PANCREATIC CANCER ACTION NETWORK®

TREATMENT APPROACHES FOR PANCREATIC CANCER

The webinar will begin shortly.

1

INTRODUCING OUR HOST

JULIE FLESHMAN JD, MBA

President and CEO, PanCAN

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THANK YOU TO OUR CURRENT SCIENTIFIC & MEDICAL AFFAIRS INDUSTRY MEMBERS

abbvie AstraZeneca FibroGen IPSEN Innovation for patient care

Pfizer RAFAEL Pharmaceuticals, Inc. "To Save a Life is To Save A Universe" TEMPUS TYME

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HOW TO PARTICIPATE

Q&A

Please enter questions in the Q&A box.

Our panelists will take your questions and comments at the end of the discussion.

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HOW WE'RE TAKING ON PANCREATIC CANCER

Research and Clinical Initiatives

Government Advocacy

Patient Services

Community Engagement

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IT'S CLINICAL TRIALS AWARENESS MONTH

PanCAN's STATEMENT REGARDING CLINICAL TRIALS

Pancreatic cancer patients who participate in clinical research have better outcomes. Every treatment available today was approved through a clinical trial. The Pancreatic Cancer Action Network strongly recommends clinical trials at diagnosis and during every treatment decision.

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TREATMENT APPROACHES FOR PANCREATIC CANCER

Vincent Chung, MD, FACP
Clinical Professor Department of Medical Oncology
Clinical Director Early Therapeutics Program
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Management of Pancreatic Cancer

Vincent Chung, MD, FACP
Clinical Professor Department of Medical Oncology
Clinical Director Early Therapeutics Program
City of Hope

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CLINICAL TRIAL DEVELOPMENT PROCESS

PHASE I Evaluation of **safety** and **tolerability** of a new therapy in humans

PHASE II Evaluation of **efficacy** in larger groups of pancreas cancer patients

This is why we perform tumor biopsies

PHASE III Confirm if new therapy is **better** than the current "standard"

No → Why not?

Yes → Why not for some patients?

FDA-approval

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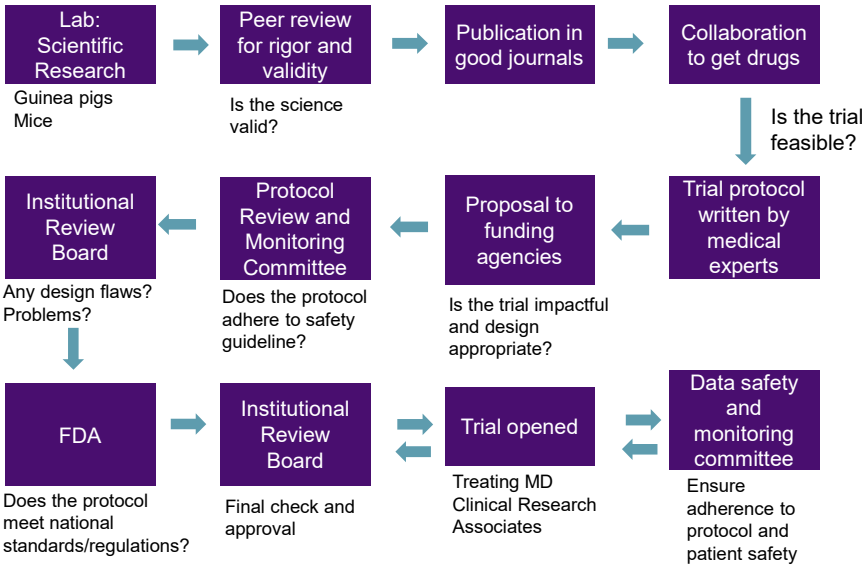
CLINICAL TRIAL DEVELOPMENT IS HIGHLY REGULATED



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COMMON MISCONCEPTIONS/MYTHS ABOUT CLINICAL TRIALS

MYTHS	TRUTHS
Patients are treated as guinea pigs.	***Patient safety is a top priority*** in clinical trials. Patients are closely monitored and have rights that protect them.
Clinical trials are for patients that have run out of options.	A clinical trial is always an option, regardless of when the patient was diagnosed or what treatments they received.
Patients may receive a placebo, not a treatment.	Placebos are never used in replacement of standard of care.
Clinical trials are more expensive for the patient.	Federal law requires most health insurance plans cover the routine care costs of a clinical trial. Research costs are those related to taking part in a trial, which are covered by the trial sponsor.
Participation in clinical trials is not important.	Participation in clinical trials is crucial. Every treatment available today was approved through a clinical trial.

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Overview – Management of Pancreatic Cancer

Clinical presentation of pancreatic cancer

Progress in the treatment of pancreatic cancer

- Adjuvant (after surgery)
- Neoadjuvant (before surgery)
- Metastatic
- Maintenance

Future directions

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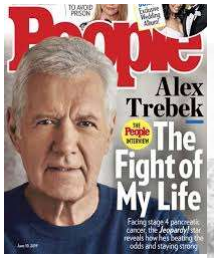
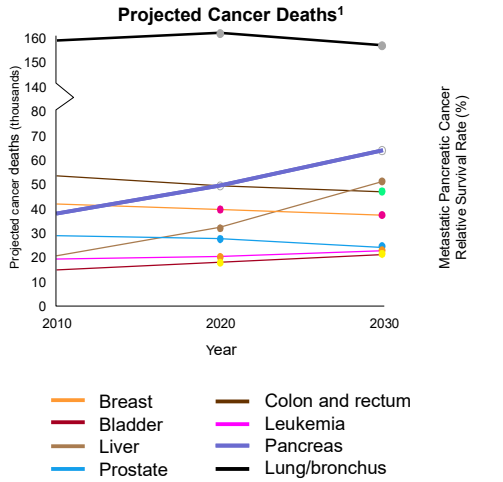
Scope of the Problem





Rahib L, *et al. Cancer Res.* 2014;74(11):2913-2921.

