Treatment Approaches for Pancreatic Adenocarcinoma

Presented by
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Treatment Approaches for Pancreatic Adenocarcinoma

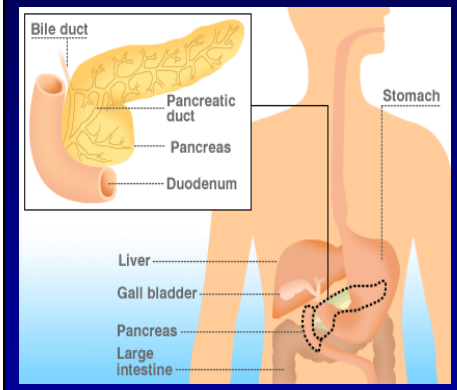
Gauri R. Varadhachary
Professor
University of Texas, M.D. Anderson Cancer Center

Webinar, Pancreatic Cancer Action Network
January 8, 2014

Pancreatic Adenocarcinoma

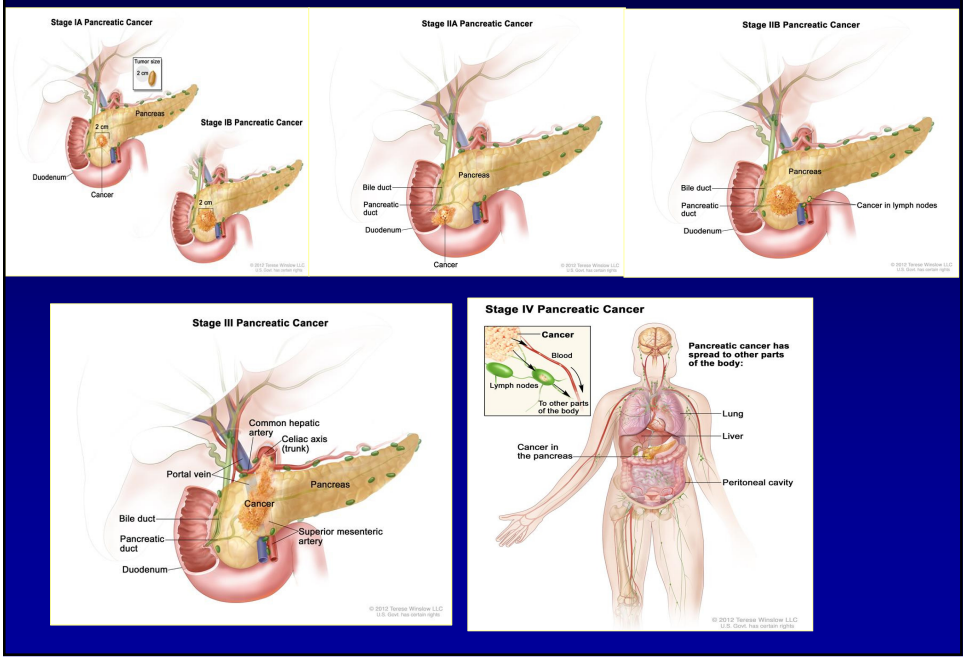
- ~ 39,000 patients diagnosed every year in the U.S.
- Systemic disease in most patients; rarely curable
- 100 Patients
  - 15-20 patients will have operable tumors
  - 80 will have inoperable, advanced cancers
  - 3 - 4% five year survival; in most survival measured in months

Pancreatic Cancer - Often presents late



- 'Nonspecific' symptoms which can mimic other common conditions
- 'Tucked away': no early symptoms
- No good screening test

Pancreatic Cancer - Staging



Staging of Pancreatic Cancer

Resectable (Stages I and II)

- Stage 1: Isolated in the Pancreas, no lymph nodes or blood vessels involved
- Stage II: Extends beyond the pancreas. No blood vessels involved

Unresectable (Stages III and IV)

- Stage III: Blood vessels involved
- Stage IV: Spread to distant organs

Clinical staging of Pancreatic cancer

I. Resectable (10-15%)

II. Locally advanced (50%)

III. Metastatic (35-40%)

Tools used: Physical examination and blood tests, CT scan, Endoscopic ultrasound, biopsy

Clinical staging of Pancreatic cancer

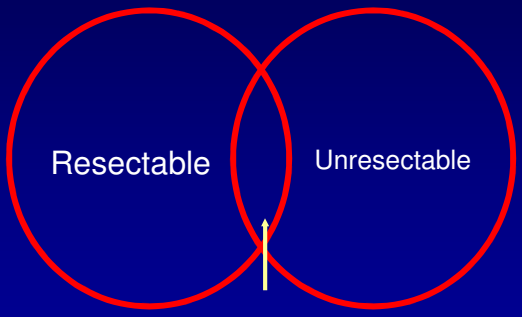
I. Resectable (10-15%)
   …..Borderline operable (5%?)

