Session II: Pancreatic Cancer Screening and Treatment
Friday, June 9, 2017 1:40 PM - 3:05 PM

FORCE 2017: Pancreatic Cancer

Dr. Jennifer Permuth: Risk factors and early detection efforts for pancreatic cancer.

Dr. Mokenge Malafa: Chemoprevention of pancreatic cancer: where are we in 2017?

Dr. Heloisa Soares: New Treatments for Pancreatic Cancer

FORCE 2017: Pancreatic Cancer
- Risk factors and early detection efforts for pancreatic cancer.

Jenny B. Permuth, PhD
Risk Factors and Early Detection Efforts for Pancreatic Cancer
by
Jennifer B. Parmuth, PhD, MS
Assistant Member
Departments of Cancer Epidemiology and Gastrointestinal Oncology
Moffitt Cancer Center
Tampa, Florida

I HAVE NO DISCLOSURES

Outline
• Introduction to pancreatic cancer (PC)
• Known risk factors
  • Environmental/Lifestyle
  • Genetic
  • Risk assessment
• Research on PC screening and early detection biomarkers
• Resources
INTRODUCTION

Leading Causes of Cancer Deaths in the US

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronch</td>
<td>14,900 27%</td>
<td>Long &amp; bronch</td>
<td>7,280 25%</td>
</tr>
<tr>
<td>Colorectum</td>
<td>27,350 8%</td>
<td>Head</td>
<td>40,610 18%</td>
</tr>
<tr>
<td>Prostate</td>
<td>20,720 6%</td>
<td>Colorectum</td>
<td>21,210 5%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,300 7%</td>
<td>Pancreas</td>
<td>20,750 7%</td>
</tr>
<tr>
<td>Liver &amp; hepato-biliary</td>
<td>14,830 6%</td>
<td>Liver &amp; hepato-biliary</td>
<td>15,020 4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,360 4%</td>
<td>Leukemia</td>
<td>20,530 4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,730 4%</td>
<td>Non-Hodgkin</td>
<td>20,530 4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11,240 4%</td>
<td>Non-Hodgkin</td>
<td>11,480 4%</td>
</tr>
<tr>
<td>Breast</td>
<td>9,490 3%</td>
<td>Breast</td>
<td>7,300 3%</td>
</tr>
<tr>
<td>All other</td>
<td>32,640 100%</td>
<td>All other</td>
<td>34,924 100%</td>
</tr>
</tbody>
</table>

American Cancer Society, 2017

Pancreatic Cancer is Projected to Become the 2nd Leading Cancer Killer around 2020

Rahib, Can Res 2014
PC poses numerous clinical challenges

- Usually very aggressive.
- Early, operable tumors are difficult to detect.
- Need strategies to identify those ‘at increased risk.’
- Most patients do not respond to standard treatment options.
- Quality of life (QOL) is sub-optimal.

RISK FACTORS AND ASSESSMENT

Modifiable and non-modifiable risk factors

- Average age: 71
- Males
- African American
- Ashkenazi Jewish
- Obesity
- Pancreatitis
- Diabetes
- Chronic & new infections
- Familial
- Inherited cancer syndrome
- Age, gender, race, and ethnicity
- Medical conditions
- Lifestyle/Environment
- Family history/genetics
### Sporadic vs. Familial vs. Inherited PC

Risk increases with # of affected first degree relatives (FDR):
- 2-4.6x (1 FDR)
- 3.6-4x (2 FDR)
- 32-57x (3 FDR)

- **Sporadic**
- **Familial**
- **Inherited Cancer Syndrome**

(Average lifetime risk = 1 in 67 (1.5%))


### Inherited Predisposition to PC

<table>
<thead>
<tr>
<th>Inherited Syndrome</th>
<th>Gene(s)</th>
<th>Risk by age 70-75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast and Ovarian Cancer</td>
<td>BRCA2, BRCA1, PALB2</td>
<td>4.5-8%</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11/LKB1</td>
<td>5%</td>
</tr>
<tr>
<td>Familial atypical multiple-mole melanoma (FAMMM)</td>
<td>CDKN2A</td>
<td>32-57x</td>
</tr>
<tr>
<td>Hereditary non-polyposis colorectal cancer</td>
<td>MSH2, MLH1, MSH6, PMS1, PMS2</td>
<td>3.7%</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
<td>1.7%</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>TP53</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Syndromes with chronic inflammation of the pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>PRTSS1, SPINK1</td>
<td>25-54%</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>CFTR</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

### Tidbits about BRCA2 carriers and PC

- 3-6x increased PC risk (vs. non-carriers)
- ~10% of BRCA2+ families have a relative with PC
- BRCA2 mutations are identified in 4-17% of families with familial PC, and are the most common alteration in this condition
- Prevalence of BRCA2 mutations in patients with sporadic PC is 4-7% vs. 0.2% in general population
- BRCA2 mutations (6174delT) are associated with 50-100% of unselected, sporadic PC in Ashkenazi Jews
- Patients with BRCA2+ PC are younger than counterparts with sporadic PC (63 vs 70 years old)
- The survival rate in patients with familial PC tends to be better than those with sporadic PC
Rare and common genetic variants contribute to PC susceptibility


What is my risk to develop PC?