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Clinical Presentation

- Early stages are often difficult to diagnose
  - Most are asymptomatic
  - Painless jaundice – may be resectable

- In later stages the symptoms depend on the location of the tumor
  - Head – stomach ache
  - Tail – back pain

- Symptoms of advanced disease
  - Fatigue
  - Anorexia
  - Weight loss

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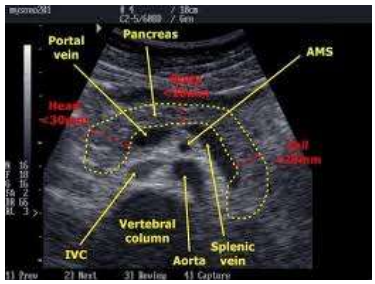
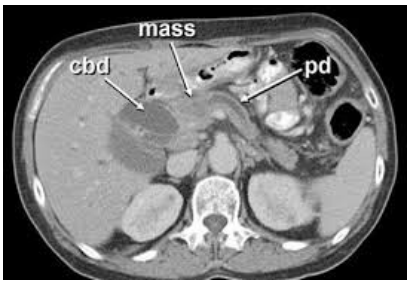
Making the Diagnosis





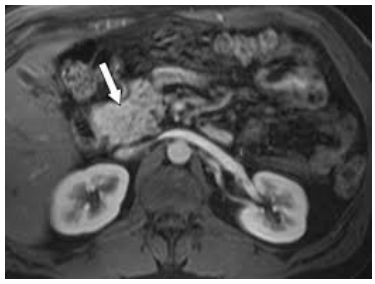
Ultrasound – operator dependent

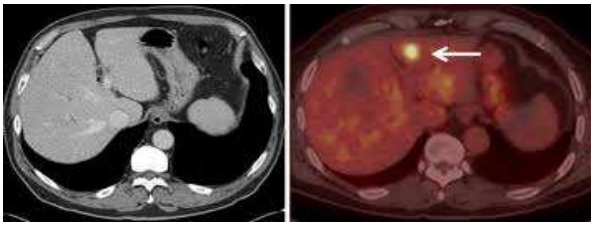
Pancreas protocol CT

- Thin slices through pancreas

MRI – Evaluating the liver

PET/CT – Prior to surgery





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Tumor markers: CA19-9

Most common elevated tumor marker in pancreatic cancer

May also be elevated with colorectal, lung, liver and ovarian cancer

Benign conditions can also elevate level

- Disease of hepatobiliary system, pneumonia, pleural effusion, renal failure and SLE

Generally CA19-9 >1000 implies advanced disease that is not amenable to resection (biliary obstruction can cause elevated CA19-9)

Cannot be used to make a diagnosis

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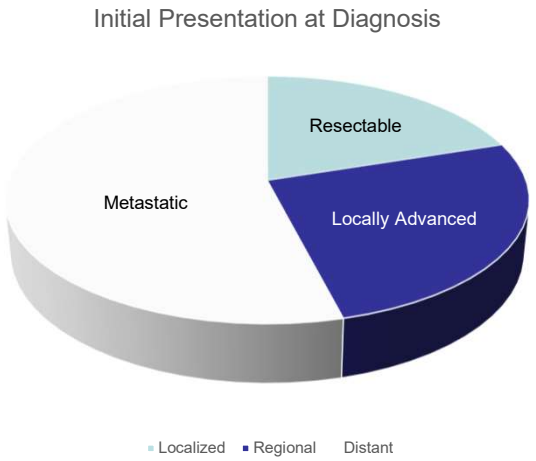
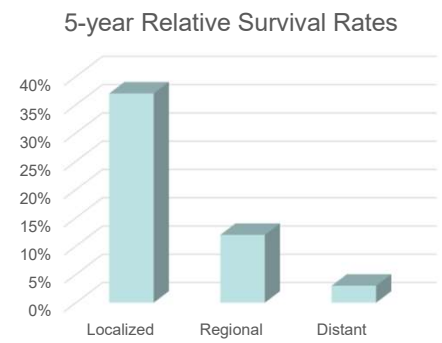
Diagnosis of Pancreatic Cancer is Usually Late





Based on people diagnosed with pancreatic cancer between 2009 and 2015
Data from American Cancer Society

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Adjuvant Treatment (Treatment after surgery)

	Pts Enrolled	Treatment	Results (Improved overall survival)
CONKO-001	368	Gemcitabine versus Observation	Gemcitabine
ESPAC-4	730	Gemcitabine + Capecitabine versus Gemcitabine	Gemcitabine + Capecitabine
PRODIGE 24	493	FOLFIRINOX versus Gemcitabine	FOLFIRINOX

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Take Home Points – Treatment After Surgery

mFOLFIRINOX is the standard treatment for good performance status patients

Removing the bolus 5FU and reducing the dose of irinotecan made the toxicity profile more manageable

- Grade 3/4 toxicity: Diarrhea 18.6%, Neuropathy 9.3%, Fatigue 11 %
- Challenging to receive chemotherapy after surgery due to side effects

Gemcitabine plus capecitabine or gemcitabine alone can be used for weaker patients

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Rationale for Neoadjuvant Treatment (Treatment Before Surgery)