II. Locally advanced (50%)

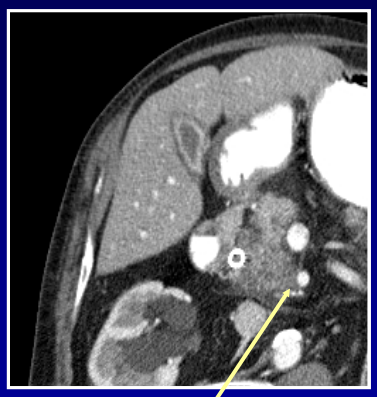
III. Metastatic (35-40%)

Tools used: Physical examination and blood tests, CT scan, Endoscopic ultrasound, biopsy

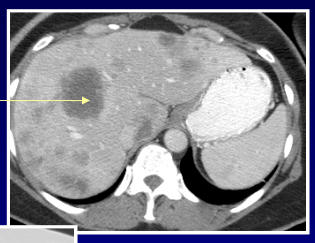
Borderline Resectable Pancreatic Cancer

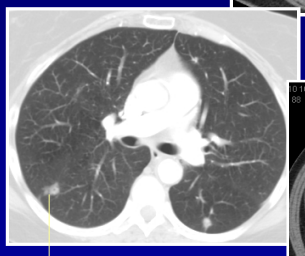


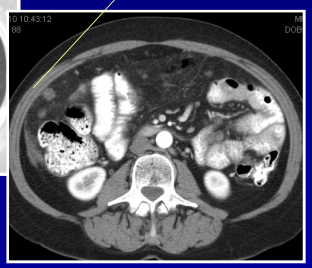
BORDERLINE RESECTABLE PANCREATIC CANCER



Patterns of Spread







- Liver
- Lung
- Lymph Nodes
- Peritoneum
- Other

Treatment options for Pancreatic Cancer

	Surgery	Radiation	Chemo
Resectable	+	+/-	+
Borderline Resectable	+	+	+
Locally Advanced	-	+/-	+
Metastatic	-	-	+

Treatment options for Pancreatic Cancer

	Surgery	Radiation	Chemo
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Locally Advanced	-	+/-	+
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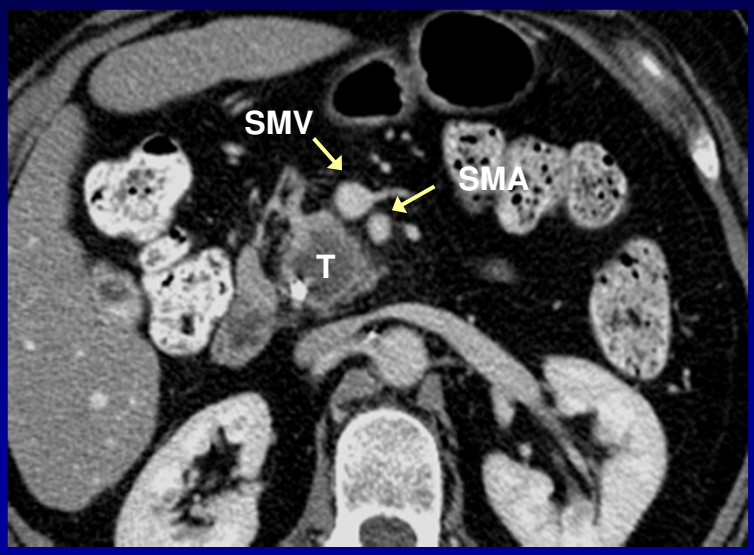
Resectable Pancreatic Cancer



Standard Approach to Resectable (head) Tumors FACTS

- Pancreaticoduodenectomy
- 15-20% long term survival
- Recurrence rate 80% to 85%
- 20 - 30% patients do not receive post-operative therapy
- Median survival 20-26 months

GITSG 1987, EORTC 1999, ESPAC 2004
J Am Coll Surg Oct 2009

Therapy options after surgery

- Chemotherapy
  - To kill any microscopic cancer floating around in the blood and other organs….
- Radiation (Controversial)
  - To prevent tumor from coming back in the surgical bed.

