Precision Medicine for Pancreatic Cancer

May 23, 2017

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Precision Medicine for Pancreatic Cancer

Michael Pishvaian, MD, PhD
Georgetown University

Lynn Matrisian, PhD MBA
Pancreatic Cancer Action Network
Outline

- Overview of Pancreatic Cancer
- Overview of Precision Medicine: The Know Your Tumor Project
- Precision Promise: Molecularly-Stratified Trials for Pancreatic Cancer
- Clinical Examples of Targeting “Actionable Alterations” in Pancreatic Cancer
- Concerns
- Resources

Pancreatic Cancer: Background
Pancreatic cancer is projected to become the 2nd major cancer killer around the year 2020.

Adapted from: Rahib et al, Cancer Research, 2014
Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC)

- 95%
- 5%

Pancreatic neuroendocrine (PNET)

- Arises in hormone (insulin)-producing part of pancreas
- 5% of pancreatic cancer cases

Characteristics of Pancreatic Ductal Adenocarcinoma Cancer

- A “deadly” or “recalcitrant” cancer
  - Defined legislatively as cancers with a 5 year relative survival rate less than 50%
- Molecular characteristics
  - KRAS mutant – 95%
- Robust “stroma”
  - Elevated pressure prevents chemotherapies from reaching the tumor cells
- Immunologically “cold”
Risk Factors

• Environmental
  – Tobacco and alcohol abuse
  – Chronic Pancreatitis
  – Obesity
  – Diabetes

• Genetic (7-10%)
  – BRCA1/2 mutation
  – PALB2 mutation
  – p16 INK4 mutation (FAMMM syndrome)
  – Peutz-Jeghers syndrome (risk > 26%)
  – Ataxia-telangiectasia
  – FAP
  – Lynch syndrome II
  – An additional 10% have a first-degree relative with disease


STAGES

• Approximately 15% of pancreatic cancer patients are eligible for surgery

• About 10-15% of initially inoperable patients can be rendered operable with pre-operative chemotherapy and radiation

• For surgically operable patients, cure rates ARE improving
  – Surgically resected patients randomized to:
    • Gemcitabine
    Vs.
    • Gemcitabine + capecitabine (Gem-cap)
  – Median overall survival
    • 25.5 months vs. 28 months
  – 5 year overall survival rate
    • 16% vs. 29%
  – Gem + cap is the new standard
**PROGRESS in Metastatic Pancreatic Cancer**

![Graph showing median overall survival over years with different treatment regimens.]

**IMMUNOTHERAPY and Pancreatic Cancer**

- Early hope with vaccine therapy
- GVAX + CRS-207 as ≥2nd line therapy
  - GVAX – irradiated, GM-CSF-secreting allogeneic pancreatic cell lines \(\rightarrow\) elicit antigenic response
  - CRS-207 - attenuated Listeria expressing mesothelin
- 90 patients
  - Median OS = 6.1 months

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Von Hoff, NEJM, 2013, 369(18): 1691-1703
Ramanathan, R., 2013, JCO
Portal, A., JCO, 2015, 33(suppl; abstr 4123)
Weinberg, B., 2015, Oncology

Le, JCO, 2014, 32(suppl 3; abstr 177)
No Success with Immunotherapy for Pancreatic Cancer

• GVAX + CRS-207 vs. Placebo Phase IIb
  – Negative results – no better than placebo
• NO BENEFIT from single agents
  – Only 1/27 responders to ipilimumab
  – Zero responders to anti-PD-1/PD-L1 Tx
    • Pembrolizumab, nivolumab, durvalumab
  – Except 2/4 MSI-H pancreatic cancers that responded to pembrolizumab

Overcoming Resistance

• Why is panc Ca so unresponsive to immunotherapy?
• Highly suppressive tumor microenvironment
  – Collectively suppresses effector T-cells
• Explore other methods to enhance immunogenicity
  – Multiple pathways to be targeted
Many, Many “Targets” for Immunotherapy Development


Precision Medicine and the Know Your Tumor Project
Precision vs Personalized Medicine

- **Precision Medicine** refers to the tailoring of medical treatment to the individual characteristics of the patient.
  - Classification of individuals into subpopulations that differ in their disease susceptibility, biology, prognosis or response to a specific treatment.
  - Preventive or therapeutic interventions are concentrated on those who will benefit, sparing expense and side effects for those who will not.
- **Personalized Medicine** is also used to convey this meaning, but is sometimes misinterpreted as implying that unique treatments can be designed for each individual.