Pancreas cancer is aggressive with most patients having recurrent disease

Patients have difficulty tolerating chemotherapy after surgery

Provides early treatment of micrometastatic disease

Primary tumor is intact and relatively well-perfused

Avoids surgery in patients with rapidly progressive disease

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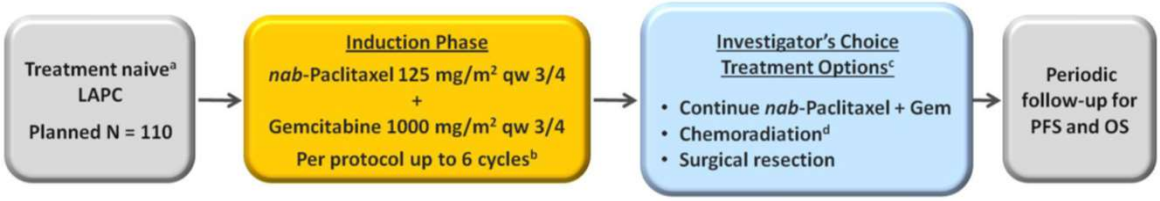
Phase 2 LAPACT Multicenter International Trial of nab-Paclitaxel Plus Gemcitabine for Patients with Locally Advanced Pancreatic Cancer

Rationale

- Approximately 30% of patients presenting with pancreatic cancer are locally advanced unresectable.
- Currently we have more effective chemotherapy regimens

Objective: To assess the safety and efficacy of 6 cycles of induction therapy.

Primary Endpoint: Time to Treatment Failure



Presented By Pascal Hammel at 2018 Gastrointestinal Cancers Symposium

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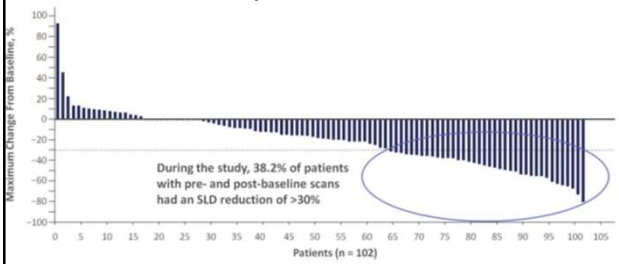
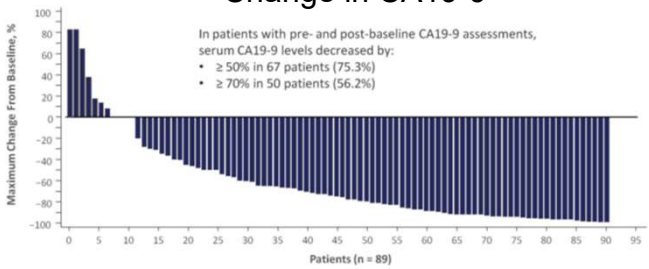
LAPACT - Results

Response Rate



Change in CA19-9



Overall response rate 33% and Disease control rate 78%

Nab-Paclitaxel plus gemcitabine induction allowed conversion from unresectable to resectable in 15% of the patients

Presented By Pascal Hammel at 2018 Gastrointestinal Cancers Symposium

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JAMA Oncology | Original Investigation

Total Neoadjuvant Therapy With FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma
A Phase 2 Clinical Trial

Janet E. Murphy, MD, MPH; Jennifer Y. Wo, MD; David P. Ryan, MD; Wenqing Jiang, MS; Beow Y. Yeap, ScD; Lorraine C. Drapek, NP, PhD; Lawrence S. Blaszkowsky, MD; Eunice L. Kwak, MD, PhD; Jill N. Allen, MD; Jeffrey W. Clark, MD; Jason E. Faris, MD; Andrew X. Zhu, MD, PhD; Lipika Goyal, MD, MPhil; Keith D. Lillemoe, MD; Thomas F. DeLaney, MD; Carlos Fernández-del Castillo, MD; Cristina R. Ferrone, MD; Theodore S. Hong, MD

- 48 pts accrued (small study)

- **Treatment**

  8 cycles of FOLFIRINOX (every 2 weeks)
  - No vascular involvement - 5Gy x 5 with protons and capecitabine
  - Persistent vascular involvement – long course chemoXRT

Results

R0 resection rate 65%

Subset Analysis-Resected patients
- Median PFS 48.6 mos
- Median OS not reached

Murphey JE, et al. JAMA Oncology 2018.

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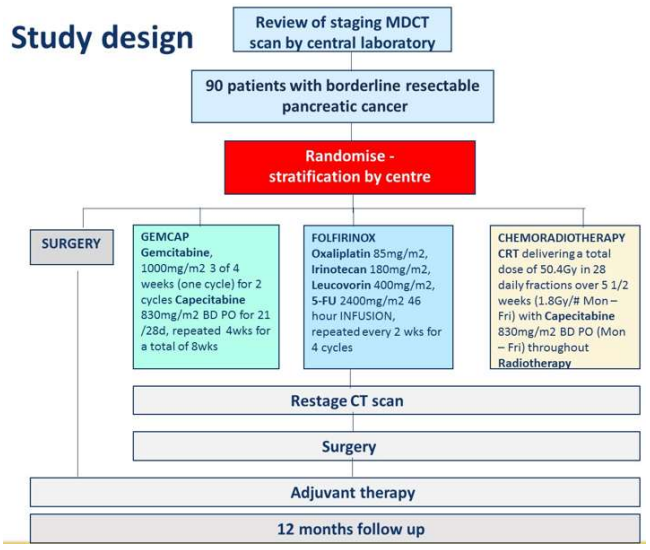
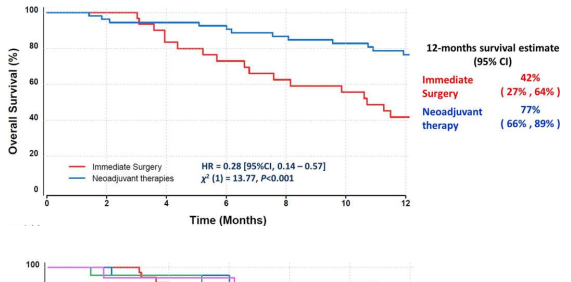
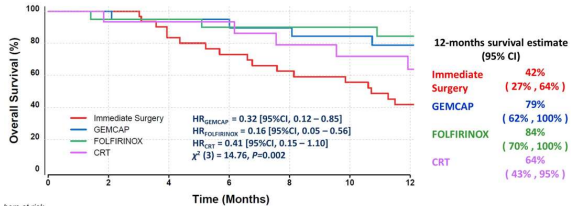
ESPAC-5F: Four-arm, prospective, multicenter, international randomized phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy (CRT) in patients with borderline resectable pancreatic cancer (ASCO 2020)