Current Status of Postoperative Adjuvant therapy for
Resected Pancreatic Cancer

Randomized Trials of Adjuvant Therapy

Study (Year)	Number of Patients	Pts with R1 Resection (%)	Treatment Median Survival Months	Treatment Median Survival Months	p value
GITSG (1985)	49	0	5-FU + XRT 21.0	Observation 10.9	0.035
EORTC 40891 (1999)	114	21	5FU + XRT 17.1	Observation 12.6	0.09
ESPAC-1 (2004)	289	18	5-FU Chemotherapy 20.1	No Chemotherapy 15.5	0.009
			5-FU- XRT 15.9	No XRT 17.9	0.05
RTOG 9704 (2006)	380 (Head lesions)	> 35	GEM then 5-FU/XRT then GEM 20.6	5-FU then 5-FU/XRT then 5-FU 16.9	0.033
CONKO 001 (2007-08)	368	19	Gemcitabine 22.8	Observation 20.2	0.005
ESPAC 3 (2009)	1088	35	5FU 23 months	Gemcitabine 23.6 months	0.39
CapRI (2010)	110	39	5FU 28.5 months	5FU/CCDP/αINF +XRT (+5FU x 2) 32 months	Not signif

Role of Post op Chemo alone in Resected PC Results from CONK0-001 and ESPAC-3

Study	No. of Pts	R1 Resection (%)	Treatment Median Survival Months	Treatment Median Survival Months	P
CONKO 001	368	19	Gemcitabine 22.8 (DFS =13.9)	Observation 20.2 (DFS=6.9)	0.05 <0.001
ESPAC 3 (V2)	1088	35	5FU 23	Gemcitabine 23.6	0.39

1. Gemcitabine stays the reference standard given better tolerability
2. BUT… we do need to figure out which chemo helps whom

CONKO 001 Oettle H, et al. JAMA, 2007

ESPAC 3 Neoptolemos JP et al. ASCO 2009

Role of Post op Radiation Therapy (RT) for Resected PC

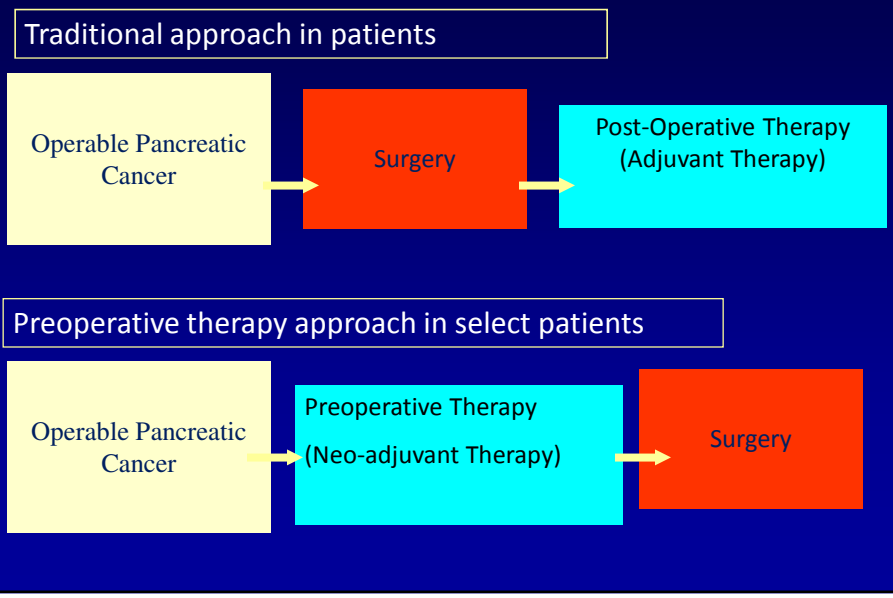
- Current role of RT in the adjuvant setting stays controversial
- Trials evaluating Chemotherapy vs. Chemo-RT (with attention to optimal design and tissue acquisition) need to be encouraged

Adjuvant therapy in Resectable Pancreatic Cancer

- Adjuvant studies suggest that something is better than nothing for patients who have recovered adequately from surgery.
- Not enough progress made in the adjuvant setting over the last 25+ yrs.
  - need to get novel agents in adjuvant setting
  - optimized trial designs

Preoperative vs. Postoperative Approach to Resectable Pancreatic Cancer

Sequencing Therapies for Resectable cancers



Rationale for Pre-Operative Therapy

- Deliver multimodality therapy to *all* patients with potentially resectable disease
- Provide early treatment of micro metastatic disease
- Avoid surgery in patients with rapidly progressive cancer
- Observe tolerance to therapy to predict tolerance to aggressive surgery
- Potentially improve negative margin resection

Summary of UTMDACC Trials of Pre-Operative Chemoradiation for Resectable Pancreatic Cancer

Preoperative therapy	Pts	Wks from Dx to Restaging	Resection rate	Path PR	Survival Resected Pts
5FU+RT (50.4 Gy)	28	10-12	61%	41%	18 mo
5FU+RT (30 Gy)	37	6-8	57%	20%	25 mo
Paclitaxel +RT (30 Gy)	35	6-8	57%	21%	19 mo
Gem + RT (30 Gy)	86	11-12	73%	59%	34 mo
Gem + Cis x 2 mo followed by Gem + RT (30 Gy)	90	17-18	66%	61%	31 mo

