Pancreatic Adenocarcinoma: Novel Targeted Regimens Using Chemotherapy
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Agenda

• Advanced disease
  – Standard therapies

• Novel therapeutics – front-line
• Novel therapeutics – second-line

• Ongoing trials
A Formidable Tumor Biology

- Complex microenvironment/ stroma
- Immunosuppression
- Multiple gene mutations
- Non-druggable tumor suppressor genes
- Drug resistance
- No validated biomarkers
Approved Drugs/Regimens in PC

- Gemcitabine
- Erlotinib
- FOLFIRINOX
- Gemcitabine Nab-paclitaxel

1994: Gemcitabine
1998: Erlotinib
2002: FOLFIRINOX
2006: Gemcitabine Nab-paclitaxel
2010: S1*
2014: 2015: MM-398?

*Approved in Japan
FOLFIRINOX vs Gemcitabine
Prodige – ACCORD 11

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

Primary Endpoint: Overall Survival

FOLFIRINOX vs Gemcitabine
Overall Survival

Number at risk
Gemcitabine  171 134 89  48 28 14 7  6 3 3 2 2 2
FOLFIRINOX  171 146 116  81 62 34 20 13 9 5 3 2 2

Median 11.1 mo
Median 6.8 mo

HR = 0.57
P < 0.0001

Conroy, T. NEJM, 2011
# FOLFIRINOX-Based Trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Group</th>
<th>Design</th>
</tr>
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<tbody>
<tr>
<td><strong>Adjuvant Therapy</strong></td>
<td></td>
<td></td>
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<tr>
<td>III</td>
<td>PRODIGE</td>
<td>mFOLFIRINOX vs Gemcitabine</td>
</tr>
<tr>
<td><strong>Borderline - Locally Advanced (LA)</strong></td>
<td></td>
<td></td>
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<tr>
<td>II (Borderline)</td>
<td>Alliance</td>
<td>FOLFIRINOX→ Cap-RT→ Surgery→ Gem</td>
</tr>
<tr>
<td>Ao221101</td>
<td>ASCO ’15</td>
<td></td>
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<tr>
<td>Borderline/ LA</td>
<td>Wash U</td>
<td>FOLFIRINOX + PF-04136309 (CCR2 antagonist)</td>
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<tr>
<td>Borderline/ LA</td>
<td>NewLink</td>
<td>FOLFIRINOX + Algenpantucel-L</td>
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<tr>
<td>Locally Advanced</td>
<td>Stanford</td>
<td>FOLFIRINOX +/- SBRT</td>
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<tr>
<td><strong>Metastatic Disease</strong></td>
<td></td>
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<tr>
<td>Phase I- Rand Phase II (S1313)</td>
<td>SWOG</td>
<td>mFOLFIRINOX +/- PEGPH20</td>
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<tr>
<td>Rand Phase II</td>
<td>JHCC</td>
<td>FOLFIRINOX +/- Ipilimumumb/GVAX (maintenance)</td>
</tr>
</tbody>
</table>
Phase IB FOLFIRINOX + PF-04136309 Borderline Resectable/LA PC

- PF-04136309 (oral) inhibits chemokine receptor CCR2 on monocytes in tumor microenvironment
  - Depletes monocytes, tumor-associated macrophages
  - 14 of 29 (48%) tumor shrinkage > 30%
  - Sequential biopsies – upregulation of protumoral cytokines in microenvironment with FOLFIRINOX; suppressed with combination
  - CCR2 relevant target in PC
  - Feasible, safe

Wang-Gillam, A. Gastrointestinal Cancers Symposium, 2015. Abst #338
MPACT: Phase III Nab-Paclitaxel + Gemcitabine vs Gemcitabine

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

HR = 0.72
95% CI (0.617-0.835)
P = .000015

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
  – Platform for addition of novel therapeutics
  – Pathway for regulatory approval
Where Do We Go From Here?