P Ghaneh, D Palmer, S Cicconi, C Halloran, E Psarelli, C Rawcliffe, R Sripadam, S Mukherjee, J Wadsley, A Al-Mukhtar, L Jiao, H Wasan, R Carter, J Graham, F Ammad, J Evans, C Tjaden, T Hackert, M Büchler, J Neoptolemos for the European Study Group for Pancreatic Cancer (ESPAC)

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Neoadjuvant Therapy: Key Points

Pancreatic cancer is a systemic disease - High recurrence rates after surgical resection

After surgical resection, patients have difficulty tolerating strong systemic chemotherapy like FOLFIRINOX

Neoadjuvant therapy improves R0 resection rates and distant metastasis free survival

Moving toward total neoadjuvant therapy (The role of radiation therapy is debatable)

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Treatment of Advanced Disease (Locally advanced or metastatic)

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Improvements in Survival and Clinical Benefit With Gemcitabine as First-Line Therapy for Patients With Advanced Pancreas Cancer: A Randomized Trial

By Howard A. Burris III, Malcolm J. Moore, John Andersen, Mark R. Green, Mace L. Rothenberg, Manuel R. Modiano, M. Christine Cripps, Russell K. Portenoy, Anna Maria Storniolo, Peter Tarassoff, Robert Nelson, F. Andrew Dorr, C.D. Stephens, and Daniel D. Von Hoff

160 pts enrolled

Gemcitabine versus 5FU

Primary endpoint: clinical benefit

Clinical benefit 23.8% vs 4.8%

Clinical Benefit Measures

1) Pain Intensity

2) Pain medication consumption

3) Performance status

4) Weight

Gemcitabine improved quality of life and overall survival

JCO. 1997. 15(6): 2403-2413.

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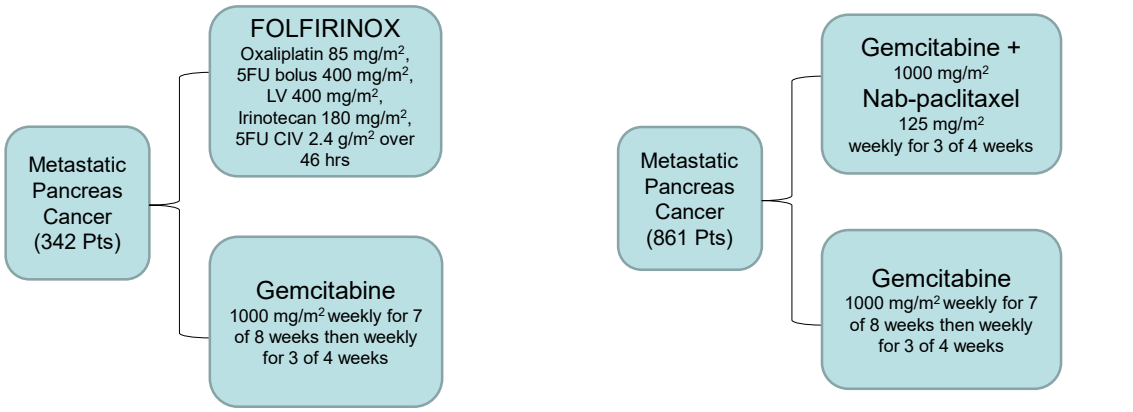
Pivotal Trials for Patients with Metastatic (Stage 4) Disease



Conroy T, et al. NEJM 2011.

Von Hoff D, et al. NEJM 2013.

Primary endpoint – overall survival

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Conclusions

mFOLFIRINOX (Partial response 31%) or gemcitabine + nab-paclitaxel (Partial response 23%) are appropriate first line treatments for patients with metastatic disease.

Decision based upon side effect profile and patient choice

Grade 3/4 toxicity	Neutropenia	Fatigue	Diarrhea	Neuropathy
Gemcitabine + nab-paclitaxel	38%	17%	6%	17%
FOLFIRINOX	45.7%	23.6%	12.7%	9%

- For weaker patients, gemcitabine remains the standard

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National Comprehensive Cancer Network® NCCN

NCCN Guidelines Version 1.2020
Pancreatic Adenocarcinoma

Summary

Always consider clinical trials

Adjuvant Treatment
- mFOLFIRINOX
- Gemcitabine and capecitabine (ESPAC-4)
- Gemcitabine (CONKO-1)
- Induction chemo then 5FU/XRT

Locally Advanced
- mFOLFIRINOX
- Gemcitabine + nab-paclitaxel
- ChemoXRT

Metastatic Treatment
- mFOLFIRINOX
- Gemcitabine + nab-paclitaxel
- Gemcitabine
- Gemcitabine + erlotinib (not used much)

Second-line Treatment
- Gemcitabine +/- nab-paclitaxel
- FOLFOX
- FOLFIRI
- Liposomal irinotecan + 5FU
- Pembrolizumab (MSI high)

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Maintenance Therapy for Pancreatic Cancer

Need to balance toxicities of the treatment with controlling the disease

FOLFIRINOX is the most effective therapy but also the most toxic

Neuropathy from oxaliplatin can be debilitating

Metastatic Disease (Maintenance Therapy)[k]

- Patients who have response or stable disease after 4–6 months of chemotherapy may undergo maintenance therapy.