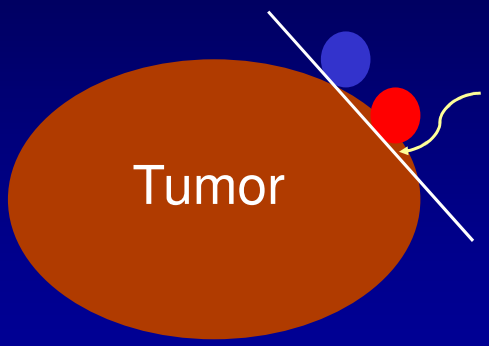
Preoperative Program at M.D. Anderson

- **Average time between start of preoperative therapy and surgery is about 3 - 4 months.**
- **Isolated local progression during therapy is rare.**
- **Patients deemed unresectable after preoperative therapy are those with distant metastasis seen on restaging scans or at the time of surgery.**

Treatment options for Pancreatic Cancer

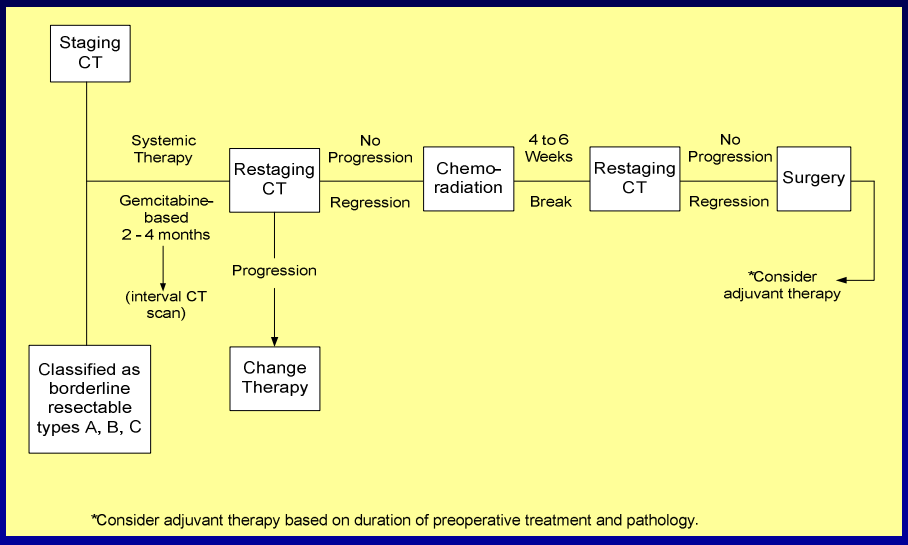
	Surgery	Radiation	Chemo
Resectable	+	+/-	+
Borderline Resectable	+	+	+
Locally Advanced	-	+/-	+
Metastatic	-	-	+

