ns)
- ORR 26% vs 12%

Borad et al, J Clin Oncol 2015;33:1475-81
Metastatic Pancreatic Adenocarcinoma

Targeting Microenvironment:

Stromal Depleting Agents:

- Stroma is dense in pancreatic adenocarcinoma with significant cross talk with neoplastic cells.

- Several targets have been investigated:
  - COX-2
  - VGEF
  - MMP
  - Hedgehog pathway
  - Hyaluronic acid.
Targeting Microenvironment:
Stromal Depleting Agents:

- **Hyaluronic acid:**
  - Believed to hinder drug delivery to cancer cells:
    - Increasing interstitial pressure
    - Compressing vasculature
  - Immune contact prevention
- Degraded by Hyaluronidase.

Brekken et al. anticancer Res, 2000, 20:3503

Hingorani, ASCO 2015
Metastatic Pancreatic Adenocarcinoma

PEGPH20:

- PEGylated Recombinant Hyaluronidase.

- PEGPH20 combined with gemcitabine remodels stroma and re-expand microvasculature in animal models

Proenzano et al, Cancer Cell 2012;21:418-29
Metastatic Pancreatic Adenocarcinoma

Halo -201 Study:

- Phase 1b study of Gemcitabine + PGPH20
- 28 patients
- MTD 3 mcg/kg

<table>
<thead>
<tr>
<th></th>
<th>HA-High</th>
<th>HA-low</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>67%</td>
<td>27%</td>
</tr>
<tr>
<td>PFS</td>
<td>219d</td>
<td>108d</td>
</tr>
<tr>
<td>OS</td>
<td>395d</td>
<td>174d</td>
</tr>
</tbody>
</table>

Toxicity | % | G >=3 |
---       |---|-------|
Edema    | 61% | 4%    |
Muscle spasms | 54% | 7%    |
Thrombocytopenia | 50% | 7%    |
Fatigue | 50% | 7%    |
Pulmonary embolism | 18% | 11%   |

Hingorani et al, ASCO GI 2015
Metastatic Pancreatic Adenocarcinoma

Phase II HALO-202 trial:
- 260 patients
- Gem+ nab-P + PGPH20
- Gem+ Nab-P

Primary endpoints:
- PFS
- TE event rate

Secondary endpoints:
- PFS by HA level
- ORR
- OS

Increased thromboembolic events in the investigational arm that necessitated a hold and update to include TE prophylaxis.

Hingorani, ASCO 2015
Metastatic Pancreatic Adenocarcinoma

**HALO-202 Trial**  Interim results after 146 pts

<table>
<thead>
<tr>
<th>Population</th>
<th>Gem+Nab-P+PEGPH20</th>
<th>Gem+Nab-p</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>41%</td>
<td>34%</td>
<td>0.48</td>
</tr>
<tr>
<td>HA-High</td>
<td><strong>52%</strong></td>
<td><strong>24%</strong></td>
<td><strong>0.038</strong></td>
</tr>
<tr>
<td>HA-Low</td>
<td>37%</td>
<td>38%</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Progression Free Survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>5.7 m</td>
<td>5.2 m</td>
<td>0.11</td>
</tr>
<tr>
<td>HA-High</td>
<td><strong>9.2 m</strong></td>
<td><strong>4.3 m</strong></td>
<td><strong>0.05</strong></td>
</tr>
<tr>
<td>HA-Low</td>
<td>5.3 m</td>
<td>5.6 m</td>
<td>0.74</td>
</tr>
</tbody>
</table>

**PFS in HA-High Patients**

- A trend in OS (12 vs 9)
- International Phase III to be launched in 2016

Of note, Ongoing SWOG 1313: randomized phase II trial with FOLFIRINOX+/- PEGPH20
Metastatic Pancreatic Adenocarcinoma

**Concerns:**
- Very early data review (interim analysis)
- Reported increased TE events
- Unknown role of heparin in stromal modulation.
- The rise and fall of Hedgehog pathway inhibitors.
  - Stromal tumor containing role? (Rhim et al. Cancer Cell 2014)
Metastatic Pancreatic Adenocarcinoma

Targeting Microenvironment:
Signal Transduction inhibitors:

• Mouse models showing JAK-STAT signaling is important for pancreatic cancer progression* and contributes to clinical cachexia **

• **Ruxolitinib** : JAK2 inhibitor

*Lesina Cancer Cell. 2011
**Gilbert, J Cell Physiol 2014
Metastatic Pancreatic Adenocarcinoma

