New Agents / Strategies on the Horizon in Pancreatic Cancer

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Progress in pancreatic ductal adenocarcinoma has been very slow.
This is a very tough disease!

• 80% of patients are diagnosed with advanced unresectable disease
• 80% of patients who have resection and adjuvant therapy relapse
• “Cure” rate is only 7%
• Median survival of patients with metastases without treatment is only about 3 months
Why is this disease so aggressive?

• No early symptoms
• Very early invasion and metastases
• Chemo-resistant (sanctuary?)
• Debilitating cytokine mediated symptoms
Progression Model of Pancreatic Cancer

Pattern of Failure

- Locally Destructive Growth
- Limited Metastases
- Controlled Local Growth
- Metastasis

PDAC Subclasses

Acinar

Quasi-Mesenchymal

Classical

Collisson EA et al. Nature Medicine April 2011
Prognostic Implications

Time (days)

Survival Function

p = 0.037

Classical
QM - PDA

Collisson EA et al. Nature Medicine April 2011
Differential Drug Responses by Subtype in Cell lines

Quasi - Mesenchymal PDA cells are gemcitabine sensitive

Collisson EA et al. Nature Medicine April 2011
Classical PDA cells are erlotinib sensitive

Collisson EA et al. Nature Medicine April 2011
We still do not have a clinically useful biomarker for treatment selection in this disease.

This is about to change!
FOLFIRINOX
Overall Survival Curve

Stratified Log-rank test, p<0.0001
HR=0.57 : 95%CI [0.45-0.73]

APACT Overall Survival

OS, months

<table>
<thead>
<tr>
<th>Events/N (%)</th>
<th>Median (95% CI)</th>
<th>75th Percentile</th>
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<tbody>
<tr>
<td>nab-P + Gem</td>
<td>333/431(77)</td>
<td>8.5 (7.89–9.53)</td>
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<tr>
<td>Gem</td>
<td>359/430(83)</td>
<td>6.7 (6.01–7.23)</td>
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HR = 0.72
95% CI (0.617–0.835)
P = 0.000015

Pts at Risk
nab-P + Gem: 431 357 269 169 108 67 40 27 16 9 4 1 1 1 0
Gem: 430 340 220 124 69 40 26 15 7 3 1 0 0 0 0

Slide courtesy of Thierry Conroy
Which is better?

These studies cannot be compared.

One was regional (1 country) and one was global. Eligibility was slightly different. In a global trial, patients in some countries may have less optimal supportive care and fewer opportunities for second line treatments.
This is not a “contest”!

Toxicity Scale?

0 5 10

gem/cap  gem/A  FOLFIRINOX

OS, PFS.
Objective RR

FOLFIRINOX > gem/A
but comparisons like this are hazardous!

Selecting Treatment
Consider comorbidities
Patient preference
Goal of treatment
Compatibility with investigational agents
Predictive biomarkers
Other Options

1. gemcitabine and capecitabine

2. gemcitabine and cisplatin

3. GTX

4. gemcitabine and erlotinib
Moving Forward?

Let’s build on both FOLFIRINOX and gemcitabine plus albumin bound paclitaxel.

Give special consideration to gemcitabine and cisplatin in selected individuals.
Randomized Phase II or First Line Phase III Studies

FOLFIRINOX: PEGPH20 (hyaluronidase)

Gemcitabine + Nab-P: ibrutinib
demcizumab
MM-141
PEGPH20

There are 54 open Phase 1 - 3 trials in the US for metastatic disease – only 2 trials incorporate FOLFIRINOX
Maintenance?

What can you do when patients have good disease control but can’t tolerate continued treatment?
Maintenance sunitinib or observation in metastatic pancreatic adenocarcinoma: A phase II randomised trial

Michele Reni a,*, Stefano Cereda a, Michele Milella b, Anna Novarino c, Alessandro Passardi d, Andrea Mambrini e, Giuseppe Di Lucca f, Giuseppe Aprile g, Carmen Belli a, Marco Danova h, k, Francesca Bergamo i, Enrico Franceschi j, Clara Fugazza a, Domenica Ceraulo a, Eugenio Villa a
Eur J Cancer. 2013 Nov;49(17):360
GVAX/Ipi Frontline Maintenance Study
GVAX Pancreas + Ipilimumab vs. FOLFIRINOX