Borderline Resectable Pancreatic Cancer

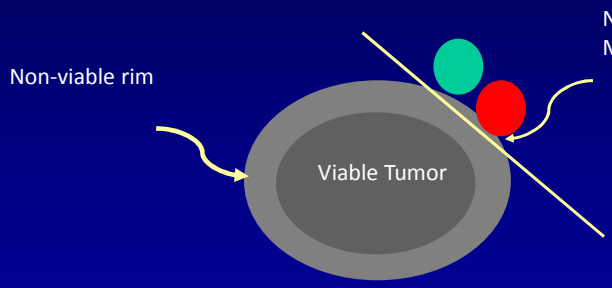


Courtesy : Dr. R. Wolff

Treatment Schema-Borderline Resectable



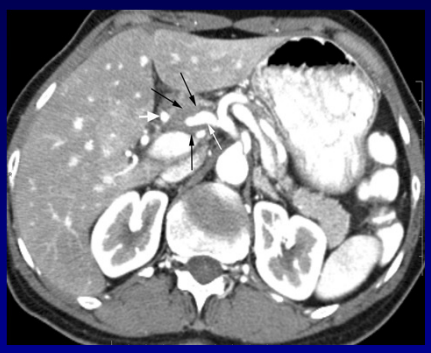
Borderline Resectable Pancreatic Cancer

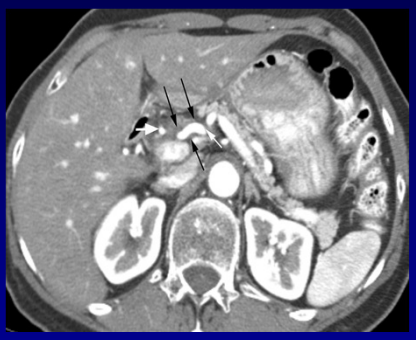


After Preoperative Chemotherapy and ChemoRT

Courtesy : Dr. R. Wolff

Borderline resectable pancreatic cancer



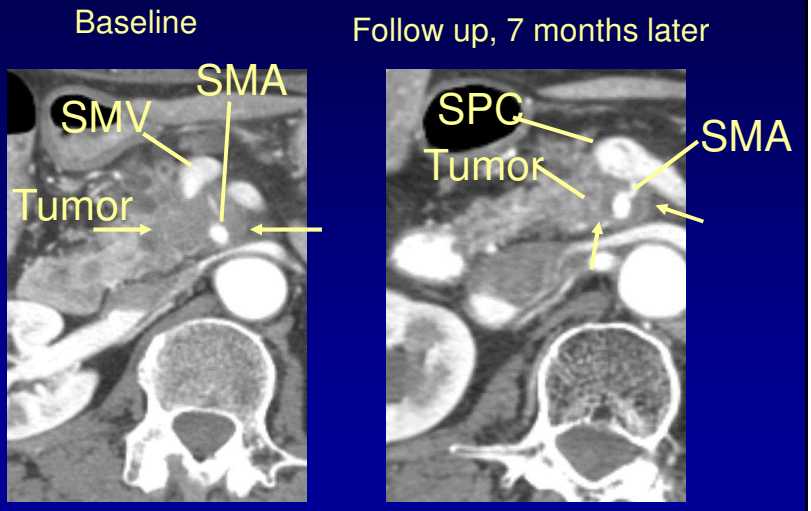


52 year old woman, presenting with borderline resectable pancreatic cancer. The hepatic artery is encased by tumor and splenoportal confluence compressed by tumor. After preoperative therapy lasting 6 months, sufficient tumor reduction to justify surgical resection with curative intent. She is without cancer spread , 50+ months

Locally Advanced Pancreatic Cancer

- Typically, chemotherapy (2-4 cycles) followed by chemoradiation in select patients is the preferred approach. This strategy allows the best candidates to benefit from locoregional therapy.
- Role of radiation in LAPC is being questioned
  - SCALOP trial – Cape + RT > Gem + RT
  - LAP07 trial – role of RT being questioned; best candidates ? (need predictive biomarkers)

Patient with Locally Advanced Disease



This patient was treated with systemic therapy for 4 months with minor response in the primary tumor followed by chemoradiation therapy.

Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study

LAPC
PS0-2
(R1 = 442 pts.)

Primary Endpoint:
- OS in R2
Secondary Endpts:
- Role of erlotinib, tolerance, predictive markers and CTCs

Gemcitabine

Gemcitabine + Erlotinib

Restaging

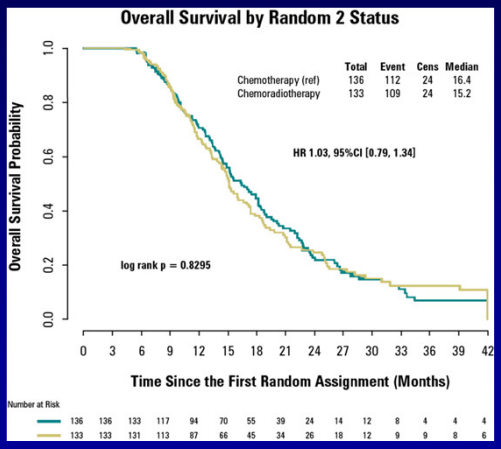
Those with controlled disease proceeded to R2 = 296

2 additional months of CT (136)

Cape + Radiation (133)

Hammel et al; J Clin Oncol 31, 2013 (suppl; abstr LBA4003)

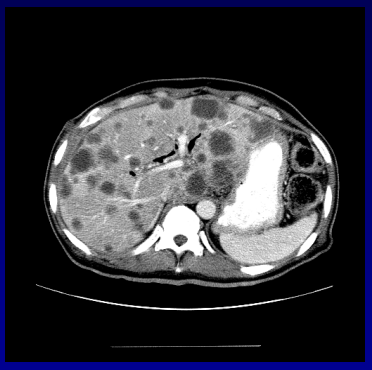
International phase III LAP 07 study

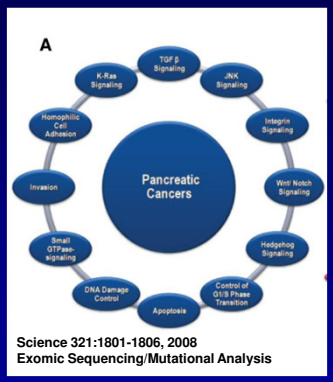


OS in R2 pts. was 16.5 m [15.5-18.5] and 15.3 m [13.9–17.3] in arms 1 and 2, respectively (HR=1.03 [0.79-1.34], p=0.83).