• Stromal depletion
• Targeting stem cells
• Targeting metabolism
• Targeted therapy for genetic subgroups
• Targeting inhibitors of key signaling pathways
• Immunotherapy
• Radioimmunotherapy
## New Targets, New Drugs

<table>
<thead>
<tr>
<th>Target/Pathway</th>
<th>Class of Drug</th>
<th>Example of Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS, RAK, MEK</td>
<td>FT inhibitor; Oncolytic virus MEK, C-Met</td>
<td>Tipifarnib, Salarasib; Reovirus, Selumetinib, Onartuzumab</td>
</tr>
<tr>
<td>Hedgehog Notch</td>
<td>Small molecule Shh inhibitor Gamma-secretase inh, Notch</td>
<td>GDC-0449, IPI-926, LDE-225 R04929097, OMP-59R5</td>
</tr>
<tr>
<td>Stroma</td>
<td>Degrades hyaluronan</td>
<td>PEGPH20; M402</td>
</tr>
<tr>
<td>SRC</td>
<td>SRC, bcr-abl inhibitor</td>
<td>Dasatinib, AZD 0530</td>
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<tr>
<td>JAK 1, 2, Inflammation</td>
<td>JAK inhibitors</td>
<td>Ruxolitinib, Momelotinib</td>
</tr>
<tr>
<td>PARP/BRCA/PALB2</td>
<td>PARP inhibitors</td>
<td>Olaparib, Veliparib, Rucaparib</td>
</tr>
<tr>
<td>Fanconi, ATM, CHK</td>
<td>Alkylating agents</td>
<td>Cisplatin, Mitomycin, Irinotecan</td>
</tr>
<tr>
<td>Vaccines/Immune</td>
<td>CTLA4, PD-1, PD-L1 Listeria, Allogeneic vaccine Hyperacute rejection Other</td>
<td>Ipilumumab, Nivolumab, MEDI4736, CRS-207, GVAX Algenpantucel-L CD40, CAR Tcells (mesothelin, CEA)</td>
</tr>
<tr>
<td>Hypoxia/Microenvironment</td>
<td>Alkylating agent</td>
<td>TH-302 (MAESTRO)</td>
</tr>
</tbody>
</table>
Therapeutic Targets for Panc Ca

Notch, Shh, TGFβ, Wnt β-Catenin

RAS, RAF, MAPK2, MAPK, MEK, ERK

PI3K, Akt, mTOR, Stat3

TGFβ, Smad4

Normal → PanIN-1 → PanIN-2 → PanIN-3 → PDAC

EGFR

Shh, TGFβ, Smad

Hyaluronan

CD40, CTLA4, IL-2

VEGFR
Targeting Stroma
Tumor Microenvironment/ Stroma
PEGPH20 Development

• Pancreas cancers – high level of hyaluronan
• Preclinical activity for pegylated hyaluronidase (PEGHP20) - break down hyaluronan
  – Facilitates drug delivery, reduced interstitial fluid pressure
  – Improved effect with cytotoxics
• Completed phase IB: Gem + PEGPH20 (ASCO, 2013)

• Randomized phase II trials underway
  – Nab-P + gemcitabine +/- PEGPH20 (Halozyme)
  – FOLFIRINOX +/- PEGPH20 (SWOG-NCI)

Targeting Notch/Cancer Stem Cells
Notch Pathway and Cancer Stem Cells

- Cancer stem cells (CSC’s) associated with chemoresistance and metastasis
- Notch pathway mediates self-renewal and proliferation
- Activation of Notch 2/3 implicated in pancreas and other cancers
- PC expressing Notch 3 – poor prognosis

**Therapeutic objective:**
Inhibit CSC renewal and/or differentiation

Mann. PloS ONE, 2012
OMP-59R5 (Tarextumab) + Nab-P+ Gem in Patient-Derived Panc Tumor Xenografts

- OMP-59R5 fully human IgG2 inhibits Notch 2/3 signaling
- OMP-59R5 anti-CSC and anti-tumor pericyte activity
- 40 mg/kg (mouse) equivalent to 15 mg/kg in pts

Antibodies: 40 mg/kg, q2w
Chemo agents: weekly dosing
Phase IB Tarextumab (OMP-59R5) + Nab-Paclitaxel + Gemcitabine

- RP2D: Tarextumab 15 mg/kg q 2 weeks + standard nab-P + gemcitabine dosing
- 1 DLT grade 3 diarrhea at 15 mg/kg cohort (N= 12)
- Med PFS 5.6 mths, med OS 11.6 mths, RR 38% (N= 40)
- Notch 3 high (gene expression) med OS – very encouraging

O'Reilly, EM. Gastrointestinal Cancers Symposium, 2015
ALPINE: Randomized Phase II