Risk assessment is provided during genetic counseling (www.nsgc.org)

PancPro
- Provides probability of:
  - carrying a concerning mutation in a PC susceptibility gene
  - developing PC
- Takes into account:
  - cancer history for counselee and family members, age(s) at diagnosis, and current age/age at last follow-up

Wang, JCO, 2007

Absolute risk model
- Provides probability of:
  - developing PC
- Takes into account:
  - Established risk factors (age, sex, ethnicity, smoking history, diabetes, alcohol use, family history, body mass index, common genetic variants)

Klein, PLoS One, 2013
What can I do about my risk?

Is it possible to prevent PC cancer or detect it really early?

**PRIME OPPORTUNITY FOR EARLY DETECTION AND PREVENTION EFFORTS**

*Precursors* to pancreatic cancer

---

**Three pancreatic cancer precursors exist**

Distler et al (2014), *Biomed Research International*
IPMNs

- Account for up to 40% of the ~150,000 pancreatic cysts detected **incidentally** each year in the general US population.
- **Detected in high-risk cohorts.**
  - Found more often in familial than sporadic cases.
  - **Challenging to manage** due to the inability to predict:
    - which lesions can be safely monitored,
    - which are likely to progress to invasion, and
    - which may have an associated invasive component.

---

Need better strategies to identify ‘concerning’ IPMNs

- Only **accurate** way to determine severity
  - surgery & pathologic evaluation
- Consensus guidelines exist to predict IPMN severity
  - based on standard clinical and radiologic features.
  - inaccurate for at least 30-70% of cases!

---

‘Screening’ for Pancreatic Cancer

- Endoscopic ultrasound (EUS) +/- fine needle aspiration (FNA)
  - Can detect lesions <1 cm; FNA allows cytological sampling, but is invasive; operator dependent
- MRI-MRCP
  - MRI-MRCP= Magnetic Resonance Imaging (MRI)-Magnetic resonance cholangiopancreatography (MRCP)
  - Best visualization of cyst communication with main pancreatic duct
- Computed Tomography (CT)
  - Can visualize large lesions; accurate in depicting vascular invasion and metastases; radiation exposure
Comparison of selected screening strategy recommendations

<table>
<thead>
<tr>
<th>Strategy</th>
<th>International Cancer of the Pancreas Screening (CAPS) Consortium</th>
<th>American College of Gastroenterology (ACG)</th>
<th>National Comprehensive Cancer Network (NCCN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History</td>
<td>Family history observed in patients with a family history of pancreatic cancer.</td>
<td>Same age 50, 60, or 65 with FDRs or 70 or older</td>
<td>Same age 50, 60, or 65 with FDRs or 70 or older</td>
</tr>
<tr>
<td>BRCA</td>
<td>BRCA-related with an increased risk of pancreatic cancer.</td>
<td>Same age 50, 60, or 65 with FDRs or 70 or older</td>
<td>Same age 50, 60, or 65 with FDRs or 70 or older</td>
</tr>
<tr>
<td>Mucinous Cyst</td>
<td>Mucinous cyst with a high risk of malignancy.</td>
<td>Same age 50, 60, or 65 with FDRs or 70 or older</td>
<td>Same age 50, 60, or 65 with FDRs or 70 or older</td>
</tr>
<tr>
<td>Serous Cyst</td>
<td>Serous cyst with a high risk of malignancy.</td>
<td>Same age 50, 60, or 65 with FDRs or 70 or older</td>
<td>Same age 50, 60, or 65 with FDRs or 70 or older</td>
</tr>
<tr>
<td>Pancreatic Cyst</td>
<td>Pancreatic cyst with a high risk of malignancy.</td>
<td>Same age 50, 60, or 65 with FDRs or 70 or older</td>
<td>Same age 50, 60, or 65 with FDRs or 70 or older</td>
</tr>
</tbody>
</table>