Administering CRT is not superior to continuing CT in patients with controlled LAPC after 4 months of CT.

Metastatic Pancreatic Cancer





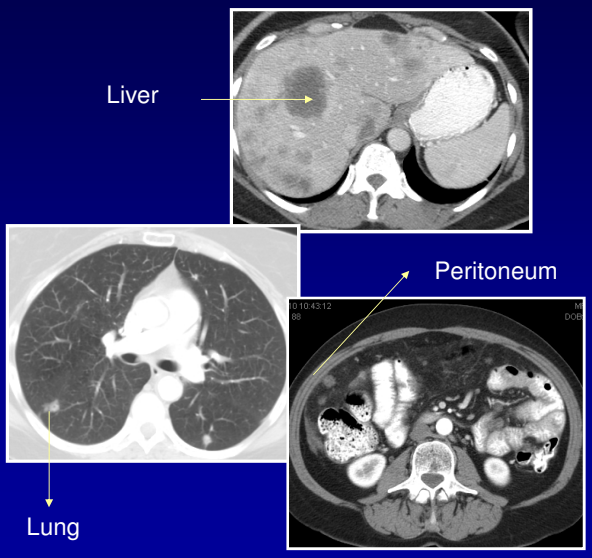
Science 321:1801-1806, 2008
Exomic Sequencing/Mutational Analysis

- Average of 63 genetic alterations/cancer
- Majority are point mutations
- Core set of 12 cellular processes are altered
- Is there a hierarchy of core signaling pathways?

Treatment options for Pancreatic Cancer

	Surgery	Radiation	Chemo
Resectable	+	+/-	+
Borderline Resectable	+	+	+
Locally Advanced	-	+/-	+
Metastatic	-	-	+

Patterns of Spread



- Liver
- Lung
- Lymph Nodes
- Peritoneum
- Other

Gemcitabine: Standard of care since 1996 Advanced Pancreatic Cancer

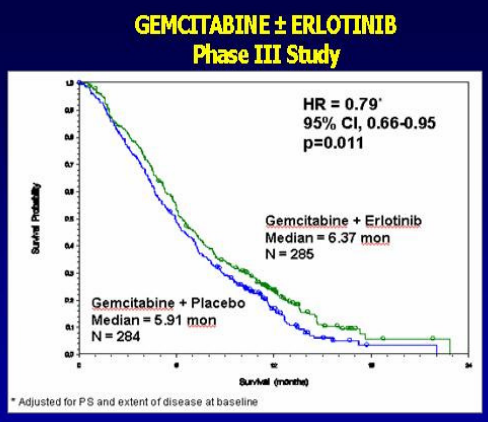
- Pivotal trial compared Gemcitabine to 5-FU

	N	RR	OS*	1-yr survival*	Clinical benefit response*
5-FU	63	0%	4.41 mo	2%	5%
Gem	63	5.4%	5.65 mo	18%	22%

P=0.0025

Burris et al, JCO 15: 2403-2413, 1997

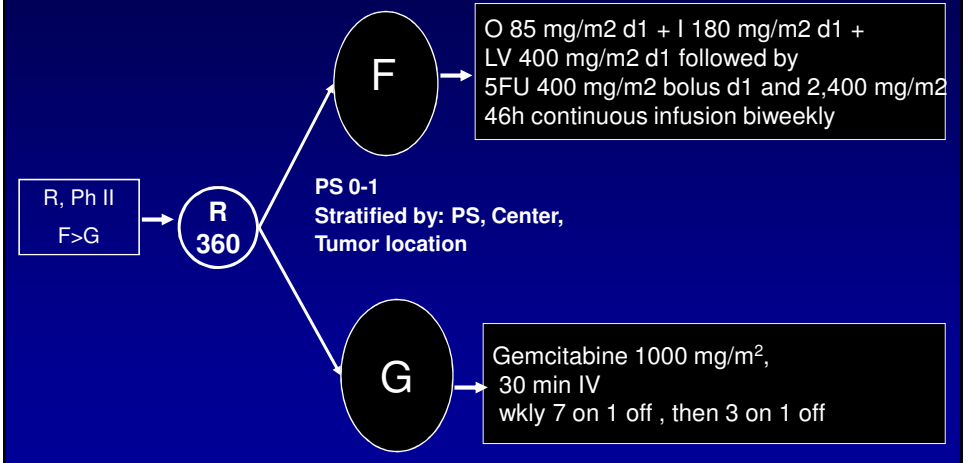
Gemcitabine and Erlotinib - Overall Survival



	Overall survival	1-year survival
Gem + P	5.91 mo	17 %
Gem + Erlotinib	6.24 mo	23 %

Moore, M. J. et al. ASCO 2006, J Clin Oncol; 25:1960-66, 2007

Randomized phase III trial comparing FOLFIRINOX (F) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma : PRODIGE 4/ACCORD 11 trial.