Precision Medicine

Two components

- **Biomarkers**
  - How to identify those who will respond
    - Genetic
    - Other
- **Targeted therapies**
  - What they respond to
    - Small molecules
    - Biologics
    - Nanomedicines
One size doesn’t fit all: precision medicine in oncology

Successes in changing the standard of care

• **Chronic Myelogenous Leukemia**
  Patients with the Philadelphia chromosome (99%) treated with imatinib increased 5-year survival from 30% to 89%

• **Breast**
  Patients with overexpressed HER-2 (20%) have a 37% improvement in overall survival if treated with trastuzumab

• **Lung**
  Patients with an EML4-ALK fusion (5%) treated with crizotinib have improved survival from 8 to 20 months

• **Melanoma**
  Patients with a V600E BRAF mutation (40%) have a 48% response rate to venurafenib or dabrafenib/trametinib

• **Lung**
  Patients with EGFR mutations (8 to 30%) have improved progression free survival from 4.6 to 13 months when treated with erlotinib

Pancreatic adenocarcinoma clinical trials
by treatment type, 2011-2015, U.S. only

Matrisian & Berlin, ASCO Educ Book e205 2016

- Increase in clinical trials with targeted therapies
- Only 5-15% are biomarker-driven precision medicine trials
A recent flurry of genomic information

Whole genomes redefine the mutational landscape of pancreatic cancer

Nature 2015

Genomic analyses identify molecular subtypes of pancreatic cancer

Nature 2016

Know Your Tumor™
real world experience

June 2014 to May 1 2017

1146 patients enrolled
588 reports completed
95% successful biopsies
34% from community physicians
48 states

Molecular profiling service offered by the Pancreatic Cancer Action Network to patients throughout the US.

www.pancan.org
Know Your Tumor - Definitions

• Actionable:
  • Literature supports high response rate in patients with that molecular abnormality (any cancer type) – “Highly actionable”
    OR
  • Possible implication of response to therapy, based on mechanism or pathway
**Know Your Tumor** results

Next Generation Sequencing
(Foundation Medicine)

- Highly actionable: 25%
- Not actionable: 22%
- Highly actionable modifies options (in pathway, WNT, MEK, MET, etc)

**Highly Actionable**

- BRCA1/2
- PALB2
- ATM
- CHEK1/2
- FANCA/C
- STK11
- AKT1/2/3
- TSC12
- CDK4/6
- FGFR1/4
- ERBB2
- RET
- NTRK1/3
- TOP2A
- BRAF
- ALK
- ROS1

- Platinum/PARP inhibitor
- mTOR/AKT inhibitor
- CDK inhibitor
- FGFR inhibitor
- HER2 inhibitor
- TRK inhibitor
- Anthracycline
- BRAF inhibitor
- ALK inhibitor
- ROS inhibitor

Identifying patients that respond to platinum chemotherapy

**Identifying patients**

DDR\textsuperscript{mut}/Plat

DDR\textsuperscript{WT}/Plat

DDR\textsuperscript{mut}/No Plat

DDR\textsuperscript{WT}/No Plat

**Survival (%)**

**Time (weeks)**

DDR = DNA damage repair

= mutations in BRCA1, BRCA2, ATM, and PALB2

First line platinum-based combinations

**P = 0.058**
NCI-MATCH

- Molecular Analysis for Therapy Choice
- Advanced solid tumors, lymphoma, myeloma
- 24 treatment arms open
  — includes several low prevalence alterations seen in pancreatic cancer
- Includes DNA sequencing
- Open in many sites across the US

https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match#1

TAPUR

- Targeted Agent and Profiling Utilization Registry
- American Society of Clinical Oncology
- Advanced solid tumors, lymphoma, myeloma
- 15 treatment arms open: includes several low prevalence alterations seen in pancreatic cancer
- DNA sequencing required
- Open in many sites across U.S.

