Pancreatic Adenocarcinoma: What Is The Optimal Treatment for Metastatic Disease?  
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Disclosures

**Research funding:** Sanofi, OncoMed, Momenta, Lilly, Genentech/Roche, Bayer, Novartis, Myriad Genetics

**Consulting:** Celgene, Incyte, Abbie, Celsion, Polaris
Agenda

• Advanced disease – front-line
  – Cytotoxic therapy
  – Treatment selection

• Advanced disease – second-line

• Ongoing trials
Front-Line Therapy
A Formidable Tumor Biology

- Complex microenvironment/ stroma
- Immunosuppression
- Multiple gene mutations
- Non-druggable tumor suppressor genes
- Drug resistance
- No validated biomarkers
FOLFIRINOX vs Gemcitabine
Prodige 4- ACCORD 11

Untreated Metastatic Panc Adenocarcinoma ECOG 0-1

Randomization 1: 1
Stratification
- PS: 0-1 vs 2; Primary tumor location, Center

Primary Endpoint: Overall Survival

FOLFIRINOX vs Gemcitabine
Overall Survival

Number at risk
Gemcitabine
FOLFIRINOX

Median 11.1 mo
Median 6.8 mo

HR = 0.57
P < 0.0001

Conroy, T. NEJM, 2011
FOLFIRINOX Delays Worsening of Quality of Life

![Graph showing the time until definitive deterioration >20 points in EORTC-QLQ C30 global health status]

Time until definitive deterioration >20 points in EORTC-QLQ C30 global health status

## FOLFIRINOX: Modifications

<table>
<thead>
<tr>
<th>Reference</th>
<th>mFOLFIRINOX Strategy</th>
</tr>
</thead>
</table>
| James ES et al\(^1\)  
LAPC/ metastatic | • 25% dose reduction irinotecan  
• Bolus 5-FU  
• Prophylactic pegfilgrastim |
| Blazer M et al\(^2\)  
Borderline resectable/ LAPC | • Dose-reduced irinotecan (165 mg/m\(^2\))  
• No bolus 5-FU  
• Pegfilgrastim added 4th day of cycle |
| Mahaseth H et al\(^3\)  
LAPC/ metastatic | • No bolus 5-FU  
• Growth-factor support |

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# FOLFIRINOX-Based Trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Group</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>PRODIGE</td>
<td>mFOLFIRINOX vs Gemcitabine</td>
</tr>
<tr>
<td>Borderline - Locally Advanced (LA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II (Borderline) A0221101</td>
<td>Alliance</td>
<td>FOLFIRINOX → Cap-RT → Surgery → Gem</td>
</tr>
<tr>
<td></td>
<td>On hold</td>
<td></td>
</tr>
<tr>
<td>Borderline Locally Advanced Wash U NCI</td>
<td>FOLFIRINOX + PF-04136309 (CCR2 antagonist)</td>
<td></td>
</tr>
<tr>
<td>Borderline Locally Advanced NewLink Genetics</td>
<td>FOLFIRINOX + Algenpantucel-L</td>
<td></td>
</tr>
<tr>
<td>Locally Advanced</td>
<td>Stanford</td>
<td>FOLFIRINOX +/- SBRT</td>
</tr>
<tr>
<td>Rand Phase II LA RTOG 1201</td>
<td>RTOG Pending</td>
<td>Arm 1: Gem/nab-P x 4 mths → CRT (63Gy/IMRT) + capecit. Arm 2: Gem/nab-P x 6 mths Arm 3: Gem/nab-P x 4 mths → CRT (50.4 Gy/28) + capecit.</td>
</tr>
<tr>
<td>Metastatic Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I- Rand Phase II (S1313)</td>
<td>SWOG On hold</td>
<td>mFOLFIRINOX +/- PEGPH20</td>
</tr>
<tr>
<td>Rand Phase II</td>
<td>JHCC</td>
<td>FOLFIRINOX +/- Ipilumumab/GVAX (maintenance)</td>
</tr>
</tbody>
</table>
**MPACT: Nab-Paclitaxel + Gemcitabine vs. Gemcitabine**

Untreated Metastatic Panc Adenocarcinoma KPS 70-100%

Randomization 1:1

Stratification
- Performance status (90-100 vs 70-80)
- Liver metastases (Present vs Absent)
- Region

