Session II: Pancreatic Cancer Screening and Treatment
Friday, October 7th 1:40 PM - 3:05 PM

FORCE 2016: Pancreatic Cancer

Agenda

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

Dr. Mokenge Malafa: Chemoprevention of pancreatic cancer: where are we in 2016?

Dr. Heloisa Soares: New treatments for pancreatic cancer using PARP inhibitors and other agents.

FORCE 2016: Pancreatic Cancer

• Risk factors and early detection efforts for pancreatic cancer.
Chemoprevention for Pancreatic Cancer: Where are we in 2016?

Mokenge P. Malafa, M.D., FACS
Professor and Senior Member
Moffitt Cancer Center, Tampa, FL

Chemoprevention for Pancreatic Cancer

Agenda

• The value of chemoprevention.
• What it takes to develop an agent.
• Example of an agent in development.
• Conclusions and future directions.
Value of Chemoprevention
Lessons from heart disease

<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>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>

What does it take to develop a chemoprevention agent?

- Data from Epidemiology studies.
- Published evidence from preclinical and clinical studies.
- In vitro screening.
- Detailed mechanistic studies in vitro and in vivo (Biomarker discovery).
- Phase I- safety, PK, and dose-finding.
- Phase II- further safety, preliminary efficacy, validation of biomarkers.
- Efficacy evidence leading to NDA and FDA approval.
<table>
<thead>
<tr>
<th>Phase</th>
<th>Agent(s)</th>
<th>Population</th>
<th>Site</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Curcumin</td>
<td>Advanced</td>
<td>MD Anderson</td>
<td>Published</td>
</tr>
<tr>
<td>II</td>
<td>Curcumin + Gemcitabine</td>
<td>Advanced</td>
<td>Ramban, Israel</td>
<td>Pending</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>
</tr>
<tr>
<td>II</td>
<td>Celecoxib</td>
<td>Premalignant</td>
<td>Indiana University</td>
<td>Closed</td>
</tr>
<tr>
<td>I</td>
<td>Vitamin E delta-tocotrienol</td>
<td>Presurgical</td>
<td>Moffitt Cancer Center</td>
<td>Published</td>
</tr>
<tr>
<td>I</td>
<td>Genistein</td>
<td>Presurgical</td>
<td>UCLA</td>
<td>Pending</td>
</tr>
</tbody>
</table>


**The Vitamin E Family**

![Vitamin E Family Diagram](image)

**What is Tocotrienol?**

- Alpha-Tocopherol (T) is the well-known form of Vitamin E
- Both Tocopherol and Tocotrienol exist as one of four isomers: α, β, γ, δ, as determined by CH₃ group positions

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>Isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>α-Tocotrienol/Tocopherol</td>
</tr>
<tr>
<td>CH₃</td>
<td>H</td>
<td>β-Tocotrienol/Tocopherol</td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>γ-Tocotrienol/Tocopherol</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>δ-Tocotrienol/Tocopherol</td>
</tr>
</tbody>
</table>
Delta-Tocotrienol is widely available in the natural supplements industry

What does it take to develop a chemoprevention agent?

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

Pre-clinical 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.
VEDT in PDAC: Preclinical

Vitamin E-\delta-Tocotrienol Levels in Tumor and Pancreatic Tissue of Mice after Oral Administration

Interactions between Vitamin E-\delta-Tocotrienol and the NF-\kappaB Pathway in Pancreatic Cancer

Prolonged survival and delayed progression of pancreatic intraepithelial neoplasia in LSL-Kras^{G12D}; Pdx1-Cre mice by vitamin E-\delta-tocotrienol

Research Article

Vitamin E-\delta-Tocotrienol Prolongs Survival in the LSL-Kras^{G12D}; Pdx1-Tet2^{D20Y} (Pdx-1-Cre [KPC]) Transgenic Mouse Model of Pancreatic Cancer

HHS Public Access

EGR-1/β3-Integrin Pathway Plays a Role in Vitamin E-\delta-Tocotrienol-induced Apoptosis in Pancreatic Cancer Cells
What does it take to develop a chemoprevention agent?

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

Pre-clinical 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.

VEDT in PDAC: Clinical

Pharmacokinetics and safety of vitamin E 3-isocrotonyl after single and multiple doses in healthy subjects with measurement of vitamin E metabolites

[Reference: [Link to article]]
VEDT in PDAC: Summary

- Most bioactive vitamin E compound.
- More than doubles survival and inhibits metastasis in preclinical models.
- Targets several oncogenic pathways.
- Safe and reaches bioactive levels in the pancreas in Phase 0/1 trials.

What does it take to develop a chemoprevention agent?

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

**Pre-clinical 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.
Rationale for Chemoprevention of Pancreatic Cancer Metastasis

- High recurrence and metastasis rate of PDAC after resection and adjuvant therapy, ranging up to 80%.
- Metastasis initiating cells (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 MICs and/or the niche supporting them can prevent relapse.

**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 / 8% 1-sided 1.74 months

**Placebo (600mg p.o. BID X 1 year)**
- N=164
Chemoprevention for Pancreatic Cancer

Summary

• There is potential for high impact with a chemoprevention strategy for pancreatic cancer.
• There are promising agents in early phase trials.
• Need a home-run proof-of-concept trial to ignite the field.

FORCE 2016: Pancreatic Cancer

• New Treatments for Pancreatic Cancer using PARP inhibitors and other agents.

Heloisa Soares, MD, PhD

10th Annual Joining FORCEs Against Hereditary Cancer Conference

New Treatments for Pancreatic Cancer using PARP inhibitors and other agents

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

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

• Familial pancreatic cancer accounts for about 5–10% of pancreatic cancers
  – mutations in BRCA1 and BRCA2 are the most prevalent germline mutations

• BRCA 1 and BRCA 2 are DNA damage response (DDR) genes
  – Inhibition of poly(ADP-ribose) polymerase (PARP) enzymes is a potential synthetic lethal therapeutic strategy in cancers harbouring specific DNA-repair defects, including those arising in carriers of BRCA1 or BRCA2 mutations

The role of PARP inhibitors in synthetic lethality

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.

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

RUCAPANC

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%)

RUCAPANC

• 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 warrants 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

**NCT01489665**: A Phase III Study of ABT-888 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) (NSC-737664) in Metastatic Pancreatic Cancer

Ongoing early clinical trials in metastatic pancreatic cancer

The role of immunotherapy in pancreatic cancer

Immunotherapy is a type of treatment that stimulates the body’s immune system to fight the cancer. They can work with the body’s immune system by:

- enhancing the body’s immune system to stop or slow tumor growth,
- changing cell signals that allow tumor growth,
- making tumors more susceptible to an immune system attack.
Immunotherapy in Pancreatic cancer

• Several studies with different immunotherapy strategies have been conducted in pancreatic cancer
  – Checkpoint Inhibitors/Immune Modulators
  – Therapeutic Vaccines
  – Adoptive Cell Therapy
  – Oncolytic Virus Therapies

Pancreatic cancer microenvironment is complex

We all need to keep trying!
Take home message

- 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!