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS	• If previous first-line FOLFIRINOX: ▸ FOLFIRI	• If previous first-line FOLFIRINOX: ▸ FOLFOX (category 2B) • Clinical trial	• If previous first-line FOLFIRINOX: ▸ Capecitabine • If previous first-line gemcitabine + nab-paclitaxel: ▸ Gemcitabine + nab-paclitaxel modified schedule (category 2B) ▸ Gemcitabine single agent (category 2B) • If previous platinum-based chemotherapy: ▸ Olaparib (only for germline *BRCA1/2* mutations)

National Comprehensive Cancer Network® NCCN Guidelines Version 1.2020
Pancreatic Adenocarcinoma

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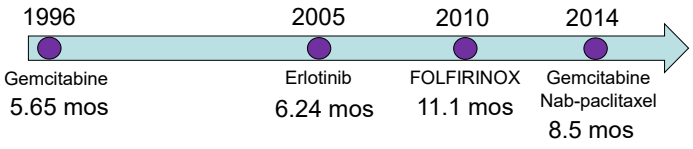
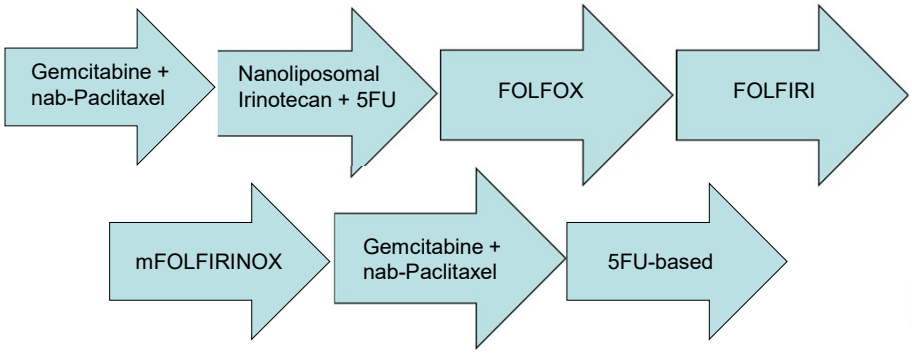
Pancreatic Cancer – Treatment Milestones



Sequencing therapy for patients with metastatic disease



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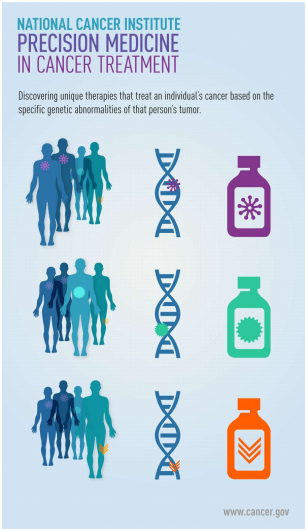
Precision Medicine for Pancreatic Cancer



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- In April 2013, ECOG-ACRIN and the NCI began development of a signal-finding clinical trial
- Select patients for treatments targeted to somatic genomic alterations.
- Challenging since somatic mutation testing was not standard of care

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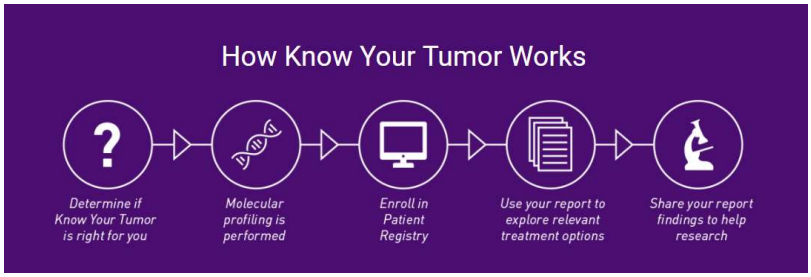

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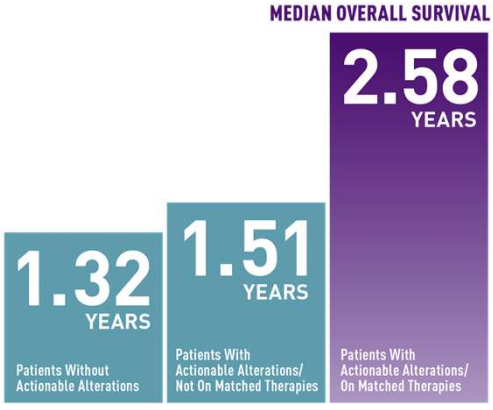
THE LANCET Oncology

Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial

Michael J Pishvaian*, Edik M Blais*, Jonathan R Brody, Emily Lyons, Patricia DeArbeloa, Andrew Hendifar, Sam Mikhail, Vincent Chung, Vaibhav Sahai, Davendra P S Sohal, Sara Bellakbira, Dzung Thach, Lola Rahib, Subha Madhavan, Lynn M Matrisian, Emanuel F Petricoin III

- 1856 patients referred to KYT between June 2014 and March 2019
- About 26% of pancreatic cancer harbor actionable molecular alterations
- Patients receiving matched therapy had significantly longer median overall survival compared to patients receiving unmatched therapies.