Primary Endpoint: Overall Survival

Von Hoff, D. NEJM, 2013
MPACT: Overall Survival

<table>
<thead>
<tr>
<th>OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>8.5 (7.89-9.53)</td>
</tr>
<tr>
<td>6.7 (6.01-7.23)</td>
</tr>
</tbody>
</table>

HR = 0.72
95% CI (0.617-0.835)

*P* = .000015

## Similarities and Differences

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRINOX N= 167</th>
<th>Nab-P + Gem N= 431</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td>Metastatic only</td>
<td>Metastatic only</td>
</tr>
<tr>
<td><strong>Median age</strong></td>
<td>61 years</td>
<td>62 years</td>
</tr>
<tr>
<td><strong>Age limit</strong></td>
<td>&lt; 76 years</td>
<td>No upper limit</td>
</tr>
<tr>
<td><strong>Performance Status</strong></td>
<td>ECOG 0-1</td>
<td>KPS 70-100%</td>
</tr>
<tr>
<td><strong>Recruitment</strong></td>
<td>France</td>
<td>US (63%), Europe, Aust Academic, Community</td>
</tr>
<tr>
<td><strong>Trial Conduct</strong></td>
<td>Stopped Interim analysis</td>
<td>Increased N</td>
</tr>
<tr>
<td><strong>Gemcitabine arm</strong></td>
<td>Med OS 6.8 mths</td>
<td>Med OS 6.7 mths</td>
</tr>
<tr>
<td><strong>Experimental arm</strong></td>
<td>Med OS 11.1 mths</td>
<td>Med OS 8.5 mths</td>
</tr>
<tr>
<td><strong>HR, p-value</strong></td>
<td>HR 0.57, p&lt; 0.001</td>
<td>HR 0.72, p= 0.001</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td><strong>Growth factors</strong></td>
<td>42%</td>
<td>26%</td>
</tr>
</tbody>
</table>
Which Regimen First For PC?

• No clear data to guide
  - Age, performance status, patient preference

• Nab-paclitaxel and gemcitabine – applicable to broader patient population
  - Older, less robust performance status
  - Easier to add other agents?

• Ability to select which regimen first will be useful
# Systemic Treatment Options

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>First Line</th>
<th>Second Line</th>
</tr>
</thead>
</table>
| PS 0-1, younger, good liver function | • Clinical trial  
• FOLFIRINOX  
• Gem+nab-paclitaxel | • Clinical trial  
• Gemcitabine-based regimen (if prior 5-FU)  
• mFOLFIRINOX or mFOLFOX6? (if prior gem)  
• FOLFIRI  
• MM-398 + 5-FU/LV?  
• Capecitabine (if prior gem) |
| PS 1-2, older, adequate liver function including good albumin | • Clinical trial  
• Gem+nab-paclitaxel  
• Gemcitabine ± erlotinib | |
| PS 2-3 +/- major liver dysfunction/poor albumin | • Gemcitabine ± erlotinib | • Capecitabine  
• Supportive care |

# Potential Biomarkers In PDAC

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Function</th>
<th>Assay</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA19-9</td>
<td>Tumor-related</td>
<td>Blood test</td>
<td>Prognostic and early predictor of response</td>
</tr>
<tr>
<td>hENT1</td>
<td>Uptake of gemcitabine</td>
<td>Protein expression</td>
<td>Benefit gemcitabine in adjuvant setting?</td>
</tr>
<tr>
<td>SMAD4</td>
<td>Tumor suppressor gene</td>
<td>Protein expression/DNA</td>
<td>Predicting local versus systemic progression</td>
</tr>
<tr>
<td>SPARC</td>
<td>Complex and not well understood</td>
<td>Protein expression</td>
<td>Predicting benefit from nab-paclitaxel?</td>
</tr>
<tr>
<td>CRP mGPS</td>
<td>Acute phase reactant</td>
<td>Blood test</td>
<td>Prognosis and benefit JAK/STAT inhibitors</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Irinotecan metabolism</td>
<td>DNA</td>
<td>Predicts toxicity to irinotecan</td>
</tr>
</tbody>
</table>

