Treatment Approaches for Pancreatic Cancer

January 27, 2016

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Treatment Approaches in Pancreatic Cancer

Janet E. Murphy, MD MPH

Pancreatic Cancer Action Network Webinar

January 27, 2016

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Disclosures

- Consulting, Merrimack Pharmaceuticals

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Treatment Approaches in Advanced PDAC

- Chemotherapy
- Targeted therapy
- Immunotherapy

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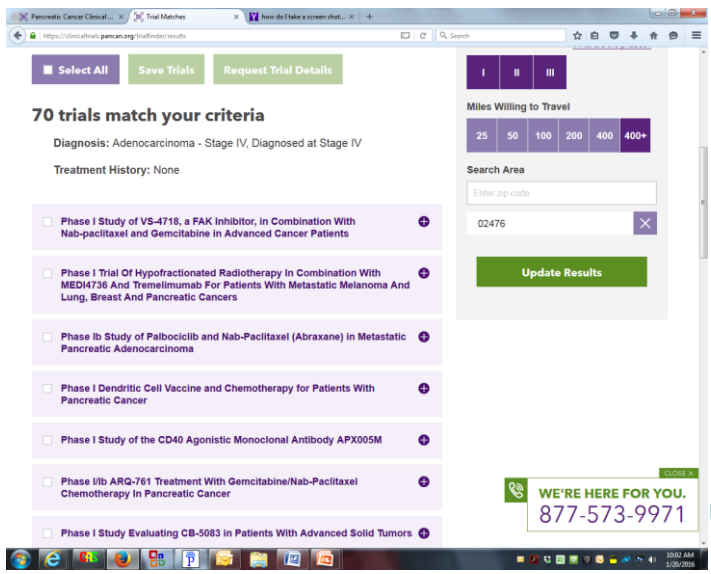
PanCan Clinical Trials Finder – An Amazing Resource… But Understanding the Trials is Daunting.



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Objectives

- Provide a framework for understanding treatment strategies in this disease
- Review state-of-the-art treatments for the different stages of the disease
  - Advanced (Stage IV)
  - Locally advanced/borderline resectable
  - Upfront resectable
- Discussion

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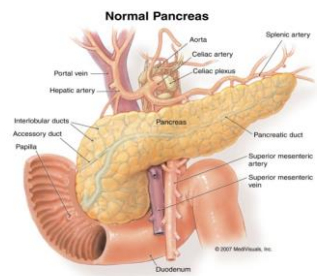
How Medical Oncologists Think About Pancreatic Cancer

Can the cancer be taken out with a surgery?

Resectable (20%) | **Borderline resectable** | **Locally Advanced** | **Metastatic (53%)**



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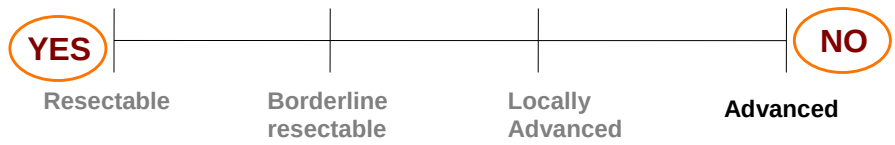

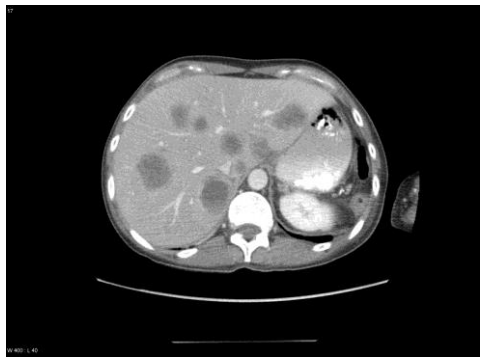

- **Chemotherapy**
- **Targeted Therapy**
- **Immunotherapy**

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Principles of **Chemotherapy**

- Since cancer, unlike infections, are “self” and not “other,” it is difficult to isolate and attack only the bad cells
- Chemotherapy targets rapidly dividing cells in the body
- The downside is the collateral damage – chemotherapy side effects
- The benefit is that strong, toxic therapy is delivered to pancreas cancer cells
- Major advances in the last 5 years

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Dawn of a new era: FOLFIRINOX 2010

PRODIGE4/ACCORD11 study –

Combination chemotherapy:

5FU + Oxaliplatin + Irinotecan

VS

Gemcitabine

Criteria for enrollment:

- **75 years old or younger**
- **Very fit**

Table 2. Objective Responses in the Intention-to-Treat Population.*

Variable	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
Response — no. (%)			
Complete response	1 (0.6)	0	
Partial response	53 (31.0)	16 (9.4)	
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Rate of objective response†			<0.001
No. (%)	54 (31.6)	16 (9.4)	
95% CI	24.7–39.1	5.4–14.7	
Rate of disease control‡			<0.001
No. (%)	120 (70.2)	87 (50.9)	
95% CI	62.7–76.9	43.1–58.6	
Response duration — mo			0.57
Median	5.9	3.9	
95% CI	4.9–7.1	3.1–7.1	

* CI denotes confidence interval, and FOLFIRINOX oxaliplatin, irinotecan, fluorouracil, and leucovorin.
† The rate of objective response was defined as the percentage of patients who had a complete response or partial response.
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Conroy *et al* NEJM May 2011

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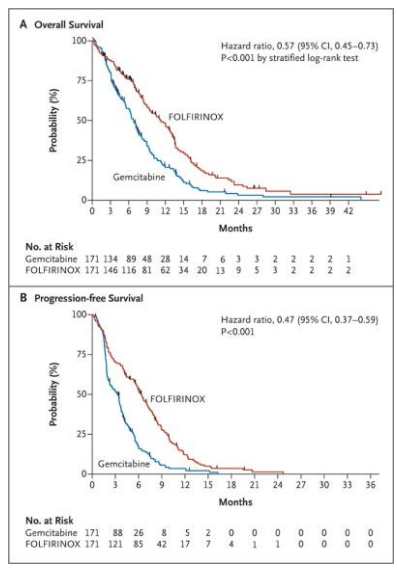
11

FOLFIRINOX prolongs survival among fit patients



Conroy *et al* NEJM May 2011

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12

Dawn of a new era: Gemcitabine-Abraxane 2013

Table 2. Overall Survival, Progression-free Survival, and Response Rates in the Intention-to-Treat Population.

Efficacy Variable	nab-Paclitaxel plus Gemcitabine (N = 431)	Gemcitabine Alone (N = 430)	Hazard Ratio or Response-Rate Ratio (95% CI)*	P Value
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Median overall survival — mo (95% CI)	8.5 (7.9–9.5)	6.7 (6.0–7.2)	0.72 (0.62–0.83)	<0.001
Survival rate — % (95% CI)				
6 mo	67 (62–71)	55 (50–60)		<0.001
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24 mo	9 (6–13)	4 (2–7)		0.02
Progression-free survival				
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Best response according to independent review — no. (%)				
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† Disease control included confirmed complete response, confirmed partial response, and stable disease for 16 weeks or more.
‡ Included are 72 patients (17%) in the nab-paclitaxel–gemcitabine group and 87 (20%) in the gemcitabine group who did not have an assessment after the baseline visit.

"MPACT" study - International

- 10% of patients were older than 75
- 7-8% of patients were less "fit"

VonHoff *et al* NEJM Oct 2013

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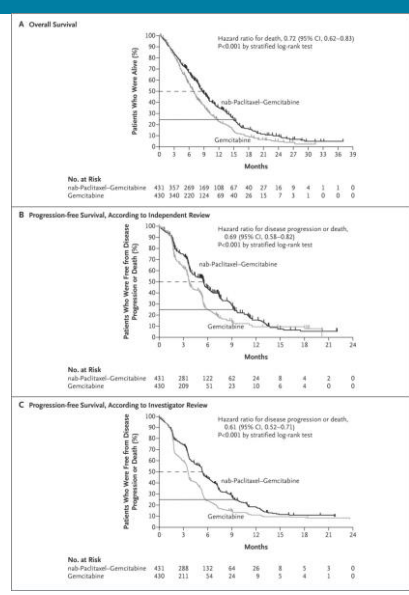
Gemcitabine-paclitaxel improves survival too.



