Treatment Approaches to Pancreas Cancer

Jordan Berlin, MD
Ingram Professor of Cancer Research
Co-Director, GI Oncology
Director, Phase I Research

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What am I going to do?

- First, give you some background language
- Second, define the stages as we discuss them
- Third, go stage by stage defining treatment options going backwards from most advanced to least advanced
  - Within these I will define the treatments, their side effects

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What else?

- Every time I switch topics I will post a gratuitous photo of one of my pets

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Nietszche

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Disclosures

- I have a lot of clinical trials and I give advice to a lot of companies. I won't list them all
- Key to know that I have given advice to Celgene, the makers of nab-paclitaxel (Abraxane) and have been paid for that work

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Background

CHANCE

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Some important background

- Of all the common cancers, pancreas cancer remains the most deadly with the lowest percentage of patients living 5 years or more
- That is starting to change
- So, scary it is, there is hope and the numbers from the past may already

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How did it change?

- Thanks to you, other pancreas cancer survivors, their families, friends and the Pancreatic Cancer Action Network:
  - There is more funding than ever going towards pancreas cancer research
  - The Recalcitrant Cancers Act has passed and pancreas cancer and Ras are now 2 of the 3 top priorities of the National Cancer Institute

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Key Point

- Numbers are based on statistics and large groups
- They cannot be used to predict anything specifically for an individual
  - Definition of individual means everybody is unique
- When doctors give a number, it is usually based on averages but a doctor cannot "give" a person x amount of time

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Some language

- Standard of care
  - Something that is used commonly
  - FDA standards are usually the same, but some standards used by your doctors have not been brought to the FDA for approval
- Staging
  - Two forms: AJCC (I-IV with some letters in between). We don't use these most of the time
  - Real life

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Real Life Staging

- Metastatic disease
  - This is stage IV only
  - Means disease has spread to a distant site
    - Can be an organ like the liver or lung
    - Can also be a lymph node that is too far from the pancreas to be considered localized
- Localized disease
  - No evidence the tumor has spread on our xrays
  - 3 sub-types

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Localized Disease

- Resectable (not a real word)
  - Appears by CT scan or MRI that it can be cut out by a surgeon
    - Note: Surgeons have varying skills so there can be a bit of variation as to what they think they can cut out
- Borderline resectable
  - A major blood vessel appears to be too involved for immediate surgery but with treatment and shrinkage this could change
- Locally Advanced, Unresectable
  - Major involvement of the blood vessel and it is extremely unlikely even with shrinkage that it can ever be removed

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Clinical Trials

- The most important hope for the future
  - Should be considered every time treatment plan is going to change
  - To learn more about trials in your area, contact the PALS program
    - pals@pancan.org
- Protocols are not always trials
  - Sometimes they are the way a practice treats a certain situation
  - More commonly called pathways now

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Guidelines

- Guidelines are being created a lot now
- These are suggestions about best practices based on the literature
- Two main ones in the US: ASCO and NCCN
  - ASCO: Focus on limited areas one at a time, will not comment much if there is no data
  - NCCN: The most commonly used guidelines worldwide use expert opinion when there is no data

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Layla

Note: the blankets were not arranged in her best interests and she opted to toss the pillows off the bed

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Treatment of Metastatic Disease

- Because the tumor has spread beyond the ability to cut it out with a knife, the focus is on systemic therapy
  - Systemic therapy is treatment that gets all around the body
  - Types are:
    - Chemotherapy
    - Targeted therapy
    - Immune therapy

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Gemcitabine single Agent Background

- Gemcitabine (Gemzar, 2’ ,2’ -difluorodeoxycytidine)-originally developed as an antiviral
  - Too toxic for this
  - Had activity against cancer cell lines in the lab
- Tested as a single agent in 2nd line and as first line (treatment after 5-FU)
  - Few responses but
  - Doctors noted that patients claimed they felt better without tumor response
    - Note: response in a clinical trial is a lot of shrinkage. Mild shrinkage counts as stable disease