- Nearly all studies reported precursor lesions (mostly IPMNs).
- Tests are complementary rather than interchangeable.
- Prevalence of lesions increased with age.
- CT, MRI, and EUS detected abnormalities in 11%, 33.3%, and 42.6% of individuals, respectively (Canto, 2012).
- Pancreatic cysts in the general population approximates 20-23%.
- Candidates for screening:
  - FDR of patient with PC from a familial PC kindred with >2 affected FDRs; patients with PJS, BRCA2, and HNPCC mutation carriers with 1 affected FDR.
  - No consensus on age to initiate screening or stop surveillance.
  - Initial screening should include EUS and/or MRI/MRCP.
  - Need long-term multicenter studies.
EARLY DETECTION BIOMARKERS FOR PC

Research in Progress at Moffitt Cancer Center

Goal: Prevent Pancreatic Cancer or Detect it Early

Low-risk/indolent
Surveillance

High-risk/aggressive
Surgery

Chemoprevention

MOLECULAR DATA
MicroRNAs (miRNAs) as attractive candidate biomarkers of early pancreatic malignancy

- regulate cancer-related pathways
- Each miRNA can regulate 1000's of genes.
- remarkably stable in tissue and biofluids
- dysregulated in PC vs. normal pancreas tissue
- a few candidate miRNAs differentiated between IPMNs and normal pancreas tissue (Habbe et al., 2009)

(Ruan et al., 2009) Cancer Letters
Developing a ‘liquid biopsy’ for pancreatic cancer: additional biomarkers we are studying at Moffitt

- Long non-coding RNAs (lncRNAs)
- Tumor DNA (ctDNA) mutations

Funding: Departmental Innovation Award (PI: Permuth)
Status: Project has been completed. Promising results obtained. Manuscript conditionally accepted at Scientific Reports.

Funding: DeBartolo Personalized Medicine Institute (PI: Permuth)
Status: Project is underway.

QUANTITATIVE IMAGING FEATURES

Radiomics
- High-throughput extraction of quantitative features (from standard-of-care images) into mineable data.

Slide courtesy of Yogendar Balagurunathan, PhD
Central/visceral adiposity as a contributor to IPMN development and/or progression?

- What about radiologic measures of obesity?
  - Total abdominal fat area (TAF)
  - Visceral fat area (VFA)
  - Subcutaneous fat area (SFA)
  - Visceral to subcutaneous fat ratio (V/A)

Vongsuvanh et al, Cancer Letters 2013
Central obesity measured by CT scan helps predict aggressive IPMNs

Permuth et al (2017), Cancer Biology and Medicine

PRE-CLINICAL MODELS

Precision medicine: Organoid model development

Applications: FAR-REACHING! Tumor modeling, study of molecular markers to target for prevention, diagnosis, and/or therapeutics.

Funding: Moffitt Team Science Award Mechanism (Co-PIs: Permuth and Jeong)

DeNicola
Eligibility

Males and females 18+ who present to the GI clinic, surgery, or endoscopy at MCC, UF, or SCCC/UM with a clinical suspicion for (or diagnosis of) a pancreatic lesion, mass, cyst or pancreatitis based on symptoms, imaging, or blood-work (and no prior treatment)

Healthy individuals 18+ without a self-reported personal history of pancreatic disease or related symptoms (companions and high-risk cohort)
Who can participate in the Florida Pancreas Collaborative (and how)

- Asymptomatic first or second degree relatives of a family member affected by pancreatic cancer
- Asymptomatic carriers of known PC predisposition mutations
- Individuals with a suspected or diagnosed condition affecting the pancreas.
- Feel free to send in the response form.
- Any q’s, email Dr. Jenny Permuth jenny.permuth@moffitt.org

Thanks to an interdisciplinary team
...and PC survivors and advocates

‘Know it. Fight it. End it. Wage Hope.’

FORCE 2017: Pancreatic Cancer

Dr. Jennifer Permutt: Risk factors and early detection efforts for pancreatic cancer.

Dr. Mokenge Malafa: Chemoprevention of pancreatic cancer: where are we in 2017?

Dr. Heloisa Soares: New Treatments for Pancreatic Cancer
Chemoprevention for Pancreatic Cancer: Where are we in 2017?
Mokenge P. Malafa, M.D., FACS
Professor and Senior Member
Moffitt Cancer Center, Tampa, FL

Chemoprevention For Pancreatic Cancer: Where are we in 2017?

Agenda

• Rationale for pancreatic cancer chemoprevention.
• Tocotrienol and pancreatic cancer.
  • Future directions.

Chemoprevention Definition

• Sporn (1976), use of drugs, biologics, or nutrients to inhibit carcinogenesis.
Chemoprevention of Pancreatic Cancer
Rationale (1)

US: Projected to be the 2nd most common cause of cancer death in 2030 (behind Lung; ahead of liver)\(^1\).