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Lancet Oncology 2020; 21:508-18.

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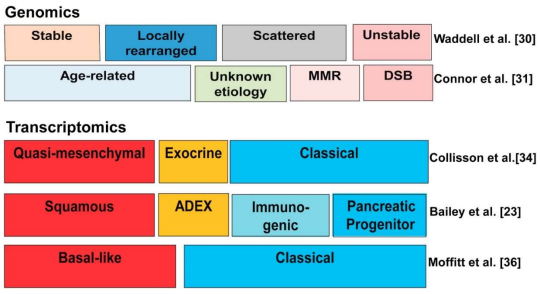
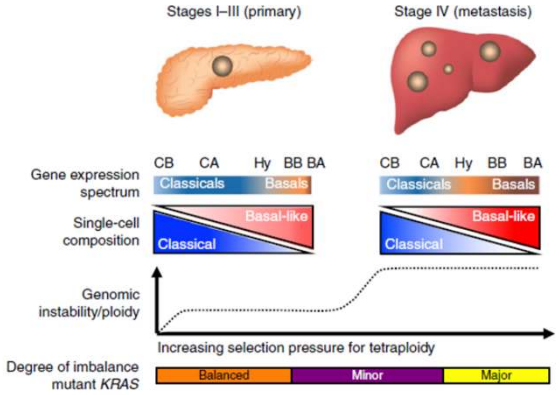
Pancreatic cancer is no longer one disease

Classifications of Pancreatic Cancer





Le Large, et al. Seminars in Cancer Biology 2017.

Chan-Seng-Yue M, et al. Nature Genetics 2020.

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Genetic Susceptibility to Pancreatic Cancer

Genetic Mutations	Syndrome	Risk Level
BRCA1/BRCA2	Hereditary breast/ovarian cancer syndrome	• BRCA2 mutation is the most common known genetic cause for familial pancreatic cancer • 3.6%-5% lifetime risk for developing pancreatic cancer
PALB2	Fanconi anemia	• Up to 3% of patients with familial pancreatic cancer
P16/CDKN2A	Familial atypical multiple-mole melanoma	• 10%-17% lifetime risk for pancreatic cancer
STK11/LKB1	Peutz-Jeghers syndrome	• 11%-36% lifetime risk for pancreatic cancer
PRSS1	Hereditary pancreatitis	• 25%-40% lifetime risk for pancreatic cancer
MLH1, MSH2, MSH6, PMS2	Hereditary non-polyposis colon cancer (Lynch syndrome)	• Approx 4% lifetime risk for pancreatic cancer

Vincent A, et al. *Lancet*. 2011;378(9791):607-20.
Grover S, Syngal S. *Gastroenterology*. 2010;139(4):1076-80.

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The NEW ENGLAND JOURNAL of MEDICINE

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

BRCA genes code for proteins that are involved in homologous recombination repair of DNA double-strand breaks

4 to 7% of patients with pancreatic cancer

PARP inhibitors prevent repair of single-strand breaks and lead to generation of double-strand breaks in replicating cells

Causes an accumulation of DNA damage and tumor-cell death

Olaparib doubled progression free survival compared to placebo

Golan T, et al. NEJM 2019;381:317-327

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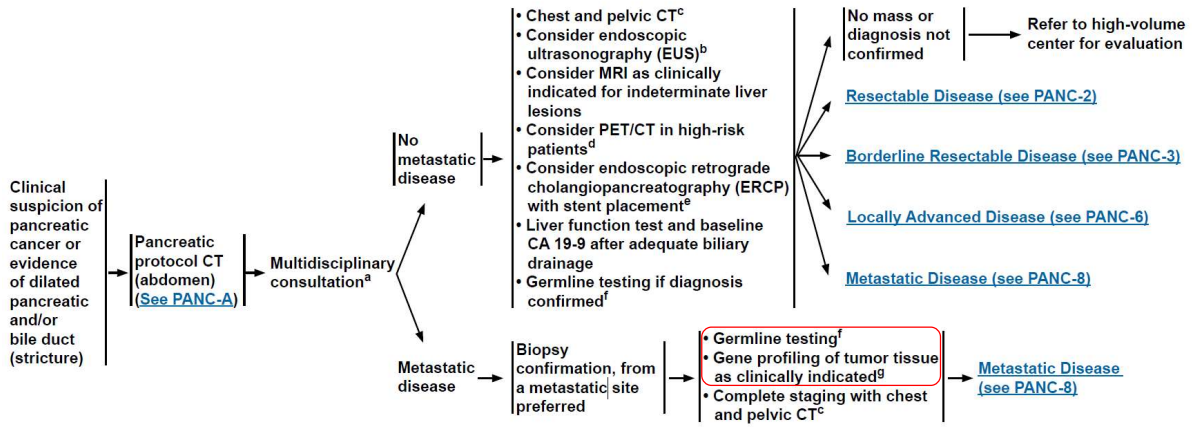
National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020 Pancreatic Adenocarcinoma