Pharmacogenomic Profiling

Use of Model For Predicting Drug Sensitivity and Resistance In Pancreas Cancer

Ken Yu - MSKCC, CellPath Therapeutics, Institute for Systems Biology
Treatment Responses Vary in PC

Yu, O'Reilly, Sanger, Hidalgo, et al. GI Cancers Symposium, 2013
Pharmacogenomics

- Validity of this modeling has been published for sensitivity to Irinotecan\(^1\) and Gemcitabine\(^2\)

- Collaborators have developed models for predicting sensitivity to many commonly used chemotherapy drugs

- NCT01196247 clinical trial in previously treated pancreatic cancer

\(^1\) Mol Cancer Ther, 2011. \(^2\) Clin Cancer Res, 2011
Pharmacogenomic (PGx) Model

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>0.90</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>0.56</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>-1.32</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>-1.32</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>0.47</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>0.10</td>
</tr>
</tbody>
</table>

**Resistant:** Score < 0  
**Intermediate:** 0 < Score < 0.7  
**Sensitive:** Score > 0.8

**Gemcitabine Resistance**  
Pathway          | Expression |
-----------------|------------|
JAK-STAT         | NEG        |
HEDGEHOG         | POS        |
TGF-β            | POS        |

**Gemcitabine Sensitivity**  
Pathway          | Expression |
-----------------|------------|
JAK-STAT         | POS        |
HEDGEHOG         | NEG        |
TGF-β            | POS        |

Score based on gene enrichment related to drug sensitivity in cell lines

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Circulating Tumor & Invasive Cells

• Innovative CTC methodology isolates cells based on phenotype of invasion

• Collagen adhesion matrices: capturing, preserving, expanding CTCs from 10 mL blood

• Isolate enrich 5-10,000 cells; small % tumor cells

MSKCC Trial Design (IRB #11-141)

Population:
Subjects with untreated stage III-IV pancreatic cancer (N= 50)

1st line chemotherapy treatment

Blood draw

2nd line chemotherapy treatment

Ongoing therapy

Tumor and clinical assessment

Questions:
1) Does PGx model predict treatment response?
2) Does PGx profile change when cancer progresses?

Individual blood samples sequentially processed to:
1) Isolate/expand circulating tumor/invasive cells
2) Extract total RNA
3) Gene expression profile
4) PGx profile
5) Perform gene and network analysis

Results (N= 20)

First-Line Treatment Sensitivity and TTP in PDA

- Patients receiving treatment predicted by model to be effective had longer TTP

Pharmacogenomic Profiling in PC

- Sequential analyses – tube of blood
- Validate model for other regimens (gemcitabine/nab-paclitaxel) and evaluate for prediction of 2nd-line therapy
- Ongoing pathway analyses

- Future clinical studies in design
  - Randomized phase II
    FOLFIRINOX or Gemcitabine/nab-paclitaxel
  
  Initial therapy selection: Model vs Investigator Choice
Where Do We Go From Here?

- Stromal depletion
- Targeted therapy for genetic subgroups
- Targeting stem cells
- Immunotherapy
- Specific inhibitors of key signaling pathways
- Radioimmunotherapy
## 1st-Line Phase III Trials: Metastatic PC

<table>
<thead>
<tr>
<th>NCT</th>
<th>Trial Design</th>
<th>N</th>
<th>Target</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>01360853</td>
<td>Gem ± Rigosertib (Ph II-III)</td>
<td>150-650</td>
<td>Mitotic inhibitor: polo-like kinase</td>
<td>Onconova, Aptium</td>
</tr>
<tr>
<td></td>
<td>Press release 12-2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DSMB – Negative study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01746979</td>
<td>Gem ± TH302 LA + Metastatic</td>
<td>660</td>
<td>Hypoxia</td>
<td>EMD Serono MAESTRO</td>
</tr>
<tr>
<td>Pending</td>
<td>Gem ± Masitinib</td>
<td></td>
<td>TKI, C-kit, PDGFR, FGFR III, mast cells</td>
<td>AB Sciences</td>
</tr>
</tbody>
</table>

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)
# Front-Line Metastatic Trials

