Clinical Trials: A Clinician's Perspective Webinar

Presented by
Pancreatic Cancer Action Network
www.pancan.org

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Patient and Liaison Services (PALS)
PANCREATIC CANCER ACTION NETWORK
ADVANCE RESEARCH. SUPPORT PATIENTS. CREATE HOPE.

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Dan Laheru, M.D.
Associate Professor of Oncology
Ian T. MacMillan Professorship in Clinical Pancreatic Cancer Research
Co-Director, Skip Viragh Center for Pancreatic Cancer Research and Clinical Care
Sidney Kimmel Comprehensive Cancer Center
The Johns Hopkins University School of Medicine

Objectives

- Review of key facts for pancreatic cancer
- Review why we need clinical trials in pancreatic cancer
- Review the approval process for new drugs and the phases of clinical trials
- What are the processes in place to protect and inform potential study participants
- Review most common myths about clinical trials
- Review some innovative new ideas in pancreatic cancer research

What do we know about pancreatic cancer (2013)

- Still the 10th leading cause of cancer in the US, 4th leading cause of cancer related death
- Majority of patients (>80%) present with locally advanced unresectable/metastatic cancer
- Approximately 15-20% of pancreatic cancer have a genetic link
- Surgery is the only cure for locally confined cancer-chemotherapy and/or chemoradiotherapy can help delay the time for recurrent cancer
- Chemotherapy for advanced cancer includes now a number of treatments (gemcitabine, gemcitabine combinations, FOLFIRINOX)

Why do we need clinical trials for pancreatic cancer?

- There is still so much to learn about pancreatic cancer!
- How does pancreatic cancer grow and develop and spread?
- How does it develop resistance to treatment?
- How do we use the information that we have learned from basic science research to help us develop new treatments?
- How do we use treatments more effectively?
- How can we treat the symptoms associated with pancreatic cancer (pain, ascites, biliary and bowel obstruction, weight loss, bleeding, blood clots)?
- How do we prevent pancreatic cancer from developing in the first place?

How do new drugs get FDA approved for use?

- Pre-clinical development
  - typically in a cancer relevant animal model
  - significant achievement in pancreatic cancer with the development of a pancreatic cancer specific mouse model by Dr. Tuveson
  - Develop rationale for testing in human studies
  - Develop understanding how the body affects the metabolism of the drug (Pharmacokinetics or pK)
    - Examples- how is the drug broken down; how quickly is it broken down; what are the interactions with other drugs
  - Develop an understanding of what the drug does to the body (pharmacodynamics or PD)
    - Examples-
      - a rash is thought to be related to tarceva and the degree of rash may also mean the drug is more sensitive;
      - a decrease in the level of a particular growth pathway in a blood sample may be a marker for clinical response to a drug

Phase I Studies

- Work from pre-clinical studies can provide some suggested starting points but the dosing and schedule of treatment in human cancers is not known
- The primary goal of a phase I study is to identify a "maximally tolerated dose (MTD)" the highest dose that is safely tolerated
- Other endpoints include identifying how the drug is broken down by the body, interactions with other drugs
- Phase I studies often are open to a number of cancer types
- These studies use increasing doses of drug (pre-determined) also known as dose cohorts
- A few patients are often enrolled at each cohort
- While shrinkage of tumors and response to treatment are important , this is not the primary goal of a phase I study

Phase II studies

- A study will move from phase I to phase II if there is any meaningful clinical activity from the phase I study
- The phase II study will often focus on a particular cancer type and often involve more patients than a phase I
- The phase II treatment dose is the Maximum tolerated dose (MTD) identified from the phase I study
- The goals of the phase II are to identify clinical efficacy
  - decrease in size of tumor by imaging
  - measure other clinical information such as time to cancer progression, survival
  - get a better understanding for the safety of the drug
  - identify any potential surrogate markers for efficacy (Pharmacodynamic markers)

Phase III studies

- A study will move from phase II to phase III if there is significant activity in a new drug or a new drug in combination with standard treatment
- Phase III studies are often randomized (standard of care treatment versus new treatment or standard of care versus standard of care + new drug)
- The goal of the phase III is to identify a statistically significant improvement in a key endpoint (for example improvement in overall survival)
- If there is a significant improvement with the new treatment, then the new drug will be submitted for approval to the FDA
  - The approval time can take several weeks to several months