2012: 330,000 individuals die of pancreatic cancer every year worldwide\(^2\).

\(\checkmark\) A 10% decrease in PDAC would prevent >30,000 deaths/yr.


Value of Chemoprevention
Lessons from heart disease

Chemoprevention of Pancreatic Cancer
Rationale (2)

- Pancreatic carcinogenesis is a multi-year process thus providing opportunity to intervene.
**Chemoprevention of Pancreatic Cancer**

**Rationale**

- Early detection and effective prevention strategies are urgently needed.

**Clinical Pancreatic Oncology**

*Early detection and effective prevention strategies are urgently needed.*

Yachida S et al, Nature 2010

**Pancreatic Oncogenesis**

PRECURSOR LESIONS OF PANCREATIC ADENOCARCINOMA

PanIN: Pancreatic Intraductal Neoplasia
MCN: Mucinous Cystic Neoplasm
IPMN: Intraductal Papillary Mucinous Neoplasm

Chemoprevention of Pancreatic Cancer
Rationale (3)

- There are a significant number of individuals that are at high risk to develop pancreatic cancer.

Chemoprevention of Pancreatic Cancer
High risk groups

- Individuals with IPMN.
- Family history.
- Genetic syndromes.
- Pancreatic cancer survivors.
FDA-APPROVED CHEMOPREVENTION DRUGS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cancer</th>
<th>Year</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>Breast</td>
<td>1998</td>
<td>SERM</td>
</tr>
<tr>
<td>Raloxifen</td>
<td>Breast</td>
<td>2007</td>
<td>SERM</td>
</tr>
<tr>
<td>HPV Vaccine</td>
<td>Cervix/Vulva/Anus</td>
<td>2006</td>
<td>Immune</td>
</tr>
<tr>
<td>Photofrin</td>
<td>Esophageal</td>
<td>2003</td>
<td>Reactive Oxygen</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Skin</td>
<td>1970</td>
<td>DNA synthesis</td>
</tr>
<tr>
<td>Diclofenac Na 3%</td>
<td>Skin</td>
<td>2000</td>
<td>Unknown</td>
</tr>
<tr>
<td>5-aminolevulinic acid + PDT</td>
<td>Skin</td>
<td>1999</td>
<td>Kills precancerous cells</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>Skin</td>
<td>2004</td>
<td>Enhances immune response and promotes apoptosis</td>
</tr>
</tbody>
</table>

Clinical trials with pancreatic cancer chemoprevention agents

<table>
<thead>
<tr>
<th>Phase</th>
<th>Agent(s)</th>
<th>Population</th>
<th>Site</th>
<th>Status</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Curcumin</td>
<td>Advanced</td>
<td>MD Anderson</td>
<td>Published</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Curcumin + Gemcitabine</td>
<td>Advanced</td>
<td>Rambam, Israel</td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Curcumin, Gemcitabine, and Celecoxib</td>
<td>Advanced</td>
<td>Tel-Aviv Sourasky Medical Center, Israel</td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Curcumin</td>
<td>Advanced</td>
<td>Kyoto University, Japan</td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Celecoxib</td>
<td>Premalignant</td>
<td>Indiana Univ</td>
<td>Closed</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Vitamin E delta-tocotrienol</td>
<td>Presurgical</td>
<td>Moffitt Cancer Center</td>
<td>Published</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Genistein</td>
<td>Presurgical</td>
<td>UCLA</td>
<td>Pending</td>
<td></td>
</tr>
</tbody>
</table>

Chemoprevention For Pancreatic Cancer: Where are we in 2017?

Agenda

- Rationale for pancreatic cancer chemoprevention.
- Tocotrienol and pancreatic cancer.
- Future directions.
Development of a Pancreatic Cancer Chemoprevention Agent

- Data from Epidemiology studies.
- Published evidence from preclinical and clinical studies.

Preclinical testing
- In vitro screening.
- In vitro safety and efficacy.
- Detailed mechanistic studies in vitro and in vivo (Biomarker discovery).

Clinical trials
- Phase I- safety, PK, and dose-finding.
- Phase II- further safety, preliminary efficacy, validation of biomarkers.
- Efficacy evidence leading to NDA and FDA approval.

Nutrition and Pancreatic Cancer Protection

<table>
<thead>
<tr>
<th>Studies</th>
<th>Benefit</th>
<th>No Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Case Control</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* Increasing vegetable, fruit, and whole grain cereal consumption may protect against pancreatic cancer

Mo Malafa, MD

Pancreatic Cancer Whole grain decreases risk

- Risk of pancreatic cancer reduced by nearly 50% with whole grain consumption.
- How? Bioactive food components?