## Selected Randomized Phase II’s

<table>
<thead>
<tr>
<th>NCT</th>
<th>Trial Design</th>
<th>N</th>
<th>Target</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>01839487</td>
<td>Gem + nab-paclitaxel ± PEGPH20</td>
<td>132</td>
<td>Hyaluronan</td>
<td>Halozyme</td>
</tr>
<tr>
<td>01959139</td>
<td>mFOLFIRINOX ± PEGPH20</td>
<td>172</td>
<td>Hyaluronan</td>
<td>SWOG/ S1313</td>
</tr>
<tr>
<td>01621243</td>
<td>Gem + nab-paclitaxel ± M402</td>
<td>148</td>
<td>Anti-stromal</td>
<td>Momenta</td>
</tr>
<tr>
<td>01647828</td>
<td>Gem + nab-paclitaxel ± OMP-59R5</td>
<td>140</td>
<td>Notch, stem cell</td>
<td>OncoMed</td>
</tr>
<tr>
<td>01844817</td>
<td>Gem + nab-paclitaxel ± OGX-427</td>
<td>132</td>
<td>HSP27</td>
<td>OncoGenix</td>
</tr>
<tr>
<td>02101021</td>
<td>Gem + nab-paclitaxel ± momelotinib</td>
<td>JAK 1/JAK2</td>
<td></td>
<td>Gilead</td>
</tr>
<tr>
<td>01016483</td>
<td>Gem ± MSC1936369B</td>
<td>174</td>
<td>MEK</td>
<td>Merck, EU</td>
</tr>
<tr>
<td>01728818</td>
<td>Gem ± afatinib</td>
<td>117</td>
<td>EGFR, HER2,4</td>
<td>Boehringer, EU</td>
</tr>
<tr>
<td>01509911</td>
<td>Gem ± TL-118</td>
<td>80</td>
<td>Angiogenesis</td>
<td>Tiltan Pharma</td>
</tr>
<tr>
<td>01505530</td>
<td>LY249555 + chemo (investig choice)</td>
<td>120</td>
<td>Myostatin</td>
<td>Eli-Lilly</td>
</tr>
<tr>
<td>01280058</td>
<td>Carbo + paclitaxel ± reovirus</td>
<td>70</td>
<td>RAS</td>
<td>NCI</td>
</tr>
<tr>
<td>01585805</td>
<td>Gem + cisplatin ± veliparib</td>
<td>~70</td>
<td>PARPi (BRCA+)</td>
<td>NCI, Lustgarten</td>
</tr>
<tr>
<td>01209111</td>
<td>Gem + erlotinib ± metformin</td>
<td>120</td>
<td>Multiple</td>
<td>U. Amsterdam</td>
</tr>
<tr>
<td>01167738</td>
<td>PEXG ± metformin</td>
<td>82</td>
<td>Stem cells</td>
<td>San Raffaele</td>
</tr>
</tbody>
</table>

www.clinicaltrials.gov
Second-Line Therapy
Second Line Therapy in Pancreas Adenocarcinoma

• No standard/ approved therapy for second-line
• About 40-50% receive a second-line therapy – impact on survival unclear
• Few patients receive therapy on trial in 2nd-line
• Data to support gemcitabine-based treatment for patients with POD on 5-FU-based regimen
• Data to support 5-FU-based therapy for patients with POD on gem-based therapy

Systematic Analysis 2\textsuperscript{nd}-Line Therapy
Gemcitabine-Previously Treated

• 44 studies, N= 1,503 patients
• Conclusions
  ▪ Med OS 6 mths for therapy
  ▪ Med OS 2.8 mths best supportive care, p= 0.013
  ▪ Modest benefit from gemcitabine/platinum or 5-FU/platinum combinations
• Limitations
  ▪ Small sample size, no randomization, patient/disease state heterogeneity, retrospective

Rahma, OE. Ann Oncol, 2013
Benefit of Oxaliplatin following POD on Gemcitabine (CONKO-003)

- N = 165, randomized phase III
  OFF: oxaliplatin, leucovorin, 5-FU
  Control arm: best supportive care