- Stable metastatic pancreatic cancer after 8-12 cycles of FOLFIRINOX; ECOG 0 or 1
  - Investigator-sponsored (PI: Dung Le)
  - Multi-Center, open-label, randomized, controlled
- Objectives
  - Primary objective: Overall survival
  - Secondary objectives: number of adverse events; progression-free survival; immune-related progression-free survival; objective response rate; duration of response; and tumor marker (CA 19-9) kinetics

Arm A, GVAX/Ipilimumab
- 1:1 randomization
- 92 Subjects with metastatic pancreatic cancer with stable disease on FOLFIRINOX chemotherapy
- every 3 weeks for 4 doses, then every 8 weeks

Arm B, Capecitabine
- one cycle every 14 days

NCT01896869

Courtesy of Dung Le
**POLO-1 Design**

- **Screen**: Patients with metastatic gBRCAm pancreatic cancer:
  1. On a 1st line Rx platinum regimen
  2. Have not progressed at time of randomization
  3. After at least 16 weeks of Rx with a Platinum but need not still be on plat

- **Randomize**:
  - Olaparib 300 mg bid tablet
  - Placebo
  - Progress by RECIST: Resume ChemoRx
  - 3:2
  - N=145

- **Primary Endpoint** is PFS (by central review) with intent to apply for accelerated approval based on target endpoint
- **Secondary Endpoints** are OS (basis of permanent registration), PFS2 by investigator assessment, ORR, DCR, safety, quality of life, and exploratory studies

Courtesy of Talia Golan
PRECISION PROMISE

Revolutionizing treatment for every pancreatic cancer patient.
Precision Promise

Mission Statement: To transform outcomes for all pancreatic cancer patients through a research and clinical trials platform that creates a culture of cooperation and learning among clinicians, researchers and drug developers, and puts the patient at the center of every decision.
Guiding Principles

- Patient centricity - through the entire journey
- Audacious goals
- Sense of urgency
- Flexibility
- Iterative between science and medicine
- Sustainability
Precision Promise

Translational Research Grants Program
• Support for translational and clinically relevant research identified by Coordinating Center
• Projects competitively reviewed through Research Grants department processes

Clinical Trials Consortium
• 10 sites initially in US
• Know Your Tumor
• Just-in-time feature to be developed
• Other Consortia to join in future

Coordinating center
• Executive Committee
• Working Groups including industry
• Infrastructure for communication & information exchange
Master Protocol with Sub-studies

- Molecularly stratified
- Small “signal seeking” studies
- Adaptive design
- Multiple “shots on goal” for each patient
- Flexible - changes in sub-studies do not affect master protocol
- Rapid transfer of patient to next sub-study when indicated
- Learn as we go
- Start with 3 sub-studies
  - Stromal Disruption
  - DNA Damage Repair
  - Immunotherapy
Tumor biopsy

Diagnostic

Immunohistochemistry
- HA
- Immunotherapy markers
- Other

Master Protocol Molecular Profiling

FFPE

Fresh frozen

Genome sequencing
In order of priority based on DNA quantity and tumor cellularity:
1. Cancer gene panel
2. WGS 80X, Normal 40X (Deeper if low cellularity or of significant interest)
3. WES 100X (only if min DNA left after panel)

Transcriptome sequencing
RNAseq on all patients
(50-135M reads depending on cellularity)
General Concept for Trial Design

1st line
- DNA Damage Repair
- Immunotherapy

2nd line
- IO

3rd line
- IO

Supportive Care

Stromal Disruption

IHC, HA hi, HA lo

IHC

DNA, RNA

Special, low prevalence alterations

MATCH, TAPUR, etc

Biopsy

Scan, and/or rise in blood markers, aim for rapid decision-making
Hyaluronan (HA): A Barrier to Therapeutic Access

• Highly hydrophilic, megadalton glycosaminoglycan (GAG) that can generate large immobile fluid phase

• Compromises Access to the Tumor
  – Increased tumor interstitial fluid pressure $^{1,2}$
  – Compresses vasculature $^{2-4}$
  – HA-rich tumor cell “coat” can hinder host immune cell access