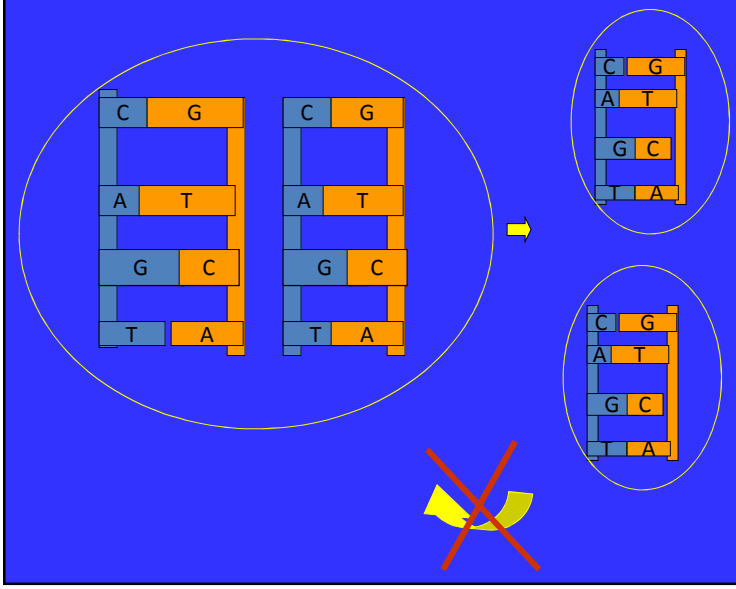
What are the processes in place to protect and inform potential study participants?

- Clinical trials have to be approved by the individual institutions. These studies have to be followed exactly
- If there is a new drug being tested or an approved drug for another cancer being tested, an Investigational New Drug (IND) will have to be filed with the FDA and approved. The FDA will need to see approval from the institution. These types of studies also have a study sponsor and is separate from the role of Principal Investigator of the study
- Conflicts of interest (financial, academic) are disclosed and updated yearly
- If this is a study sponsored by a pharmaceutical company, this study will have to be approved by pharma and by institution
- For multi-institutional studies, each institution will have to approve
- Studies need to be renewed every year
- Potential participants are provided with an informed consent of the study prior to enrollment. Once consented the potential participant must meet study eligibility
- For pharmaceutical sponsored studies or multi-institutional studies, study participants names are not shared and are therefore protected
- If any new safety or efficacy information is identified, this information will be shared with the institutional IRB, FDA, study sponsor and study participants

Common myths about clinical trials

- In a clinical trial, you are a human guinea pig in nothing more than an experiment
- Because you are being cared for at an academic institution, all patients treated there must take part in a study
- Once you are enrolled in a study you must continue on study even if you change your mind
- Health insurance will not cover the costs of a cancer clinical trial
- If you take part in a study, you might receive a placebo instead of real medicine
- You should enroll in a study only if there are no other options left

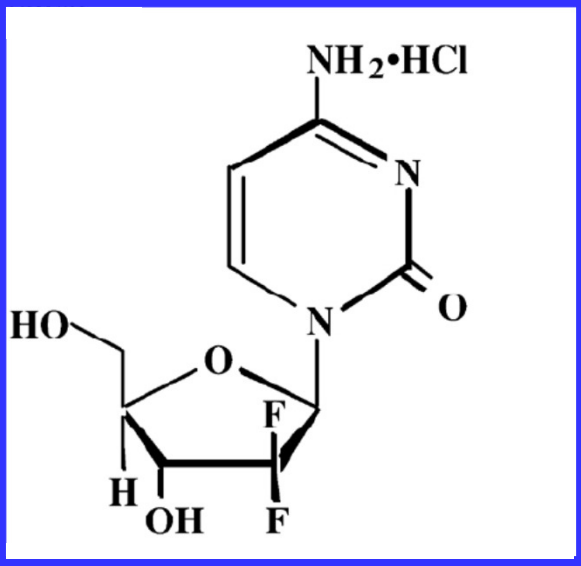
How does chemotherapy work?