Chan, JM. *Epidemiol* 2007;166:1174-1185
Development of a Pancreatic Cancer Chemoprevention Agent

Agent Selection
- Data from Epidemiology studies.
- Published evidence from preclinical and clinical studies.

Preclinical Testing
- In vitro screening.
- In vivo safety and efficacy.
- Detailed mechanistic studies in vitro and in vivo (Biomarker discovery).

Clinical Trials
- Phase I: safety, PK, and dose-finding.
- Phase II: further safety, preliminary efficacy, validation of biomarkers.
- Efficacy evidence leading to NDA and FDA approval.
Tocotrienols in Pancreatic Cancer
Preclinical studies

- Delta-tocotrienol was the most effective vitamin E compound against pancreatic cancer.[1]
- Mice receiving delta-tocotrienol showed inhibition of pancreatic tumor growth[1] and carcinogenesis[2].
- Adequate levels of delta-tocotrienol in the pancreas of mice was achieved with well tolerated oral dosing[3].


Development of a Pancreatic Cancer Chemoprevention Agent

Agent Selection
- Data from Epidemiology studies.
- Published evidence from preclinical and clinical studies.

Preclinical testing
- In vitro screening.
- In vivo safety and efficacy.
- Detailed mechanistic studies in vitro and in vivo (Biomarker discovery).

Clinical trials
- Phase I: safety, PK, and dose-finding.
- Phase II: further safety, preliminary efficacy, validation of biomarkers.
- Efficacy evidence leading to NDA and FDA approval.

Tocotrienol and Pancreatic Cancer Clinical

Pharmacokinetics and safety of vitamin E, tocotrienol after single and multiple doses in healthy subjects with measurement of vitamin E metabolites

Phase I Study of Vitamin E δ-Tocotrienol in Pancreatic Neoplasia

Springett et al., EBIOMEDICINE, 2015.

Tocotrienol and Pancreatic Cancer Summary

- Tocotrienol is the most bioactive compound.
- More than doubles survival and inhibits metastasis in preclinical models.
- Targets several oncogenic pathways.
- Safe and reaches bioactive levels in the pancreas in Presurgical biomarker clinical trial.
Tocotrienol and Pancreatic Cancer: Hope for Chemoprevention

Agenda

• Rationale for pancreatic cancer chemoprevention.
• Tocotrienol and pancreatic cancer.
  • Future directions.

Development of a Pancreatic Cancer Chemoprevention Agent

Agent Selection

• Data from Epidemiology studies.
• Published evidence from preclinical and clinical studies.

Preclinical testing

• In vitro screening.
• In vivo safety and efficacy.
• Detailed mechanistic studies in vitro and in vivo (Biomarker discovery).

Clinical trials

• Phase I: safety, PK, and dose-finding.
• Phase II: further safety, preliminary efficacy, validation of biomarkers.
• Efficacy evidence leading to NDA and FDA approval.

Chemoprevention of Pancreatic Cancer Phase 2 in which high-risk group?

• Individuals with IPMN.
• Family history.
• Genetic syndromes.
• Pancreatic cancer survivors.

Mo Malafa, MD
Chemoprevention of Pancreatic Cancer Relapse

Rationale

- Metastasis rate of PDAC after resection and adjuvant therapy, with 5 year OS 28.8%.
- Metastasis initiating cells (Pancreatic Cancer Stem Cells/ Dormant disseminated tumor cells) and the niche in target organs supporting these cells are critical components of the mechanisms underlying PDAC relapse.
- Targeting PCSCs and/or the niche supporting them can prevent relapse.

1. ESPAC 4 Trial, ASCO 2016.

TOCOTRIENOL PANCREATIC CANCER
VEDT targets PCSCs

Husain et al., Oncotarget, 2017
TOCOTRIENOL PANCREATIC CANCER RELAPSE PREVENTION STUDY (TOPCARPS): A DOUBLE-BLIND, PLACEBO-CONTROLLED RANDOMIZED PHASE II TRIAL

Eligibility:
- Stage I/II PDAC.
- R0/R1 resection.
- Completed Adjuvant Rx.

Stratification:
- Resection status: R1/R0.
- Nodal status: N+ or N-.
- Tumor grade: Well or Moderate vs. Poor.
- Neoadjuvant Rx: Yes or No.
- Adjuvant Rx: Gem vs Gem + Abraxane vs Gem + Capecitabine

VEDT (600mg p.o. BID X 1 year) N=164
- Primary endpoint: PFS.
- Secondary endpoints: OS, and safety.
- Correlative studies: VEDT and metabolites, inflammatory and oxidative stress biomarkers.
- Statistics: 80% power / PFS 13.4 to 17.4 months.