Von Hoff DD et al. N Engl J Med 2013;369:1691-1703

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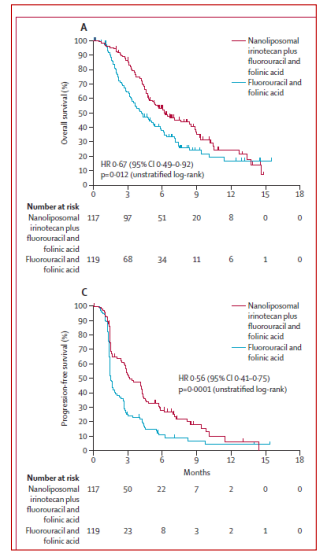
Nal-irinotecan (MM 398) – new kid on the block

- Phase III study, in patients **previously treated** with gemcitabine based treatment
- Nal-iri + 5FU improved outcomes over 5FU alone
- *First second-line study showing survival benefit*



Wang-Gillam et al. Lancet Nov 2015

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An important benefit to our new choices

- Incremental addition of *multiple lines of therapy* leads to much, much better outcomes
- In pancreas cancer, *choice* of options can also lead to *SEQUENCING* of options.
- Common path in fit patients with metastatic disease:
  1) FOLFIRINOX
  2) Gem-Abraxane
  3) Clinical trial

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16

Treatment Approaches in Advanced PDAC

- Chemotherapy
- Targeted therapy
- Immunotherapy

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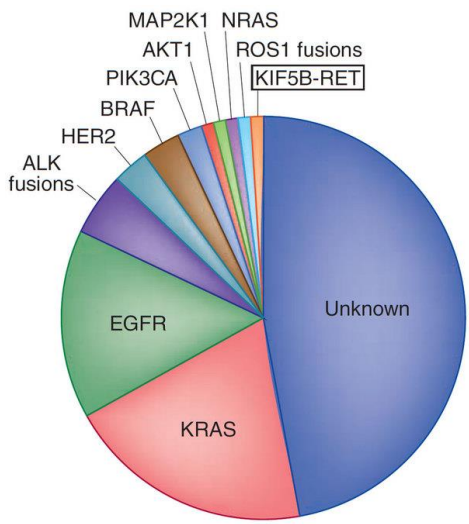
Targeted Therapy in Stage IV Lung Cancer



Pao et al. Nature Medicine 2012

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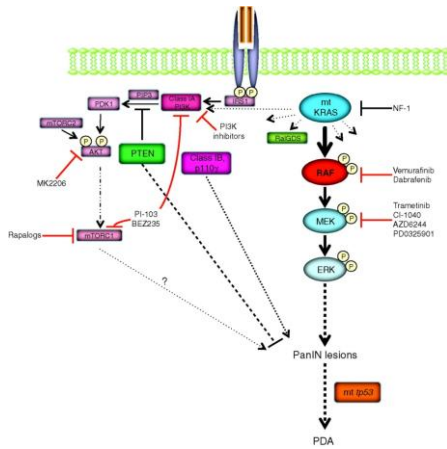
Targeted Therapy: The Pancreatic Cancer "Genome"



Hanrahan et al.
Cancer Discovery 2012

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BRCA2 (inherited mutation) as target for therapy

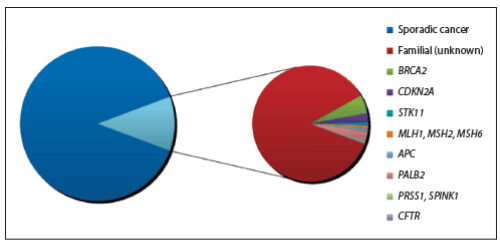
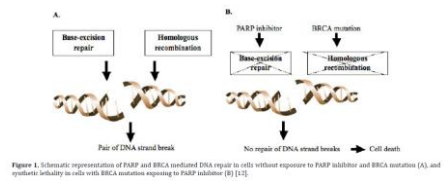


Figure 2: Familial Pancreatic Cancer—All cases of pancreatic cancer, with proportionate delineation of genes known to comprise part of the familial subset, are shown. Data from: Hahn et al. J Natl Cancer Inst. 2003[7]; Lowenfels et al. J Natl Cancer Inst. 1997[23]; Rebours et al. Am J Gastroenterol. 2008[24]; Sheldon et al. Br J Cancer. 1993[25]; Couch et al. Cancer Epidemiol Biomarkers Prev. 2007[60]; McWilliams et al. Eur J Hum Genet. 2011[61]; Witt et al. Nat Genet. 2000[62]; Rittenhouse et al. J Gastrointest Surg. 2011[63]; McWilliams et al. Cancer. 2010[64].