**RECAP Trial**

**Entire population (n=127):**
- OS: 136 d vs 129.5 d
- 6 mo survival 42% vs 35%
- HR 0.79 (P=0.25)

**CRP >13mg/L (n=60):**
- OS: 83d vs 55 d
- 6 mo survival **42% vs 11%**
- HR 0.47 (p=0.001)

**Phase III JANUS I & II**
- 2nd line with Capecitabine +/- Ruxolitinib
- Patients with CRP > 10 (Biomarker driven)

Hurwitz, J. Clin Oncol 32:5s, 2014(suppl; abstr4000)
Metastatic Pancreatic Adenocarcinoma

**Immunotherapy:**

- Pancreatic cancer is immunosuppressive disease:
  - High accumulation of T-reg cells
  - Cancer cells induce T cell apoptosis through FAS ligand secretion
- Pancreatic cancer stroma:
  - Pancreatic cancer stellate cells and its role in formation of Myeloid derived suppressor cells

Mace et al. OncoImmunology 2:7 July 2013
Metastatic Pancreatic Adenocarcinoma

Vaccines:

GVAX/CRS-207:

GVAX:
GM-CSF secreting irradiated pancreatic cancer cell lines

CRS-207:
Attenuated Listeria monocytogenes engineered to produce mesothelin in APC cytosol

- Preclinical work suggested synergy
Metastatic Pancreatic Adenocarcinoma

Kaplan-Meier estimates of overall survival (OS) according to treatment group.

ECLIPSE Trial (Phase III, 2nd line)
- Arm A: Cy/GVAX X2> 4 x CRS-207
- Arm B: CRS-207 X 6
- ARM C: Chemotherapy dealer choice

Dung T. Le et al. JCO doi:10.1200/JCO.2014.57.4244
Metastatic Pancreatic Adenocarcinoma

Immune Checkpoint Blockade:

• Initial reports have been largely futile
  • Royal Re et al, J immunother 2010,Oct;33(8):828-33
Metastatic Pancreatic Adenocarcinoma

Immune checkpoint Blockade:
Strategies of combining multiple therapies

<table>
<thead>
<tr>
<th>Combination</th>
<th>Phase I-II TrialS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab+ Nab- P +/- Gemcitabine</td>
<td>NCT02309177 Celgene</td>
</tr>
<tr>
<td>Pembrolizomab +ACP-196</td>
<td>NCT02362048 Acerta/Merck(keynote144)</td>
</tr>
<tr>
<td>GVAX+CRS-27+/- Nivolumab</td>
<td>NCT02243371 Hopkins/ BMS</td>
</tr>
<tr>
<td>Gem/nab-paclitaxel+ IDOi</td>
<td>NCT02077881 Newlink</td>
</tr>
</tbody>
</table>
Metastatic Pancreatic Adenocarcinoma

**Pancreatic Cancer Stem Cells:**

- Distinct population of PDAC cells that are able to self-renew and to produce the heterogeneous lineages of cancer cells that comprise the tumor.\(^1\)

- Distinct surface markers: CD44, CD24, and epithelial-specific antigen (ESA).\(^2\)

- Highly resistant to chemotherapy and radiation

- Subpopulation of which were hypothesized to be responsible for metastasis (CD133+ cells)\(^3\)

\(^1\) Clarke et al, Cancer Res., 66 (2006)  
\(^2\) Li et al, Cancer Res., 67 (2007)  
\(^3\) Hermann et al, Cancer Stem Cell, 2007
Metastatic Pancreatic Adenocarcinoma

Pancreatic Cancer stem Cell:

- Overexpression of developmental pathways including:
  - NOTCH
  - WNT
  - DR5
  - Hepatocyte growth factor receptor

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent/s</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOTCH</td>
<td>Demzicumab</td>
<td>NCT02289898</td>
</tr>
<tr>
<td>DR5</td>
<td>Conatumumab</td>
<td>NCT02289898</td>
</tr>
<tr>
<td>WNT</td>
<td>LGK974</td>
<td>NCT01351103</td>
</tr>
<tr>
<td>MET</td>
<td>Tivantinib</td>
<td>NCT01351103</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT01351103</td>
</tr>
</tbody>
</table>
Metastatic Pancreatic Adenocarcinoma

Pancreatic Cancer stem Cell:

- NOTCH pathway
  - Survival proliferation and Vessel maturation
- Important element: DLL4

- Anti-DLL4 (Demcizumab)
  - Currently undergoing investigation in pancreatic, NSCLC, ovarian cancer.
  - Randomized phase II trial with gemcitabine + nab-paclitaxel for first line
Metastatic Pancreatic Adenocarcinoma

Molecular Targets:
- EGFR overexpression
- KRAS
- CDKN2A/P16
- P53
- DPC4
Pancreatic Adenocarcinoma
Thank You
Laith Abushahin