Conroy, et al NEJM 2011

Randomized phase III trial comparing FOLFIRINOX versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): PRODIGE 4/ACCORD 11 trial.

	F Grade ¾ (%)	G Grade ¾ (%)
Diarrhea	12.3	1.6
Nausea	15.6	6.3
Vomiting	17.2	6.3
Fatigue	24	14.3
Neutropenia	47.9	19.2
Febrile Neutropenia	5.7	0

T Conroy et al, ASCO 2010
NEJM, May 2011

PRODIGE 4/ACCORD 11 trial – FOLFIRINOX SURVIVAL AND RESPONSE DATA

	FOLFIRINOX (n=171)	GEM (n=171)	
Overall Survival mo	11. 1 mo	6.8 mo	HR 0.57 *P* <0.001
Progression Free Survival mo	6. 4 mo	3.3 mo	HR 0.47 *P* < 0.001
Response Rate %	32 %	9%	
Disease Control Rate %	70 %	51 %	

Randomized Phase III Study of Weekly *nab*-Paclitaxel plus Gemcitabine vs Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas (MPACT)

Planned N = 842
- Stage IV
- Untreated
- KPS ≥70

nab-Paclitaxel: 125 mg/m2 IV qw 3/4 weeks +
Gemcitabine: 1000 mg/m2 IV qw for 7/8 weeks then qw 3/4 weeks

Gem 1000 mg/m2 IV qw for 7/8 wks then qw 3/4 weeks

Primary Endpoint:
- OS
Secondary Endpoints:
- PFS & ORR by Independent review

With 608 events, 90% power to detect OS HR = 0.769 (2–sided α = 0.049)
•1 interim analysis for futility
•Treat until progression
•CT scans every 8 weeks

Von Hoff et al., NEJM 2013

nab-Paclitaxel plus Gemcitabine (MPACT)

SAFETY

	nabP + GEM (n=421)	GEM (n=402)
Febrile Neutropenia	3 %	1 %
Fatigue	17 %	7%
Peripheral neuropathy	17 %	< 1 %
Diarrhea	6 %	1 %

44% patients with peripheral neuropathy resumed nab-P after improvement
(median to improvement to grade ≤1 = 29 days)

Von Hoff et al., NEJM

nab-Paclitaxel plus Gemcitabine (MPACT)

SURVIVAL AND RESPONSE DATA

	nabP + GEM (n=431)	GEM (n=430)	
Overall Survival mo	**8.5 mo**	**6.7 mo**	**HR 0.72** ***P*** **<0.001**
Progression Free Survival mo	**5.5 mo**	**3.7 mo**	**HR 0.69** ***P*** **<0.001**
Response Rate % (independent review)	**23 %**	**7%**	
Disease Control Rate % (independent review)	**48 %**	**33 %**	

DCR : Includes CR + PR + SD ≥16 weeks

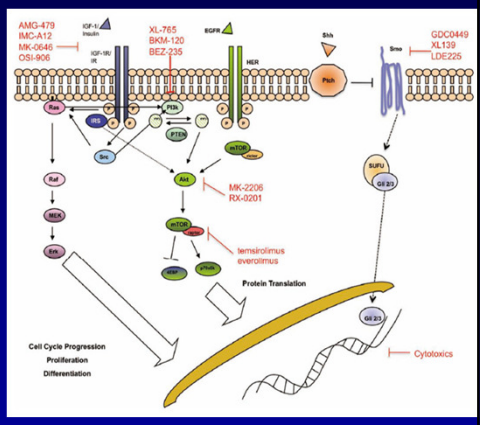
Von Hoff et al., NEJM

Clinical trials: Definitions

- PHASE I TRIALS: An experimental drug is tested in a small group of patients
  - with different cancers (20-40 pts.) for the first time to determine safety,
  - identify side effects and to gain some early evidence of effectiveness
- PHASE II TRIALS: Experimental drug is given to a larger group of patients
  - Usually with same cancer to determine effectiveness,
  - monitor side effects, compare it to commonly used drugs
- PHASE III TRIALS: Experimental treatment given to large groups of patients
  - to confirm effectiveness, compare it to commonly used drugs (standard of care)
  - if positive, may establish change in standard of care