CLINICAL PRESENTATION AND WORKUP



2019 Molecular profiling added to the NCCN guidelines

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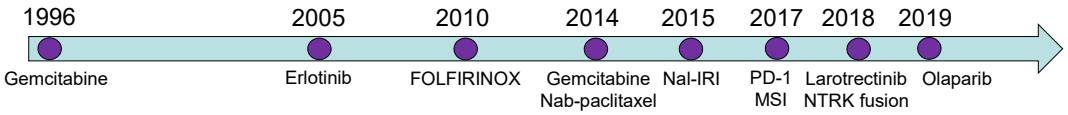
Pancreatic Cancer – Treatment Milestones



- Pancreatic cancer research has been a slow and rocky process
- Recently we have seen new therapies get approved
- Pancreatic cancer can be divided into molecular subtypes
- Targeted treatment for select patient can improve overall survival

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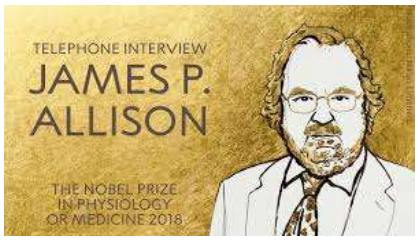
Immunotherapy for Pancreatic Cancer



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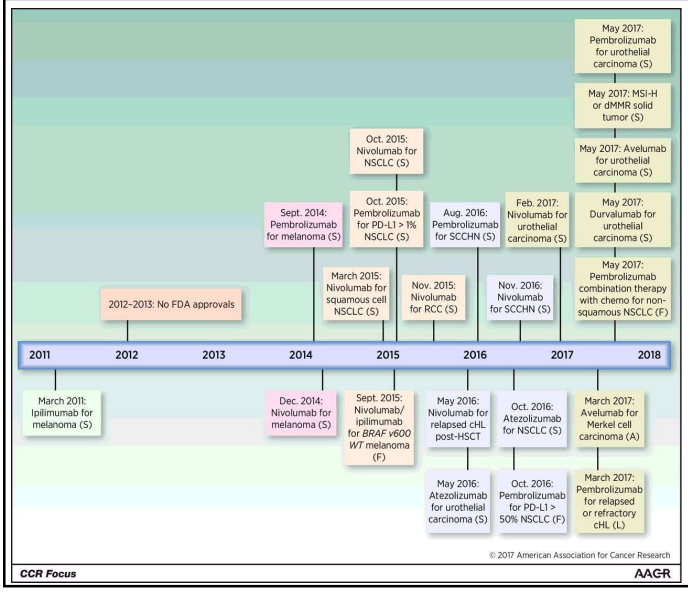
Approval of immunotherapy for multiple solid tumors



Pancreatic cancer is missing from the list

In 2017 pembrolizumab was approved for any MSI-H solid tumor

1-2% of pancreatic cancer is MSI-H

Baik C., *et al. Clin Cancer Res; 23(17); 4992–5002.*

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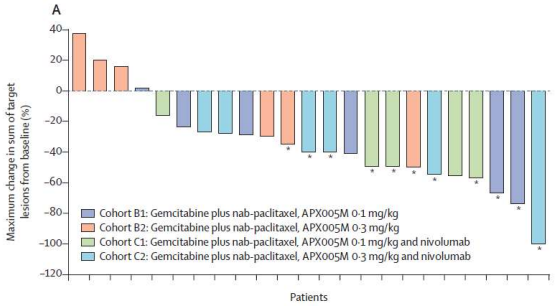
Phase 1b Study of Gemcitabine, nab-paclitaxel, APX005M with or without Nivolumab in Patients with Metastatic Pancreatic Cancer

APX005M – CD40 agonist (binds to and activates the receptor)

- Activates the antigen-presenting cells including dendritic cells, B cells and monocytes

- The chemotherapy may release tumor antigens while APX005M may sensitize the tumor to immunotherapy

- Small study with only 24 evaluable patients



A larger study will need to be done to confirm the results

Lancet Oncol 2021; 22: 118–131

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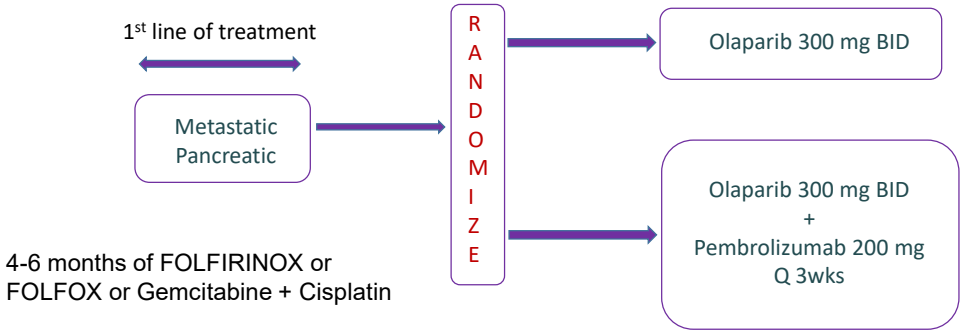
S2001:Randomized Phase II Study of Olaparib + Pembrolizumab vs. Olaparib Alone as Maintenance Therapy in Metastatic Pancreatic Cancer Patients with Germline BRCA 1 / 2 Mutations

Vincent Chung, MD and Michael Pishvaian, MD, PhD

Treatment Schema



Germline BRCA 1 or 2 mutated pancreatic cancer determined by standard CLIA certified testing
No signs of disease progression after at least 4 months of treatment (no more than 6 months of tx)