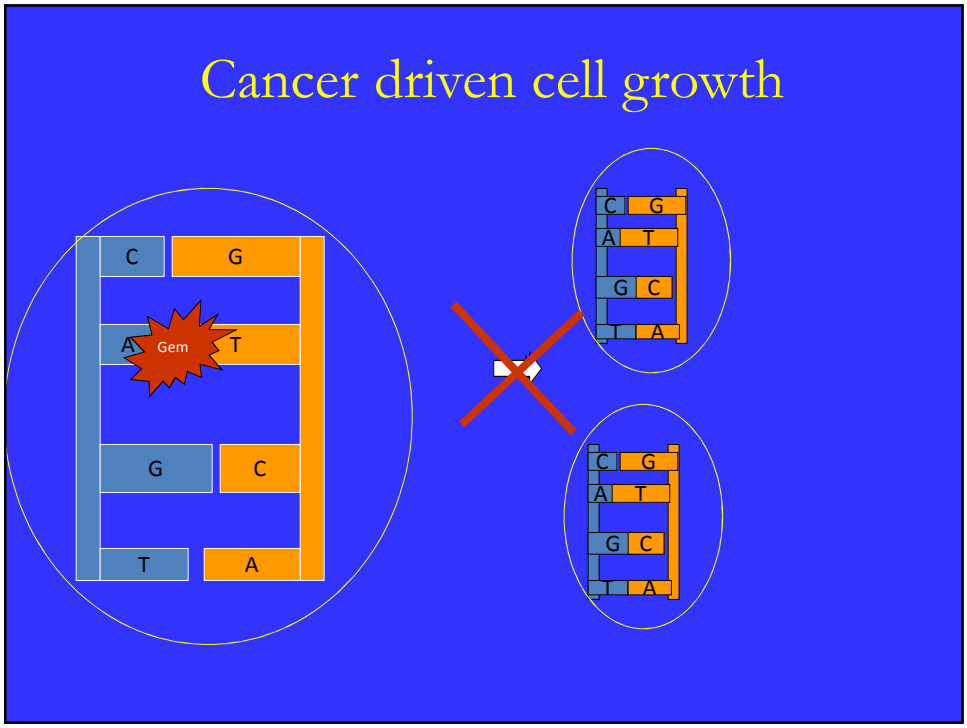


Approved chemotherapy drugs for pancreatic cancer

- Gemcitabine (gemzar)
- Erlotinib (Tarceva)
- Capecitabine (Xeloda)
- Oxaliplatin (not FDA approved but in NCCN guidelines and in NCCN drug compendium)

Gemzar ® (Gemcitabine): How does it work?