• HA also signals through surface receptors

• PEGPH20 degrades HA

PFS in HA-High Patients

- **PAG**
  - Free Survival: 9.2 months
  - HR: 0.39 (0.15, 1.04)

- **AG**
  - Free Survival: 4.3 months
  - **p=0.05**

**At Risk**

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<th>MPM</th>
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**At 24 Months**

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Global Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Compare Efficacy and Safety of PEGylated Recombinant Human Hyaluronidase (PEGPH20) Plus Nab-Paclitaxel and Gemcitabine vs Placebo Plus Nab-Paclitaxel and Gemcitabine in Patients With Previously Untreated, Hyaluronan (HA)-High, Stage IV Pancreatic Ductal Adenocarcinoma

*All patients will receive enoxaparin prophylaxis.

- Randomized (2:1, PAG:AG), double-blind, placebo-controlled, global
- Patients enrolled based on HA-High tumors
- Initiated March 2016
- Interim analysis when target number of PFS events reached
- Statistical powering to support PFS with a hazard ratio of 0.59

Courtesy of Halozyrne
Randomized Phase II
Cisplatin, Gemcitabine +/- Veliparib
Germline BRCA/PALB2

Untreated Stage III- IV PDAC
ECOG 0-1
N= 50- 70

Randomization 1:1
Primary Endpoint: Response Rate

Arm A:
Cisplatin, Gemcitabine + Veliparib

Arm B:
Cisplatin, Gemcitabine
Key Molecular Mechanisms and Potential Novel Vulnerabilities (n = 457 multiplatform -omic analysis)

- KRAS
- ROBO SLIT Pathway
- RNA Processing
- CELL CYCLE
- DNA REPAIR
- TGFBeta Signaling
- NOTCH Signaling
- WNT Signaling
- CHROMATIN
- SWI/SNF

- 92%
- 15%
- 16%
- 24%
- 78%
- 47%
- 24%
- 12%
- 25%
- 24%
- 14%
- 25%
- 14%
- 24%
- 12%
- 14%
- 92%

References:
- Hudson et al. Nature 2010
- Biankin et al. Nature 2012
- Mann et al. PNAS 2012
- Alexandrov et al. Nature 2013
- Weissmueller et al. Cell 2014
- Waddell et al. Nature 2015
- Biankin et al. Nature 2015
MMR Deficient non CRC - Pembrolizumab Rx
Target Lesion Measurements

% Change from Baseline SLD
Istiratumab (MM-141) (bispecific antibody vs. IGF-1R and HER3)
Randomized phase 2 study (CARRIE) of istiratumab for metastatic pancreatic cancer

Previously untreated metastatic PC
High serum free IGF-1 level
ECOG 0/1

Istiratumab + nab-paclitaxel + gemcitabine

Placebo + nab-paclitaxel + gemcitabine

Primary endpoint: PFS
Screened 260 patients to identify ~146 eligible subjects

Considering genetic heterogeneity in cancer, adaptive immunity may be our best asset in controlling disease progression.

However, PDAC is not enriched with CD8 T cells, so standard approaches with checkpoint inhibitors do not work.
SU2C Collaboration

SU2C Dream Team: “Transforming pancreatic cancer from a death sentence into a treatable disease”

Figure 4. Schematic of Tiered Approach

INNOVATIVE CLINICAL TRIALS:
- GVAX/LM-MSLN + anti-PD-1
- Targeting CD-40
- Targeting BTK
- Targeting CD47
- Targeting CXCR4

Biospecimen Bank
Clinical Database

Exome sequencing:
Patient-specific T cell targets

Genetic Biomarkers
Immune Biomarkers

PRE-CLINICAL STUDIES:
- Identify best combination therapy
- Biomarker identification
- Biomarker validation

Design 2nd generation clinical trials:
Combinatorial Immunotherapy
Vaccine + best TME targeting agent(s)
Summary

- We now have multiple options for stabilizing chemotherapy
- Robust efforts underway to target RAS
- Biomarker driven trials are now in progress
- Precision Promise will launch in 2017
- Stromal associated targets, especially immune targets, are being addressed
- Windows of opportunity trials are feasible after response to chemotherapy
Thank you!