www.tapur.org
Linda’s Know Your Tumor Story

• Linda was referred to PanCAN and Know Your Tumor by her doctor
• She enrolled in Know Your Tumor
• Her test results showed a BRAF V600E mutation, rarely found in pancreatic cancer
• Linda enrolled in a clinical trial with treatments designed to target this mutation
• While on the trial, her first scan showed a 50% reduction in the tumor
• A later scan showed an additional reduction of 25% to the tumor
• Linda has gained 10 pounds, hiking 3 miles/day, and working half-time
• She is very thankful for the Know Your Tumor service!
**Summary:** Precision Promise

**What:** Largest precision medicine adaptive clinical trial platform designed specifically for pancreatic cancer patients

**Why:** Opportunity to accelerate the clinical trial process to expedite the discovery of new treatment strategies

**How:** Partner with clinicians, researchers and diagnostic and drug developers with the patient at the center of every decision

**Timeline:** Enroll first patient in 2017

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**Precision Promise**

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

**Coordinating center**
- Executive Committee
- Working Groups including industry
- Infrastructure for communication & information exchange

**Clinical Trial Consortium**
- 12 sites initially in U.S.
- Other Consortia to join in future
Initial Precision Promise Clinical Trial Sites

A very exciting endeavor that has the potential to change the way clinical research is conducted.

Steven Leach, MD
Memorial Sloan Kettering Cancer Center

"A very exciting endeavor that has the potential to change the way clinical research is conducted."

Precision Promise leverages a renewed, national focus to find altogether new treatments for this relentless and common form of cancer.

Robert Vonderheide, MD, DPhil
University of Pennsylvania
Clinical Examples of Benefit of Targeting Actionable Findings

Targeted therapy for DNA Damage Repair Deficiency

- BRCA-2 mutations in pancreatic cancer
  - 5 – 17% of pancreatic cancer patients carry BRCA-2 mutations
  - 3-5% in the general population
  - Up to 17% with a strong family history
- BRCA-1/2 (Breast Cancer 1/2, FANC S/D1) & PARP (Poly ADP ribose polymerase) are involved in the repair of single stranded DNA breaks
- Defects in BRCA-1/2, PALB2, FANC → increased sensitivity to DNA-damaging chemotherapy (e.g. platinum) and to PARP inhibition

Rowe and Glazer Breast Cancer Research, 2010
Goggins, M. Cancer Res, 1996
Murphy KM, Cancer Res, 2002
Ozçelik, H. Nat Genet, 1997
PARP Inhibition in BRCA-1/2-Associated Cancers

- Multiple clinical trials of PARP inhibitors (FDA-approved for ovarian cancer)
  - Consistent evidence of increased efficacy in BRCA-1/2 mutant tumors
- Anecdotal evidence in pancreatic cancer
  - MSKCC - 15 patients with known BRCA-1/2 mutations
    - 4 patients with PARP inhibitor-based therapy
    - 3PRs and one SD for 6 months
  - Multicenter phase II study of olaparib in 298 pts with recurrent, BRCA-1/2 mutated cancers
    - Tumor responses seen across spectrum of malignancies
    - Most pancreatic cancer patients received olaparib as third-line treatment

<table>
<thead>
<tr>
<th>Response, %</th>
<th>Ovarian (n = 193)</th>
<th>Breast (n = 62)</th>
<th>Pancreas (n = 23)</th>
<th>Prostate (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor response</td>
<td>31</td>
<td>13</td>
<td>22</td>
<td>50</td>
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<tr>
<td>SD ≥ 8 wks</td>
<td>40</td>
<td>47</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>PD</td>
<td>21</td>
<td>37</td>
<td>39</td>
<td>25</td>
</tr>
</tbody>
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Notable molecularly-stratified clinical trials: DDR