Schrader et al
Oncology 2012

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20

Targeting the Tumor Microenvironment

Figure 4. Cellular Components of Pancreatic Ductal Adenocarcinoma (PDA) Currently Being Targeted and Pursued—T cells figure in the extrinsic, immunotherapeutic targeting of the PDA cell, while in the tumor microenvironment, stromal components and desmoplasia—which may restrict and/or facilitate tumor growth—are targeted. Attacking the microenvironment could enhance the delivery of targeted therapies and currently used chemotherapeutic agents.

Angiogenesis inhibitors

Collagen inhibitors

Hyaluronic Acid inhibitors

Weinberg et al. Oncology Nov 2015

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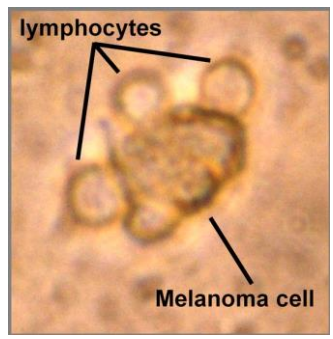
Treatment Approaches in Advanced PDAC

- Chemotherapy
- Targeted therapy
- Immunotherapy



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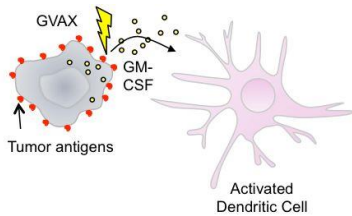
Immunotherapy: Vaccines



Randomized Phase II study at Johns Hopkins:

Patients randomized to GVAX alone versus combination with Listeria vaccine, CRS-207.

The two vaccine combination doubled the survival time of a small group of patients with advanced pancreatic cancer.

First positive study that suggests immune therapy has a potential ROLE in pancreas cancer!

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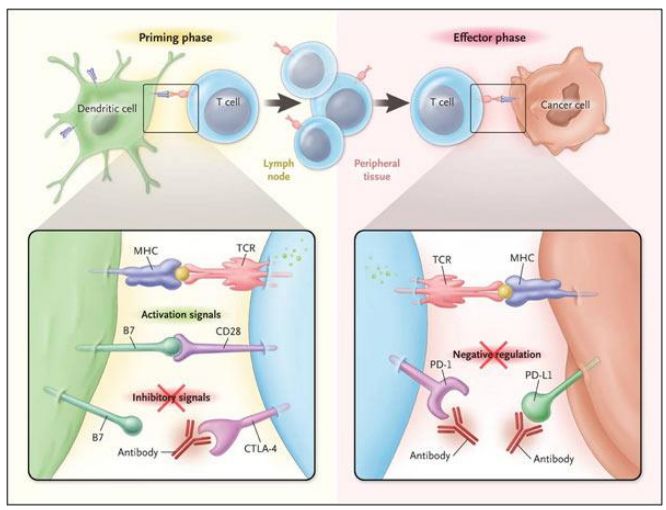
Immunotherapy: Checkpoint Inhibitors



- **Anti-CTLA-4**
- **Anti-PD-1**
- **Anti-PD-L1**

Tested as single agents and in combination in pancreas cancer in ongoing trials

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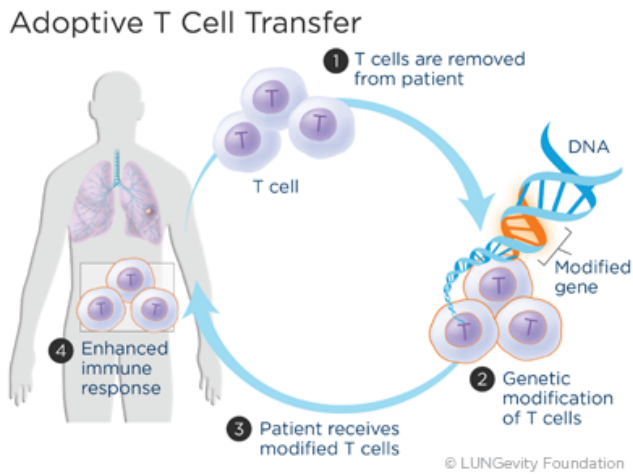
Immunotherapy