- Second-line survival
  4.8 vs 2.3 months, P= 0.008

- OS
  9.1 vs 7.9 months, P= 0.031

PANCREOX Phase III Trial
mFOLFOX vs Infusional 5-FU/LV in Gem-Pre-Treated PDAC

<table>
<thead>
<tr>
<th></th>
<th>mFOLFOX</th>
<th>Infus 5-FU/LV</th>
<th>HR, P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65 years</td>
<td>67 years</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>92.6%</td>
<td>94.4%</td>
<td></td>
</tr>
<tr>
<td>ECOG 0</td>
<td>13</td>
<td>18.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75.9%</td>
<td>75.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.1%</td>
<td>5.7%</td>
<td></td>
</tr>
<tr>
<td>PFS (median)</td>
<td>3.1 mths</td>
<td>2.9 mths</td>
<td>HR 1, p= 0.99</td>
</tr>
<tr>
<td>OS (median)</td>
<td>6.1 mths</td>
<td>9.9 mths</td>
<td>HR 1.78, p= 0.02</td>
</tr>
<tr>
<td>Response Rate</td>
<td>13.2%</td>
<td>8.5%</td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-C30</td>
<td>65 days</td>
<td>92 days</td>
<td>HR 1.47, p= 0.27</td>
</tr>
</tbody>
</table>

Gill, S. Proceedings ASCO, 2014. Abst #4022
Dilemma...

• No clear benefit to oxaliplatin 2\textsuperscript{nd}-line
• Main value oxaliplatin front-line (FOLFIRINOX)
• Alternatives
  ▪ FOLFIRI
  ▪ MM-398 + infusional 5-FU/LV
  ▪ Targeting inflammation
  ▪ Clinical trial
The JAK-STAT Pathway

Targeting JAK-STAT in PDAC (RECAP)

- Randomized phase II capecitabine ± ruxolitinib
- N = 138 with progressive met PDAC following gem
- Primary endpoint: OS
- Intent-to-treat HR = 0.79, P= 0.12 NS
- **BUT**: Subgroup with CRP > 13 mg/L, mGPS 1 or 2
  - HR= 0.47, P= 0.005
  - 6 month OS 42% vs 11%
  - PFS HR 0.62, p= 0.2

Hurewitz, H. J Clin Oncol 32:5s, 2014 (suppl; abstr 4000)
# 2nd-3rd-Line Phase II-III Studies

**Metastatic Pancreatic Adenocarcinoma**

<table>
<thead>
<tr>
<th>NCT</th>
<th>Trial Design</th>
<th>N</th>
<th>Drug</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>01494506</td>
<td>Randomized phase III MM-398 ± 5FU/LV POSITIVE</td>
<td>405</td>
<td>Liposomal irinotecan</td>
<td>Merrimack Pharm NAPOLI-1</td>
</tr>
<tr>
<td>02117479</td>
<td>Randomized phase III trials (2) Capecitabine ± ruxolitinib</td>
<td>310</td>
<td>JAK1, JAK2</td>
<td>Incyte Corporation JANUS 1, 2</td>
</tr>
<tr>
<td>02119663</td>
<td></td>
<td>270</td>
<td></td>
<td></td>
</tr>
<tr>
<td>01121848</td>
<td>Randomized phase III 5FU/LV ± oxaliplatin (prior gem) ASCO 2014 – NEGATIVE for Oxaliplatin</td>
<td>107</td>
<td>Cytotoxic</td>
<td>Sanofi PANCREOX</td>
</tr>
<tr>
<td>01658943</td>
<td>Randomized phase II (Accrual complete) FOLFOX vs selumetinib + MK-2206</td>
<td>133</td>
<td>MEK, AKT</td>
<td>SWOG S1115</td>
</tr>
<tr>
<td>02004262</td>
<td>Randomized phase II (ongoing) Cyclop/GVAX/CRS-207 vs CRS-207 vs chemo</td>
<td>240</td>
<td>Listeria GVAX</td>
<td>ECLIPSE Aduro Biotech</td>
</tr>
<tr>
<td>01956812</td>
<td>Randomized phase III (ongoing) Gemcitabine + ⁹⁰Y hPAM4/placebo</td>
<td>440</td>
<td>hPAM4</td>
<td>Immunomedics</td>
</tr>
</tbody>
</table>
Conclusions

• Increasing treatment options available for good PS patients with good organ function

• Multiple targets/pathways being evaluated in pancreatic adenocarcinoma – especially phase II

• Second-/third-line therapy trials feasible and area for drug development

• Ongoing needs
  ▪ Validated biomarkers for patient selection
  ▪ Tissue acquisition
  ▪ Enhanced clinical trial participation