Randomization 1: 1

Untreated Metastatic Panc Adenocarcinoma ECOG 0-1 N= 160

Primary Endpoints: Overall Survival (revised from PFS) Notch 3 high expression; All

nab-Paclitaxel + Gemcitabine + Placebo

nab-Paclitaxel + Gemcitabine + Tarextumab
Targeting Metabolism
Arginine Metabolism

- Arginine – semi-essential amino acid
- Most human cells synthesize arginine from citrulline via argininosuccinate synthase (ASS)
- Dietary glutamine, proline – precursors for arginine synthesis
- Arginine-depleting enzyme (ADI) hydrolyzes L-arginine → L-citrulline

- Efficacy, safety of ADI-PEG20 established in HCC

ADI-PEG20, Arginine Deprivation in PC

- Most pancreatic cancers are ASS deficient
  - 35/46 (89%)

- ADI-PEG20
  - Inhibits ASS deficient PC cells in tissue culture
  - At least additive with gemcitabine in xenografts
  - Enhances gemcitabine by blockade of ribonucleotide reductase M2 (RRM2), in addition to arginine depletion

ASS Expression in Pancreas Cancer

Negative

Of 46 tumors, 11% were positive for ASS

89% lacked ASS, making arginine an essential amino acid

Bowles, TL. Int J Cancer, 2009
Phase IB Nab-P, Gem + ADI-PEG20 in PC
MSKCC IRB #14-133

• Phase IB trial aims
  – Safety, tolerability of ADI-PEG20, nab-P + gemcitabine
  – MTD, recommended phase II dose (RP2D)
  – PFS, OS, duration of disease control
  – PK, Immunogenicity

• 3+3 design
  – ADI-PEG20 dose levels: 18, 36 mg/m² IM weekly (N= 6-12); Untreated or 1 prior regimen
  – Expansion cohort untreated PC
Targeting Genetic Subgroups
BRCA and Pancreas Adenocarcinoma

• 5-8% of PDAC patients germline BRCA 1 or 2 mutation
  – Ashkenazi Jewish 5-16%
  – Familial PDAC 5-19%
  – Familial breast/ovary cancer 5-10%

• BRCA Founder mutations in AJ descent (2-3%)
  – BRCA 1: 185delAG, 5382insC
  – BRCA 2: 6174delT

BRCA Mutations and PC Cont.

- Median age at diagnosis
  - Approx 10 yrs younger than SEER

- Prognostic effect of BRCA
  - Ovary ca: Longer OS for BRCA vs non-BRCA 53.7 vs 37.9 mths, p= 0.002
  - Breast Ca: No clear differences in OS
  - Pancreas Ca: Data suggests BRCA-associated PC better than non-BRCA; Utility to platinum

Advanced Pancreas Adenocarcinoma

- Current cytotoxics
  - FOLFIRINOX
  - nab-paclitaxel + gem
  - Median survival < 1 year

- Novel Targets
  - DNA damage control?

Therapeutic opportunity?


Courtesy Michael Pishvaian, M.D.
Loss of Functional BRCA-1/2 Affects DNA Double-Strand Break Repair Pathway

Normal Cells

- DNA Damage
- Repair by HR
  - Genomic stability
  - Survival
- Alternative repair (NHEJ or SSA)

BRCA-Deficient Cells

- DNA Damage
- Repair by HR
  - Gross genomic instability
  - Cell death or survival with chromosomal deletions or exchanges
- Alternative repair (NHEJ or SSA)

# Phase IB Cisplatin, Gemcitabine + Veliparib
Untreated Met PC + Fm Hx or BRCA mut

<table>
<thead>
<tr>
<th>DL</th>
<th>Veliparib PO BID</th>
<th>N</th>
<th>Dose-Limiting Toxicity</th>
<th>BRCA Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20mg BID, day 1-12</td>
<td>3</td>
<td>-</td>
<td>N= 2: 1 PR, 1 SD</td>
</tr>
<tr>
<td>1</td>
<td>40mg BID, day 1-12</td>
<td>3</td>
<td>-</td>
<td>N= 1: 1 PR</td>
</tr>
<tr>
<td>2</td>
<td>80mg BID, day 1-12</td>
<td>6</td>
<td>-</td>
<td>N= 5: 3 PR, 2 SD</td>
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<tr>
<td>2A</td>
<td>80mg BID, day 1-21</td>
<td>5</td>
<td>2 (grade IV plts, ANC)</td>
<td>N= 1: 1 PR</td>
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</tbody>
</table>