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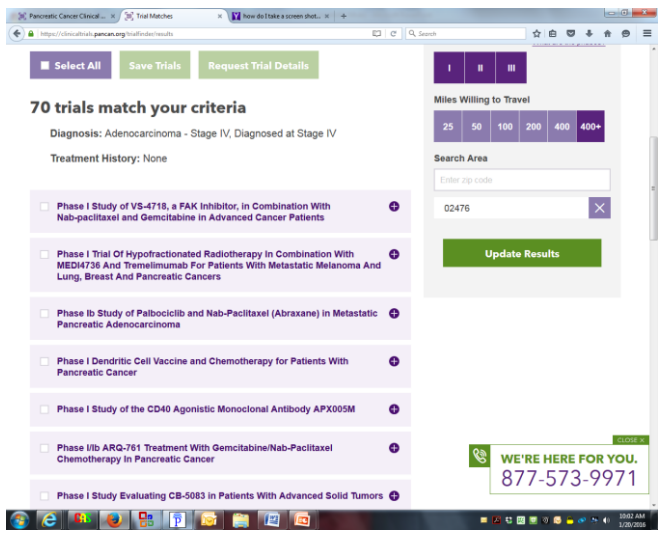
Clinical Trials in Advanced Disease – let's classify



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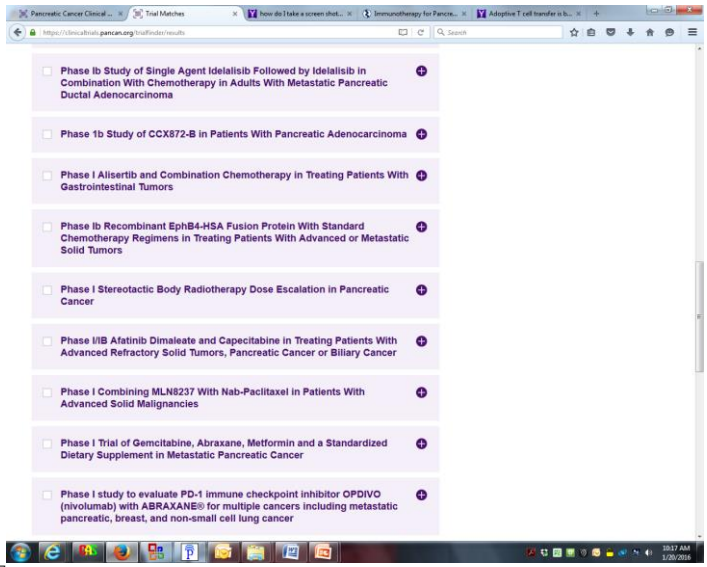

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Can the cancer be taken out with a surgery?

YES — **NO**

Resectable | **Borderline resectable** | **Locally Advanced** | Metastatic

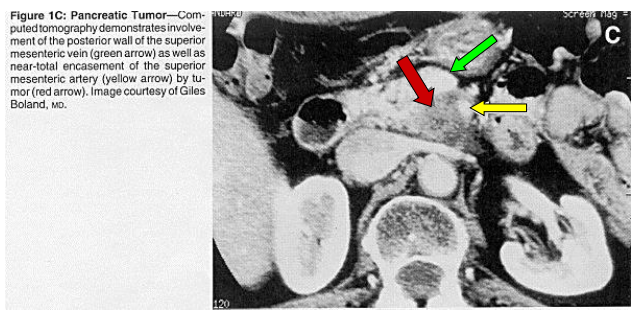

Figure 1C: Pancreatic Tumor—Computed tomography demonstrates involvement of the posterior wall of the superior mesenteric vein (green arrow) as well as near-total encasement of the superior mesenteric artery (yellow arrow) by tumor (red arrow). Image courtesy of Giles Boland, MD.

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Superior Response Rates of both Gem-Abraxane and FOLFIRINOX

Table 2. Overall Survival, Progression-free Survival, and Response Rates in the Intention-to-Treat Population.