Cancer driven cell growth
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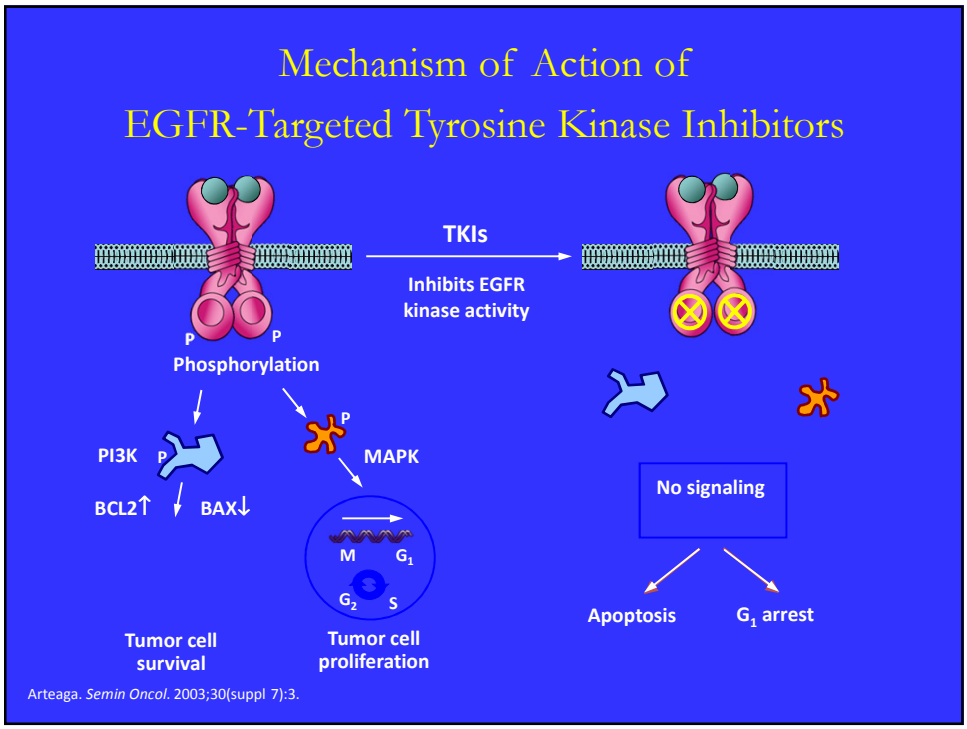
Mechanism of Action of
EGFR-Targeted Tyrosine Kinase Inhibitors
TKIs
Inhibits EGFR
kinase activity
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P
Phosphorylation
PI3K
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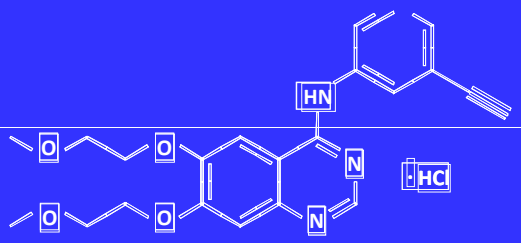
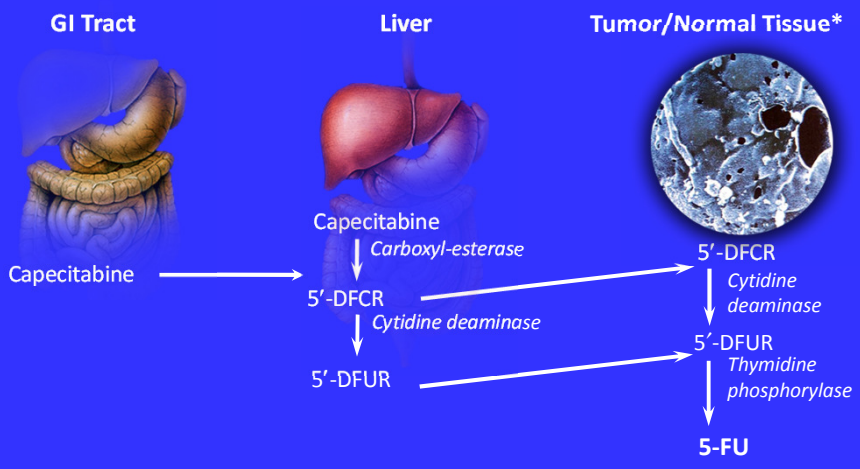
BCL2↑
BAX↓
P
MAPK
M
G1
G2
S
Tumor cell
survival
Tumor cell
proliferation
No signaling
Apoptosis
G1 arrest
Arteaga. Semin Oncol. 2003;30(suppl 7):3.

TARCEVA® (erlotinib)



- Quinazolinamine-derived small-molecule inhibitor of the EGFR kinase
- TARCEVA inhibits the intracellular phosphorylation of the tyrosine kinase associated with EGFR

Xeloda ® (Capecitabine)



Common Chemotherapy Combinations

- Gemcitabine + Taxotere + Xeloda (GTX)
- FOLFIRINOX
- Gemcitabine + nab-paclitaxel
- Gemcitabine + cisplatin
- FOLFOX
- Xeloda + Oxaliplatin

Gemcitabine/Taxotere/Xeloda (GTX)

- Schedule

Gemcitabine IV days 4 and 11 of a 21 days cycle

Taxotere IV days 4 and 11 of a 21 day cycle

Xeloda by mouth start with 500 mg tablets X 2 twice a day X 14 days of a 21 day cycle