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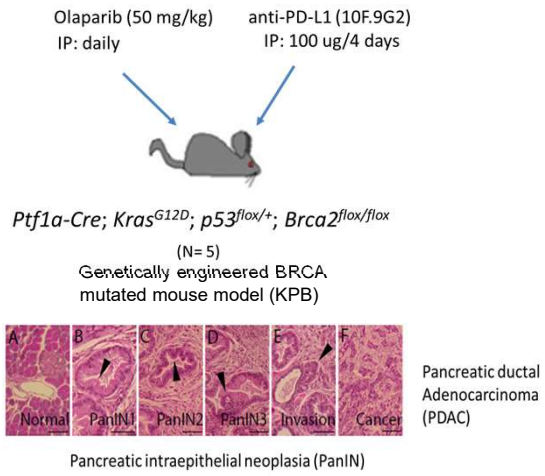
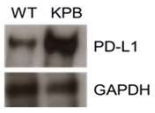
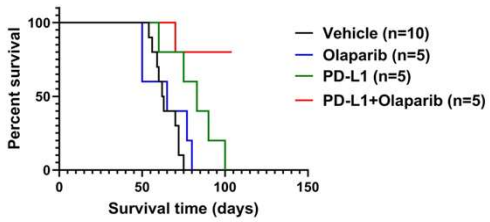
Preclinical Data in Pancreatic Cancer



Xiaochun Yu, PhD

KPB tumors have increased expression of PD-L1





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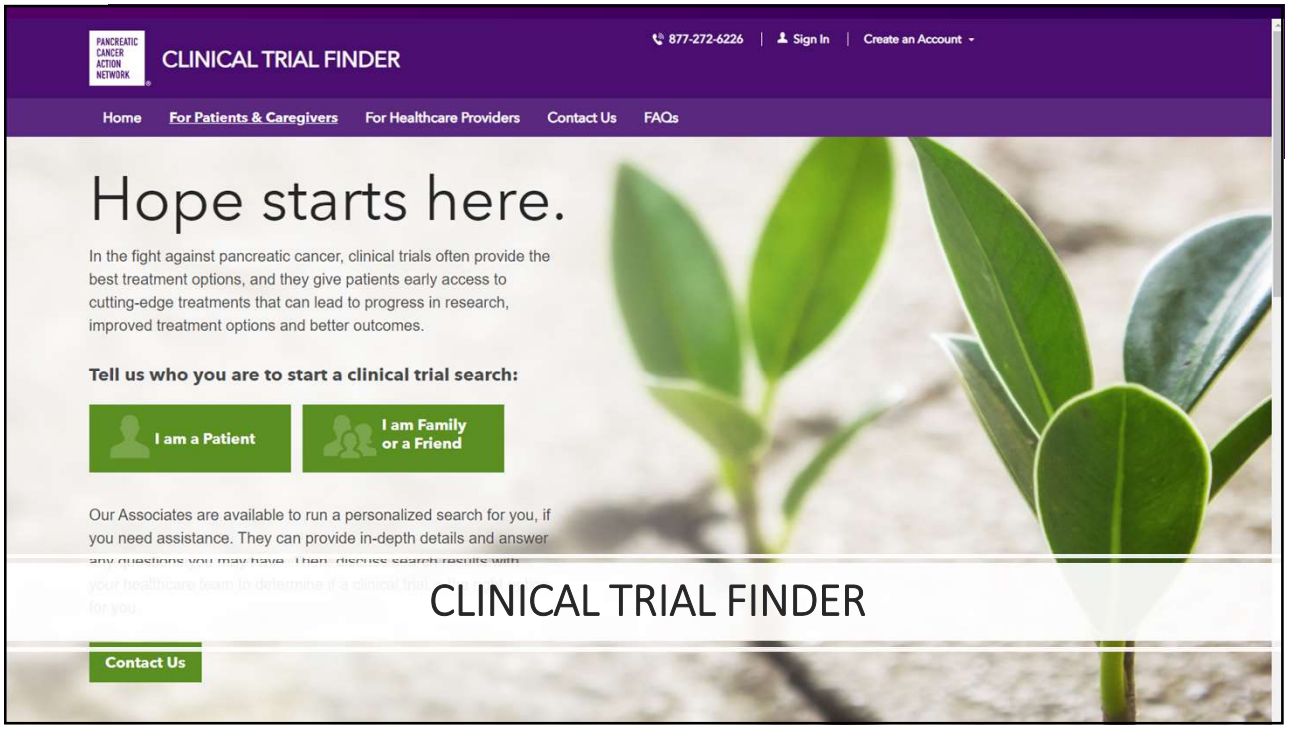

CLINICAL TRIAL FINDER

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PanCAN's PRECISION PROMISE ADAPTIVE CLINCAL TRIAL

Has a unique statistical approach, which allows it to "adapt"

Tests multiple drugs simultaneously

Experimental treatment arms stop if they are not working, or go faster if they are

Only requires 175 patients per experimental arm

As little as 3.5 years to complete

Patient can receive up to 2 treatments

We learn every step of the way

PANCREATIC CANCER ACTION NETWORK

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QUESTIONS?

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HOW TO PARTICIPATE

Q&A

Please enter questions in the Q&A box.

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WE WELCOME YOUR QUESTIONS

Julie Fleshman, JD, MBA
PanCAN, President and CEO

Vincent Chung, MD, FACP
City of Hope
Clinical Professor/Clinical Director Early Therapeutics

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CONTACT PanCAN'S PATIENT SERVICES

If you or a loved one has pancreatic cancer, contact PanCAN's Patient Services at 877-2-PANCAN or patientcentral@pancan.org

877-2-PANCAN

Monday – Friday, 7 a.m. – 5 p.m. PT

patientcentral@pancan.org

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THANK YOU FOR YOUR PARTICIPATION

If you have questions, please contact Patient Central: 877-2-PANCAN or e-mail patientcentral@pancan.org

pancan.org

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