Recommended phase II dose of veliparib combined with fixed dose cisplatin and gemcitabine is 80 mg PO BID day 1-12, q 3 wks
Conclusions Phase IB Trial

• Phase II dose of veliparib is 80mg PO BID day 1-12 combined with cisplatin/gemcitabine

• Substantial anti-tumor activity in BRCA-mutated pts
  – RR 66%, disease control > 88%,
  – Long duration on study, 78% alive
  – Responses in both BRCA 1 and BRCA2

• No significant activity in non BRCA patients
  – No objective responses
  – Short duration on study (< 3 months), 56% RIP

• Ongoing randomized phase II evaluating the addition of veliparib + cisplatin/gem in BRCA/PALB2-mutated PC

O'Reilly, EM. AACR, 2014, ASCO, 2014
Randomized Phase II Trial

Untreated BRCA/PALB2m PDAC Stage III/IV

Arm A
Gemcitabine 600 mg/m²
Cisplatin 25 mg/m²
Veliparib PO BD day 1-12
G, C day 3, 10 q 3 weeks

Arm B
Gemcitabine 600 mg/m²
Cisplatin 25 mg/m²
G, C day 3, 10 q 3 weeks

NCT01585805 O’Reilly, EM
Phase II Olaparib: BRCAmut PDAC Subset

- Germline BRCAmut PDAC: N= 23
  - Gemcitabine pre-treated
  - Olaparib single-agent
  - 5/23 (22%) objective response
  - 8/22 (35%) stable disease at 8 weeks
  - Median survival 9.8 months
  - 1-year survival 41%

Kaufmann, B. J Clin Oncol, 2014
Platinum Therapy ➔ Olaparib/Placebo Phase III POLO Trial

Metastatic PDAC
Germline BRCAm
Prior Platinum
ECOG 0-1
N= 145

Randomization 3: 2
Primary Endpoint: PFS (Central review mRECIST 1.1)

Olaparib
300 mg PO BID

Placebo

NCT02184195 (Astra Zenica, Myriad)
# Other PARPi Studies in PDAC

<table>
<thead>
<tr>
<th>NCT</th>
<th>Design</th>
<th>N</th>
<th>Sponsor</th>
</tr>
</thead>
</table>
| 01489865  | FOLFOX + Veliparib  
Wild-type + Germline BRCA  
Untreated, previously treated (phase I-II) |         | AbbVie           |
| 01585805  | Cisplatin, Gemcitabine +/- Veliparib  
Germline BRCA, PALB2 (randomized phase II; Untreated) | 50      | MSKCC/NCI Lustgarten |
| 01585805  | Veliparib  
Germline BRCA, PALB2 (completed) | 15-25   | MSKCC/NCI Lustgarten |
| 01296763  | Irinotecan, Cisplatin, Mitomycin C +/- Olaparib  
Wild-type + Germline BRCA (phase I-II) |         | John Hopkin’s    |
| 01482715  | Rucaparib  
Germline BRCA (previously treated) | 100     | Clovis           |
| 01286987  | BMN-673  
Germline BRCA (any solid tumor; phase I) |         | BioMarin         |
| 02184195  | FOLFIRINOX maintenance +/- Olaparib (Phase III)  
Germline BRCA | 145     | Astra-Zenica POLO Trial |
# Front-Line Metastatic Trials Phase III

<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 Non-ATP inhibitor</td>
<td>Onconova, Aptium</td>
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<tr>
<td></td>
<td>Med OS 6.1 vs 6.4 mths</td>
<td></td>
<td>Negative trial 2015</td>
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<tr>
<td>01746979</td>
<td>Gem ± TH302</td>
<td>660</td>
<td>Hypoxia</td>
<td>EMD Serono MAESTRO</td>
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<tr>
<td></td>
<td>LA + Metastatic</td>
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# Front-Line Metastatic Trials
Selected Randomized Phase II’s