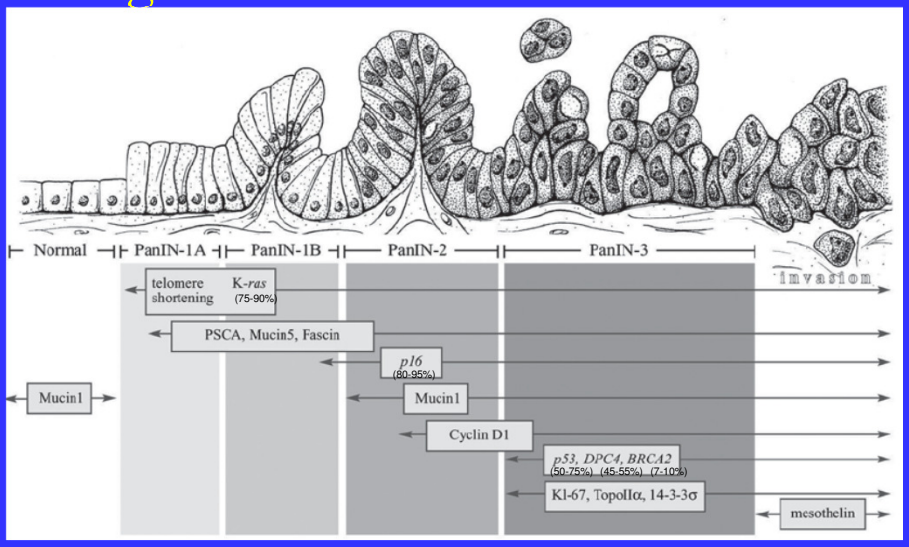
FOLFIRINOX (Oxaliplatin,Irinotecan, Leukovorin, 5-FU)

Chemotherapy Drug	Pre-medications/ Precautions	Route	Schedule
Oxaliplatin	Avoid exposure to cold (food, liquids, air) for 24 hours after each dose	IV	Day 1 every 2 weeks
Irinotecan		IV	Day 1 every 2 weeks
Leukovorin		IV	Day 1 every 2 weeks
5-Fluorouracil As bolus		IV	Day 1 every 2 weeks
5-Fluorouracil continuous infusion	Need a port	IV	day 1 over 46 hours every 2 weeks
Growth factor support		SQ	Day 3 every 2 weeks

New Ideas

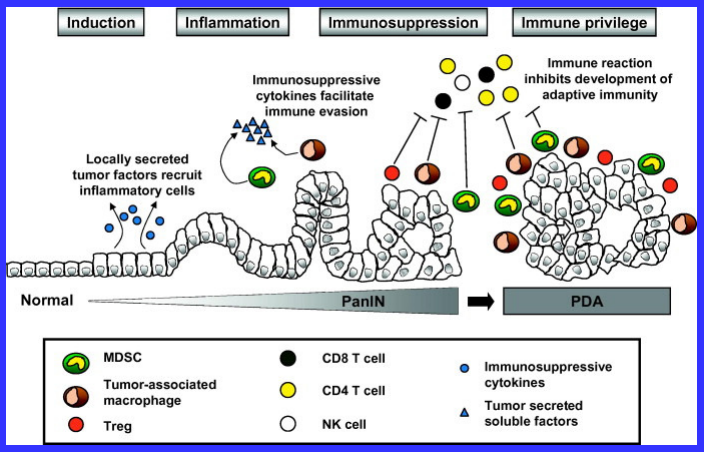
- Understanding how pancreatic cancer develops
- Understanding how immune system interacts with pancreatic cancer
- Pancreatic Cancer Sequencing
- New Targets
  - Tumor microenvironment
    - Nab-paclitaxel (abraxane)
    - hyaluronidase
  - CD40 ligand
- Chemosensitivity/Resistance
  - Cytidine deaminase
- Tumor metabolism
  - autophagy