Placebo (600mg p.o. BID X 1 year) N=164

Tocotrienol and Pancreatic Cancer: Hope for Chemoprevention
Summary
- There is potential for high impact with a chemoprevention strategy for pancreatic cancer.
- Tocotrienol is a promising agent in early phase trials.
- Need a home-run proof-of-concept trial to ignite the field.
Funding: NIH 1R01CA129227

FORCE 2017: Pancreatic Cancer

Dr. Jennifer Pernuth: Risk factors and early detection efforts for pancreatic cancer.

Dr. Mokenge Malafa: Chemoprevention of pancreatic cancer: where are we in 2017?

Dr. Heloisa Soares: New Treatments for Pancreatic Cancer

FORCE 2017: Pancreatic Cancer

- New Treatments for Pancreatic Cancer.

Heloisa Soares, MD, PhD
2017 Annual Joining FORCEs Against Hereditary Cancer Conference

Treatment of pancreatic cancer in patients with mutations associated with hereditary cancer

Heloisa P. Soares MD, PhD
Assistant member
Department of Gastrointestinal Oncology
Moffitt Cancer Center
Tampa, FL

The Scope of the Problem: For Pancreatic Cancer, Incidence = Mortality

<table>
<thead>
<tr>
<th>Stage Classification</th>
<th>% at Diagnosis</th>
<th>5-Yr Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>Locally advanced/ unresectable</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>Metastatic</td>
<td>53</td>
<td>2</td>
</tr>
</tbody>
</table>

Pancreatic Cancer by Stage (SEER Database)

Treatment

Metastatic disease

The Basis of Gemcitabine as the backbone for treatment regimens

Pivotal study defining role for gemcitabine as first-line treatment for patients with advanced pancreatic cancer

- Median survival (vs bolus 5-FU): 5.65 vs 4.41 mos. ($P = .0025$)
- 1-year survival: 18% vs 2%
- Clinical benefit*: 23.8% vs 4.8% ($P = .0022$)
- Response rate: 5.4% vs 0% ($P = N.S.$)

*Composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight. Clinical benefit required ≥4 weeks improvement in at least 1 parameter without worsening in others.

Phase III Studies: No Survival Benefit for Gemcitabine Combination (excluding target therapy) vs Monotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients, n</th>
<th>Control Arm, Mos</th>
<th>Study Arm, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine vs (gem + cisplatin)</td>
<td>192</td>
<td>6.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Gemcitabine vs (gem + oxaliplatin)</td>
<td>313</td>
<td>7.1</td>
<td>9.0</td>
</tr>
<tr>
<td>Gemcitabine vs (gem + 5-FU)</td>
<td>322</td>
<td>5.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Gemcitabine vs (gem + capcitabine)</td>
<td>533</td>
<td>6.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Gemcitabine vs (gem + pemetrexed)</td>
<td>565</td>
<td>6.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Gemcitabine vs (gem + irinotecan)</td>
<td>360</td>
<td>6.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Gemcitabine vs (gem + oxatecan)</td>
<td>349</td>
<td>6.2</td>
<td>6.7</td>
</tr>
</tbody>
</table>

The role of target therapy in pancreatic cancer is still limited

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Sample Size, n</th>
<th>Median Survival, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marimastat</td>
<td>Matrix metalloproteinase inhibitor</td>
<td>239</td>
<td>5.4 Gem Alone, 5.4 Gem + Drug X</td>
</tr>
<tr>
<td>Tipifarnib</td>
<td>Farnesyl transferase inhibitor</td>
<td>688</td>
<td>6.3 Gem Alone, 6.0 Gem + Drug X</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Oral TKI, EGFR</td>
<td>569</td>
<td>5.9 Gem Alone, 6.4 Gem + Drug X</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>mAb, VEGF</td>
<td>602</td>
<td>6.0 Gem Alone, 5.7 Gem + Drug X</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>mAb, EGFR</td>
<td>735</td>
<td>6.0 Gem Alone, 6.5 Gem + Drug X</td>
</tr>
</tbody>
</table>


Survival Results of Erlotinib trial

Emerging role of FOLFIRINOX

Prodigie - ACCORD 11 trial design

- Metastatic pancreatic cancer
- FOLFIRINOX
- Gemcitabine
- For both arms:
  - 5 cycles
  - 4 weeks of chemotherapy recommended

Indication:
- Carcinoma
- Performance status: 0 versus 1
- Location of the tumor: head versus other locations of the primary