<table>
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<tr>
<th>NCT</th>
<th>Trial Design</th>
<th>N</th>
<th>Target</th>
<th>Sponsor</th>
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</thead>
<tbody>
<tr>
<td>01839487</td>
<td>Gem + nab-P ± PEGPH20</td>
<td>132</td>
<td>Hyaluronan</td>
<td>Halozyme</td>
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<tr>
<td>01959139</td>
<td>mFOLFIRINOX ± PEGPH20</td>
<td>172</td>
<td>Hyaluronan</td>
<td>SWOG/ S1313</td>
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<tr>
<td>01621243</td>
<td>Gem + nab-P ± M402 (Necuparanib)</td>
<td>148</td>
<td>Anti-stromal</td>
<td>Momenta</td>
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<tr>
<td>01647828</td>
<td>Gem + nab-P ± Tarextumab (Alpine)</td>
<td>140</td>
<td>Notch, stem cell</td>
<td>OncoMed</td>
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<tr>
<td>01844817</td>
<td>Gem + nab-P ± OGX-427 (Rainier)</td>
<td>132</td>
<td>HSP27</td>
<td>OncoGenix</td>
</tr>
<tr>
<td>02101021</td>
<td>Gem + nab-P ± momelotinib</td>
<td>336</td>
<td>JAK 1/JAK2</td>
<td>Gilead</td>
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<tr>
<td>02289898</td>
<td>Gem + nab-P ± Demcizumab (Yosemite)</td>
<td>201</td>
<td>Anti-DLL4, stem</td>
<td>OncoMed</td>
</tr>
<tr>
<td>0207781</td>
<td>Gem + nab-P ± Indoximod</td>
<td>80</td>
<td>IDO</td>
<td>NewLink Genetics</td>
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<tr>
<td>02109445</td>
<td>Gem + nab-P ± PF-03084014</td>
<td>193</td>
<td>γ-Secretase inh</td>
<td>Pfizer</td>
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<tr>
<td>02194829</td>
<td>Gem + nab-P ± MK-1775</td>
<td>133</td>
<td>Wee-1 inhibitor</td>
<td>Merck</td>
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<tr>
<td>01509911</td>
<td>Gem ± TL-118</td>
<td>80</td>
<td>Angiogenesis</td>
<td>Tiltan Pharma</td>
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<tr>
<td>01505530</td>
<td>LY249555 + chemo (investig choice)</td>
<td>120</td>
<td>Myostatin</td>
<td>Eli-Lilly</td>
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<tr>
<td>01585805</td>
<td>Gem + cisplatin ± Veliparib</td>
<td>70</td>
<td>PARPi (BRCA+)</td>
<td>NCI, Lustgarten</td>
</tr>
</tbody>
</table>
Second-Line Therapy
Second-Line Therapy in Pancreas Adenocarcinoma

- No standard/approved therapy for second-line
- About 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

The JAK-STAT Pathway

Targeting JAK-STAT in PDAC RECAP Trial

- 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>
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</thead>
<tbody>
<tr>
<td>01494506</td>
<td>Randomized phase III MM-398 ± 5FU/LV&lt;br&gt;<strong>POSITIVE – WORLD GI CONGRESS 2014</strong></td>
<td>405</td>
<td>Liposomal irinotecan</td>
<td>NAPOLI-1 Merrimack</td>
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<tr>
<td>02117479</td>
<td>Randomized phase III trials (2) Capecitabine ± ruxolitinib</td>
<td>310</td>
<td>JAK1, JAK2</td>
<td>JANUS 1, 2 Incyte Corporation</td>
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<tr>
<td>02119663</td>
<td>Randomized phase II (Accrual complete) FOLFOX vs selumetinib + MK-2206&lt;br&gt;<strong>ASCO 2015</strong></td>
<td>133</td>
<td>MEK, AKT</td>
<td>SWOG S1115</td>
</tr>
<tr>
<td>01658943</td>
<td>Randomized phase II (ongoing) Cyclop/GVAX/CRS-207 vs CRS-207 vs chemo&lt;br&gt;ECLIPSE</td>
<td>240</td>
<td>Listeria GVAX</td>
<td>ECLIPSE Aduro Biotech</td>
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<tr>
<td>01956812</td>
<td>Randomized phase III (ongoing) Gemcitabine + ⁹⁰Y hPAM4/placebo</td>
<td>440</td>
<td>hPAM4</td>
<td>PANCRIPT-1 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 Gemcitabine + nab-paclitaxel platform FOLFIRINOX – regulatory path forward unclear

• Second-third-line therapy trials feasible and area for drug development and integration of novel agents