Novel targets and therapies : Pancreatic Cancer

- Kras
- Immune checkpoint blockade drugs
- IGFR
- Notch
- cMET
- AKT and PI3K



Novel targets and therapies : Pancreatic Cancer

- Kras : Kras mutation occurs in 90%+ pancreatic cancers
  - Could provide a rational therapy for pancreatic cancer
  - With the mutation, Ras gene signalling function is unable to be turned "off"
  - A number of drug companies are investigating ways to halt the signalling function of Ras,
- Immune checkpoint blockade drugs (these drugs harness patient's own immune system to treat cancers)
  - antiCTLA4, anti PD-1
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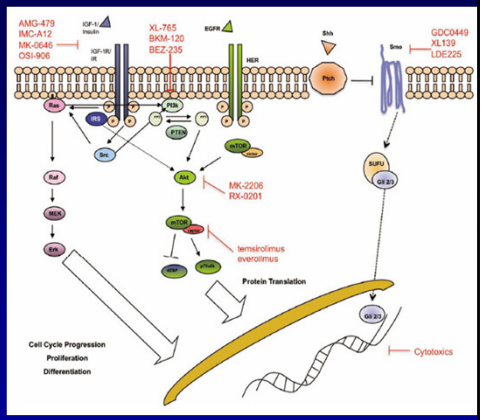

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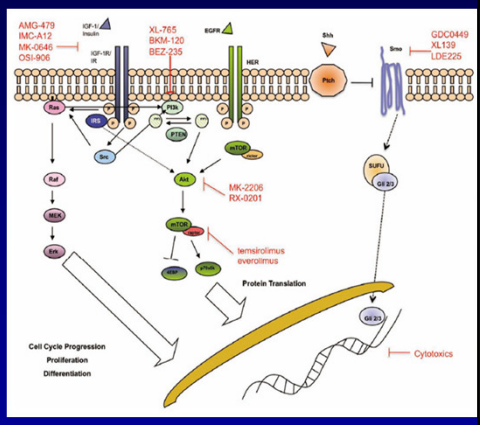

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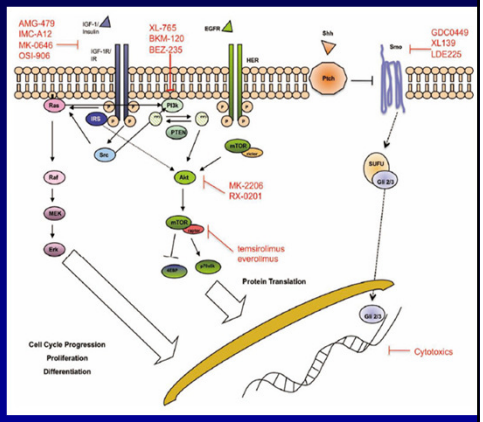
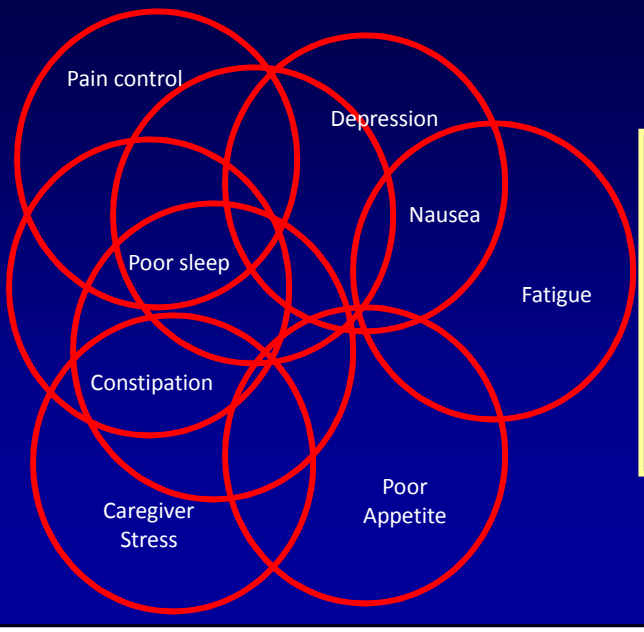


Challenge going ahead is how best to combine some of the targeted drugs with minimal toxicity and how to determine which ones are actually going to be beneficial

It is important to tackle all symptoms – they feed on each other..domino effect



Communication with the health care team is important

- Is it a side effect of treatment or symptom of cancer
- Many supportive care options to improve quality of life

Summary: Pancreatic Cancer

- Pancreatic cancer is a local disease and a systemic disease
- Accurate staging is essential
- Do not make treatment decision in haste (especially surgery)
- The research teams are working toward personalizing therapies and trials to match the patient
  - More options available with approval of new drugs in the last 2 years
- We have a long way to go but we are definitely making progress

Questions?

Thank you for your participation!

Pancreatic Cancer Action Network
www.pancan.org

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

Patient and Liaison Services (PALS)
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