Progression Model Pancreas Cancer



Courtesy of Dr. Ralph Hruban

Relationship between Immune system and pancreatic cancer progression model

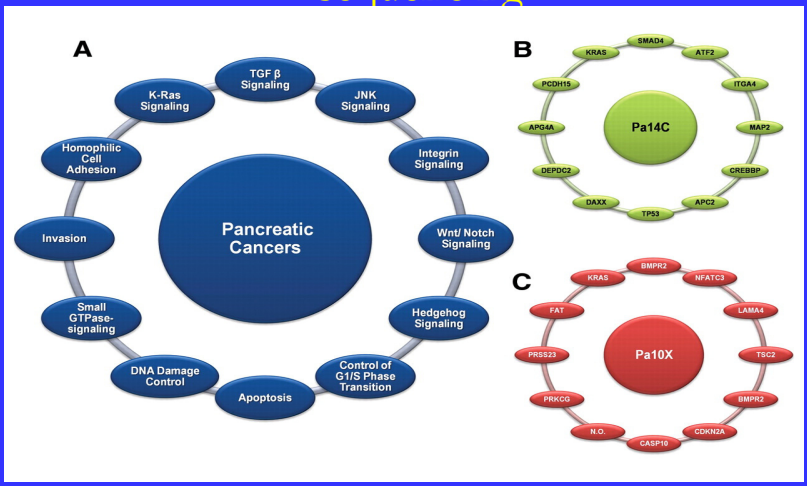


Vonderheide R et al: Cancer letters 2009; 279:1-7.

Clinical Trials using Immunotherapy in pancreatic cancer

- Whole cell pancreatic cancer vaccine
  - Studied in patients with resected pancreatic cancer and also in patients with metastatic cancer
  - In patients on resected pancreatic cancer studies who remain cancer free, immune system is able to recognize overexpressed pancreatic cancer protein (example: mesothelin)
  - Open at Johns Hopkins for patients with resectable pancreas cancer (NCT01595321 and NCT00727441)
- Next generation vaccines
  - Mesothelin, Kras peptide based vaccine
- Anti-Mesothelin modified lymphocytes
  - Uses a chimeric T cell antigen receptor (CAR) that recognizes mesothelin + IL-2 (NCT01583686)- open at NCI
- Vaccines + immune modulating drugs
  - Anti PD-1, anti CTLA-4
- Other immunotherapy approaches
  - CD40 antigen + gemzar in resectable pancreas ca followed by surgery and CD40 antigen + gemzar (NCT01456585)- open at U Penn

What have we learned from research so far? Lessons from pancreatic cancer gene sequencing

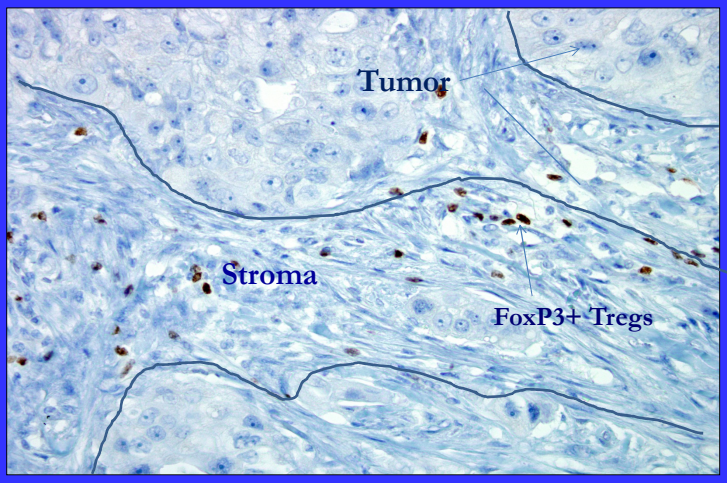


Vogelstein B et al: Science 2008;321:1801-6

Pancreatic cancer and tumor micro-environment

- Primary pancreatic tumor is known to be "hypovascular" by imaging
- Surrounding supporting environment (stroma) is known to hinder chemotherapy from penetrating the tumor
- The tumor microenvironment and systemic signals effectively inhibit a robust immune response
- Drugs that target the stroma + chemo are more effective than chemo alone in a pancreatic transgenic mouse model