Med Survival: 11.1 vs 6.8 months
Med PFS: 6.4 vs 3.3 months
1-ys OS: 48.4% vs 20.6%
ORR: 31.6% vs 9.4%
*FFX reduced QoL impairment compared with gemcitabine in patients with metastatic pancreatic cancer

Slide courtesy of Thierry Conroy
Safety: hematological AEs

<table>
<thead>
<tr>
<th>AE, % per patient</th>
<th>Folfirinox N=167</th>
<th>Gemcitabine N=169</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade 3/4</td>
<td>All Grade 3/4</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>79.9</td>
<td>54.8</td>
<td>18.7</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>7.2</td>
<td>5.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>90.4</td>
<td>94.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75.2</td>
<td>54.8</td>
<td>2.4</td>
</tr>
</tbody>
</table>

45.5% of the pts received G-CSF in the F arm vs 5.3% in the G arm

One toxic death occurred in each arm

Safety: main non-hematological AEs

<table>
<thead>
<tr>
<th>AE, % per patient</th>
<th>Folfirinox N=167</th>
<th>Gemcitabine N=169</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade 3/4</td>
<td>All Grade 3/4</td>
<td></td>
</tr>
<tr>
<td>Infection without neutropenia</td>
<td>6</td>
<td>1.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>70.5</td>
<td>9</td>
<td>0.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>61.4</td>
<td>14.5</td>
<td>43.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>87.3</td>
<td>23.2</td>
<td>78.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>73.3</td>
<td>12.7</td>
<td>30.8</td>
</tr>
<tr>
<td>Alopecia (grade 2)</td>
<td>32.5 (11.4)</td>
<td>3.0 (0.6)</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>64.8</td>
<td>7.3</td>
<td>83.8</td>
</tr>
</tbody>
</table>

Considerations

- Study was unintentionally biased with low number of head of pancreas lesions and thus, fewer patients with biliary ductal obstruction and stents → 50% patients have stents
- Age < 76 → 41% of patients are older than 75 ys
- PS 0 and 1 → What is the real % of PS2 patients in real life

But:
- Markedly positive survival results; exceed those seen in any previous randomized phase III trial in advanced PDAC—close to 1 year
- Was considered the new gold standard for first-line metastatic pancreatic cancer (for patients with good performance score)
Randomized Phase III Study of Weekly nab-Paclitaxel Plus Gemcitabine vs Gemcitabine Alone in Patients With Metastatic Adenocarcinoma of the Pancreas (MPACT)

DD Von Hoff, T Ervin, FP Arena, EG Chiorean, J Infante, M Moore, T Seay, SA Tjulandin, M Ma, MN Salah, M Harris, M Reni, RK Ramanathan, J Tabernero, M Hidalgo, E Van Cutsem, D Goldstein, X Wei, J Iglesias, MF Rischin®

nab-Paclitaxel is a registered trademark of Celgene Corporation.


Study Design

Planned N = 842

Stage IV
No prior treatment for metastatic disease
Karnofsky PS ≥ 70
Measurable disease
Total bilirubin ≤ ULN

nab-Paclitaxel
125 mg/m² IV qw 3/4 weeks

Gemcitabine
1000 mg/m² IV qw 3/4 weeks

Gemcitabine
1000 mg/m² IV qw for 7 weeks then qw 3/4 weeks

Overall Survival

Median OS: 8.5 versus 6.7 months
1ys OS: 35% vs 22%

Hazard ratio for death: 0.72 (95% CI, 0.62-0.83)
P=0.001 by stratified log-rank test

No. at Risk
nab-Paclitaxel-Gemcitabine
532 457 269 260 108 67 46 27 16 9 4 1 2 0

Gemcitabine
431 357 269 260 108 67 46 27 16 9 4 1 2 0
Progression Free Survival

Median PFS: 5.5 versus 3.7 months

By investigator was 29%

Toxicity

<table>
<thead>
<tr>
<th>AEs</th>
<th>nab-P (n = 421)</th>
<th>Gem (n = 402)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 grade 3 treatment-related AE</td>
<td>77</td>
<td>51</td>
</tr>
<tr>
<td>Grade ≥3 hematologic AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Receipt of growth factors</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Grade ≥3 non-hematologic AEs in &gt;5% pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>17</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Pancreatic ductal adenocarcinoma (PDAC) remains one of the greatest challenges in oncology

- Around 95 percent of pancreatic tumors are driven by mutations in a gene called KRAS, which signifies a very aggressive and treatment-resistant tumor. Mutated KRAS has been dubbed "undruggable"

- Pancreatic tumors are surrounded by more dense fibrotic tissue, known as the stroma, than are most other solid tumors