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Gemcitabine vs. 5FU

- Gemcitabine beat 5-FU
  - Median survival (most important but not the primary endpoint of the study)
  - 1-year survival
  - Clinical benefit response (almost 5 times better than 5-FU)
  - Note: We now know that 5FU was not given in the most effective manner

Burris, JCO 15:2403, 1997

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Side effects of Gemcitabine

- Immediate
  - Nausea/vomiting
  - Fatigue
  - Flu-like symptoms
  - Irritation to the vein
  - Rash
  - Shortness of Breath
- Delayed
  - Hair loss
  - Lower blood counts
  - High liver blood tests
  - Rash
  - Edema (swelling)
- Rare
  - HUS/TTP
  - Interstitial pneumonitis
  - Can bring back effects of radiation

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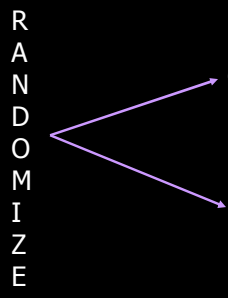
A lot of drugs have been compared to gemcitabine



5-FU

lots of things that ended in TECAN

Everything we found that blocked VEGF

A bunch of things that ended in nib and mab

None of these beat gemcitabine. Some nearly tied it, but this ain't horseshoes

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What has combined with gemcitabine?

- Drugs that didn't work
  - Bevacizumab
  - Cetuximab
  - Sorafenib
  - Axitinib
  - Irinotecan
  - Sunitinib
  - Many others
- Drugs that bordered on working
  - Cisplatin
  - Oxaliplatin
  - 5FU
  - Capecitabine

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Drugs that combined with gemcitabine and won

- Erlotinib
  - Hazard ratio = 0.81
- Nab-paclitaxel
  - Hazard ratio = 0.72
- What is a hazard ratio?
  - Compares curves to curves rather than time point to time point
  - 0.72 means there is a 28% better chance at any time of being alive on gemcitabine + nab-paclitaxel compared to gemcitabine alone

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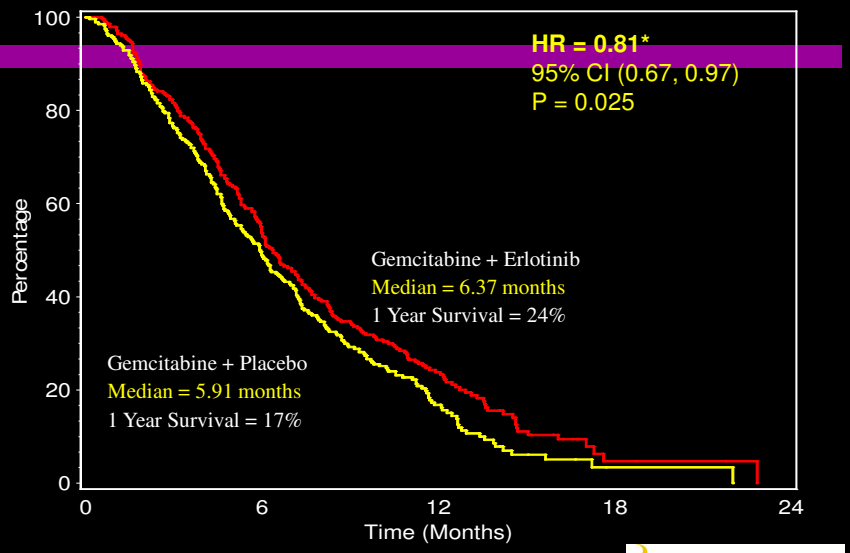
NCIC Study PA3: Survival Curve