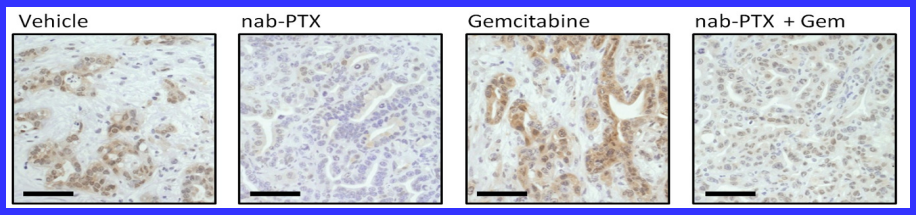
Pancreatic tumor and associated stroma



Courtesy of Dr. Elizabeth Jaffee

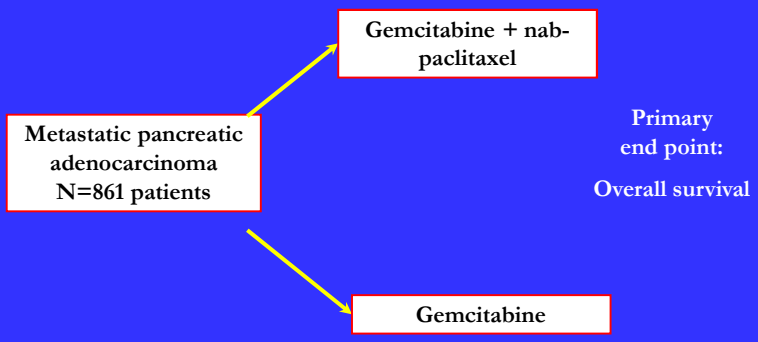
New Target: nab Paclitaxel

Nab-Paclitaxel potentiates Gem activity by reducing cytidine deaminase levels in transgenic kras pancreas mouse model (presumably by degrading ROS)



Tuveson et al: Cancer Discovery 2012;2:260-9.

Gemcitabine + nab-paclitaxel: MPACT study



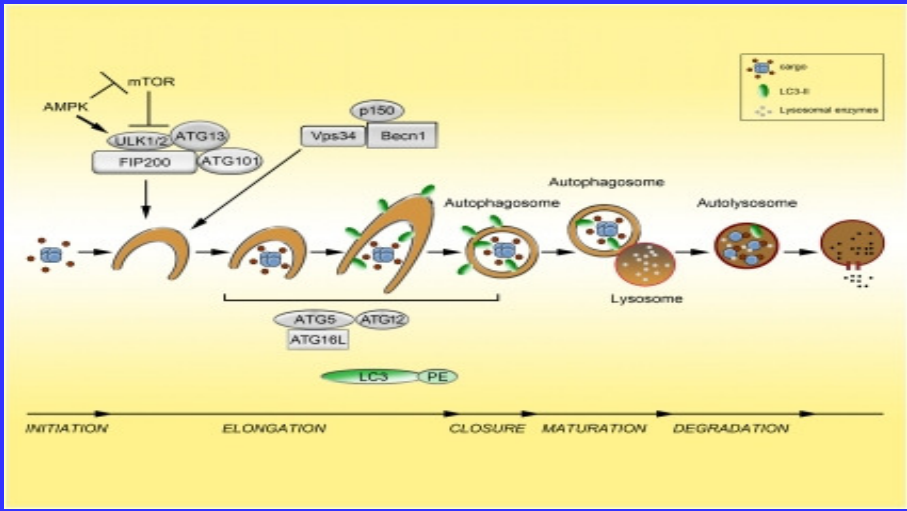
Gemcitabine: 1000 mg/m2 weekly X 3 every 4 weeks
Nab-paclitaxel 125 mg/m2 weekly X 3 every 4 weeks

Dr. Dan Von Hoff, Principal Investigator

Clinical trials using stroma depleting agents in pancreatic cancer

- Recombinant Hyaluronidase (Halozyme- PEGPH20) + Gemzar for metastatic cancer (NCT01453153)
- Nab-paclitaxel (Celgene- randomized phase III gemzar - to be presented GI ASCO January 2013)
- Hedgehog inhibitor
  - Borderline resectable cancer (LDE-225 (Novartis)+ gemzar-NCT01431794 -open at Johns Hopkins
  - Metastatic cancer (IPI-926 (infinity) + FOLFIRINOX- NCT01383538 -open at UCSF

Autophagy and Pancreatic Cancer
NCT01506973- Gemzar + nab-paclitaxel + Hydroxychloroquine



Kimmelman A: Genes and Development 2011: 25(19) 1999-2010

Thank you for your participation

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If you have any questions about our Patient and Liaison Services (PALS) program, please contact (877) 272-6226 or e-mail pals@pancan.org.

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