- A 2016 study identified four subtypes of pancreatic cancer based on molecular changes
Pancreatic cancer as a hereditary disease

- An estimated 10 to 15 percent of PCs are attributable to genetic causes
- Approximately 5 to 10 percent of individuals with PC have a family history of the disease
- There are two broad categories of hereditary risk for PC:
  - Genetic predisposition syndromes associated with PC
  - Familial pancreatic cancer (FPC), which is defined as a family with a pair of affected first-degree relatives (parent-child or sibling pair) who do not meet criteria for a known PC-associated genetic predisposition syndrome

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mutation(s)</th>
<th>Lifetime risk of pancreatic cancer, percent</th>
<th>Cause(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited hereditary cancer</td>
<td>BRCA1</td>
<td>7-10</td>
<td>Mutation in DNA repair genes</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>BRCA1</td>
<td>50-90</td>
<td>Mutations in DNA repair genes</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>BRCA1</td>
<td>0-10</td>
<td>Mutations in DNA repair genes</td>
</tr>
<tr>
<td>Hereditary non-polyposis colorectal cancer (HNPCC)</td>
<td>BRCA1</td>
<td>10-30</td>
<td>Mutations in DNA repair genes</td>
</tr>
</tbody>
</table>

BRCA

- Mutations in BRCA1 and BRCA2 are the most prevalent germline mutations
- BRCA1 and BRCA2 are DNA damage response (DDR) genes

How can we use this knowledge to treat pancreatic cancer?

- PARP and BRCA1/2 normally function to repair daily DNA damage
- Allows cells to grow in a healthy way
- Too much DNA damage -> cell death
Pre-clinical data

- Selectively inhibition of growth of cells with defects in either BRCA1 or BRCA2 genes
- *In vitro* models: cells with BRCA mutations > 1000 times more sensitivity to PARP inhibitors than wild-type cells
- *In vivo* models using PARP inhibitors also showed promising results

Clinical studies

**RUCAPANC**: An open-label, phase 2 trial of the PARP inhibitor rucaparib in patients (pts) with pancreatic cancer (PC) and a known deleterious germline or somatic BRCA mutation.

*J Clin Oncol* 34, 2016 (suppl; abstr 4110)

**Summary:**
- 19 patients who progressed after 1 or 2 chemotherapy regimens received oral rucaparib daily until disease progression.
- 79% had a BRCA2 mutation by local testing
- ORR was 11% (1 partial response [PR] and 1 complete response [CR]).
- Disease control rate (PR or stable disease [SD] for ≥ 12 weeks) was 32% (6/19) in all pts
  - 50% (3/6) in pts with only 1 prior regimen
- Enrollment was stopped due to lack of responses in the first 15 pts evaluated; the 3 PRs occurred in the last 4 pts enrolled
Common treatment-emergent AEs (in ≥20% of patients) included nausea (63.2%) and anemia (47.4%).

The most common treatment-emergent grade ≥3 AE was anemia (31.6%).

Rucaparib provided clinical benefit to several patients (disease control rate, 31.6%; 95% CI, 12.6%–56.6%) with advanced BRCA mut pancreatic cancer

- Less heavily pretreated patients derived durable clinical benefit, which warranted investigating rucaparib earlier in the treatment course of patients with BRCA mut pancreatic cancer

- Rucaparib had an acceptable safety profile

- These findings will inform future rucaparib study designs in patients with advanced BRCA mut pancreatic cancer

Ongoing PARP inhibitors clinical trials

POLO: A Phase III, Randomised, Double Blind, Placebo Controlled, Multicenter Study of Maintenance Olaparib Monotherapy in Patients With BRCA Mutated Metastatic Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

NCI 8993: A Randomized Phase 2 Study of Gemcitabine, Cisplatin +/- Veliparib in patients With Pancreas Adenocarcinoma and a known BRCA/ PALB2 Mutation

NCT01498865: A Phase III Study of ABT-888 (Veliparib) in Combination With 5-fluorouracil and Oxaliplatin (Modified FOLFOX-6) in Patients With Metastatic Pancreatic Cancer

NCT02890355: Randomized Phase II Study of 2nd Line FOLFIRI Versus Modified FOLFIRI With PARP Inhibitor ABT-888 (Veliparib) (NCT-737674) in Metastatic Pancreatic Cancer
Other ongoing trials

Other novel therapies and targets in pancreatic cancer

Ongoing early clinical trials in metastatic pancreatic cancer
We all need to keep trying!

• Slowly we are making progress in pancreatic cancer
• Understanding the tumor biology is key to advance in the field
• Clinical trials! Clinical trials! Clinical Trials!

Thank you to all my patients and families!