- POLO (NCT02184195) – Olaparib in germline BRCA mutated pancreatic cancer whose disease has not progressed on first line platinum-based chemotherapy.
  - Randomized Phase III, double blind, placebo controlled
  - Germline BRCA-1 or -2 mutation
- NCT01585805 - Gemcitabine + Cisplatin +/- Veliparib
  - Randomized Phase II trial
  - BRCA-1 or -2, or PALB2 mutation
- Studies being designed to test responsiveness of tumors with other alterations in the DNA Damage Repair pathway
  - NCT02677038 - Olaparib for BRCAiness Phenotype in Pancreatic Cancer
- Combination studies
  - NCT02498613 - A Phase 2 Study of Cediranib in Combination With Olaparib in Advanced Solid Tumors
  - NCT02723864 - Veliparib (ABT-888), an Oral PARP Inhibitor, and VX-970, an ATR Inhibitor, in Combination With Cisplatin in People With Refractory Solid Tumors
  - NCT02734004 - A Phase I/II Study of MEDI4736 in Combination With Olaparib in Patients With Advanced Solid Tumors. (MEDIOLA)
Notable molecularly-stratified clinical trials: stroma

- Halo 301 (NCT02715804) – PEGylated recombinant hyaluronidase in combination with Nab-Paclitaxel plus Gemcitabine in participants with hyaluronan-high stage IV previously untreated pancreatic ductal adenocarcinoma
  - Randomized Phase III, double blind, placebo-controlled
  - Above cut-off in IHC assay for hyaluronan (HA)

Notable molecularly-stratified clinical trials: Immunotherapy

- NCT01876511 – Pembrolizumab in patients with microsatellite unstable (MSI-H) tumors
  - Phase II, non-randomized
  - DNA assay for microsatellite stability – defect in mismatch repair leading to thousands of somatic mutations
  - Excellent response of positive colorectal cancer patients to anti-PD-1 to checkpoint inhibition by anti-PD-1 (pembrolizumab)
  - Arm for non-colorectal positive patients
  - <1% of pancreatic cancer patients are MSI-positive

Le et al, NEJM 5, 2509, 2015
Other Potential Targets

- Other single patient/anecdotal benefits
  - NTRK rearrangements
  - Alk/Ros rearrangements
- Meki + CDK4/6 Inhibitor
  - True responders in KRAS mutant NSCLC
- HER2 amplification
  - Improvement in OS with trastuzumab for gastric cancer
  - Benefit of trastuzumab + lapatinib in HER2+ CRC

Shapiro, TAT, 2016
Sharma, Nature Reviews Cancer, 2010 10; 241-253
Mazieres, et al, JCO, 2013

Pitfalls and Concerns on Precision Medicine in pancreatic cancer

- Feasibility
  - Sufficient tissue
  - Adequate resources
  - Bioinformatics
- Cost
  - Covered by insurance
  - Access to off indication therapies?
  - Is it cost effective?
    - Does it cost less than giving ineffective therapy?
- Resistance
- All these need to be taken into consideration
“Value” of Molecular Profiling in Pancreatic Cancer

• 25% highly actionable
  – 11% DNA repair deficient → PARP inhibitor
  – 5% STK11 mutation → mTOR inhibitor-based combination
  – 2% HER2 amplified → HER2 targeted therapy
  – 7% “other”
    • RET, NTRK, TOPO2A amplification, BRAF

• Is it “worth” testing 100 patients to benefit 25?
  – Or even just 11 (DNA repair deficient)

Resources for patients and caregivers

• Disease information
• Treatment options
• Pancreatic cancer specialists
• Diet and nutrition
• Side effects and symptom management tips
• Clinical trials, including a personalized clinical trial search through Clinical Trial Finder
• Survivor and Caregiver Network
• Support resources such as support groups
• Know Your Tumor
• The Patient Registry
• Educational Webinars

Call Patient Central
(877) 2-PANCAN or patientcentral@pancan.org
Monday-Friday, 7:00 am – 5:00 pm PST