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29

"Neoadjuvant" FOLFIRINOX in Borderline disease

Preoperative FOLFIRINOX followed by CRT and surgery in borderline resectable PDAC (Alliance A021101)

Treatment Schema

- Real-time centralized review of all radiographic studies and enrollment criteria
- Prospective QC of all treatment modalities

PRESENTED AT: ASCO Annual '15 Meeting

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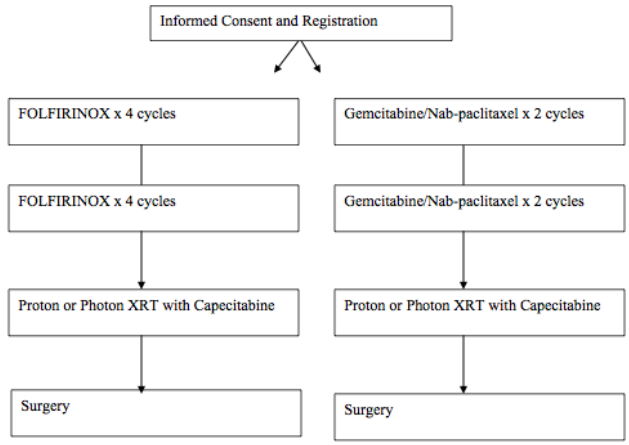
30

Giving neoadjuvant chemotherapy – MGH Clinical Trial in patients with UPFRONT RESECTABLE disease



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31

PanCan Clinical Trials Finder for Locally Advanced Disease

- **Study of Neo-adjuvant RO7009789 Alone or Neo-adjuvant RO7009789 Plus Nab-Paclitaxel and Gemcitabine Followed by Adjuvant RO7009789 Plus Nab-Paclitaxel and Gemcitabine for Patients With Newly Diagnosed Resectable Pancreatic Carcinoma**
- **Phase I study of Intraoperative Radiation Therapy for Resectable Pancreas Cancer**
- **Phase I Dendritic Cell Vaccine and Chemotherapy for Patients With Pancreatic Cancer**
- **Phase I Study of the CD40 Agonistic Monoclonal Antibody APX005M**
- **Phase I Stereotactic Body Radiotherapy Dose Escalation in Pancreatic Cancer**
- **Phase I Study Gemcitabine, Nab-Paclitaxel, Radiation Therapy, Sorafenib, Vorinostat in Previously Untreated Pancreatic Cancer Patients**
- **Phase I Study of Nab-Paclitaxel Plus Gemcitabine with Concurrent MR-Guided IMRT in Locally Advanced Pancreatic Cancer**
- **Phase I Trial Using Single Dose PEGPH20 and Cetuximab in Pancreatic Adenocarcinoma Prior To Surgical Resection**
- **Phase I Pilot Trial of Neoadjuvant Paricalcitol to Target the Microenvironment in Resectable Pancreatic Cancer**
- **Phase I Pilot Study Using Neoadjuvant FOLFIRINOX and Stereotactic Body Radiotherapy (SBRT) Followed by Surgery in Borderline Resectable Pancreatic Cancer**

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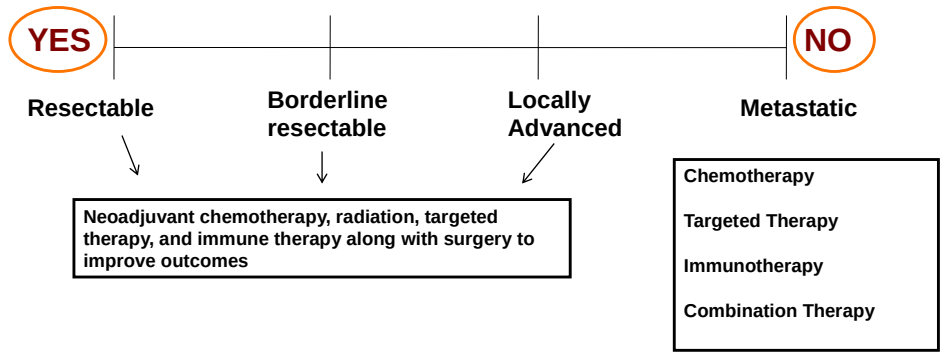
32

Conclusion: Current Clinical Trials



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33

Meeting PanCan's Mission

VISION OF PROGRESS / $200 MILLION BY 2020

OUR VISION: DOUBLE PANCREATIC CANCER SURVIVAL BY 2020

Of the major cancers, pancreatic cancer has the lowest survival rate.

In 2010, our organization declared a bold and aggressive vision: After seeing too little progress in pancreatic cancer survival in over half a century, the Pancreatic Cancer Action Network put a stake in the ground to double pancreatic cancer survival by 2020.

This is our Vision of Progress.

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34

Thank you for your participation.

If you have questions, please contact our Patient Central at
(877) 272-6226 or e-mail patientcentral@pancan.org.

www.pancan.org