* Adjusted for PS, pain and disease extent at randomization

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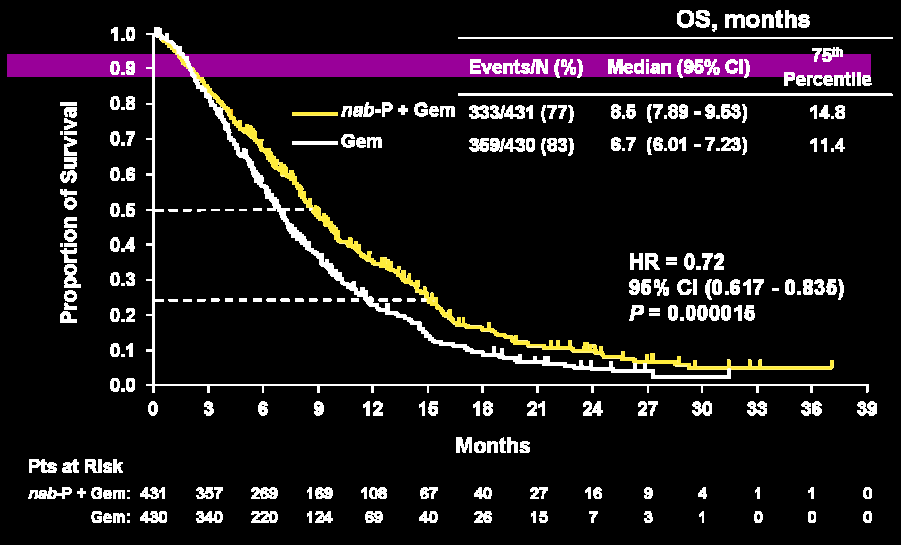
MPACT Survival Curve



Gem, gemcitabine; *nab*-P, *nab*-paclitaxel.

Von Hoff DD, Ervin T, Arena FP, et al. Randomized Phase III Study of Weekly *nab*-Paclitaxel plus Gemcitabine vs Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas (MPACT) [abstract LBA148]. *Oral presentation at: The Gastrointestinal Cancers Symposium*; January 23-25, 2014; San Francisco, CA.

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FOLFIRINOX

- This is actually 4 drugs, 3 of which are chemo
  - FOLinic acid—like folic acid
  - 5-FU
  - IRINotecan
  - Oxaliplatin
- Showed a lot of promise in a phase II so the study was continued to phase III

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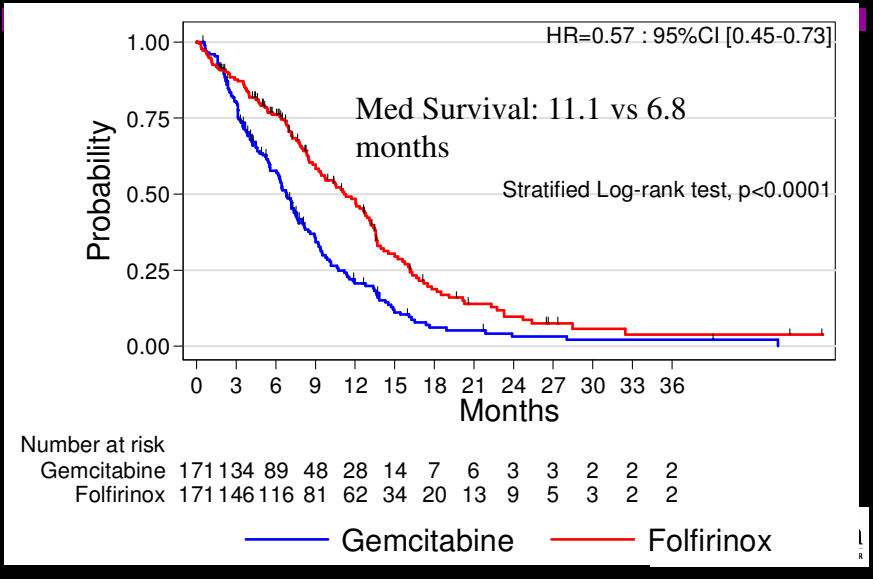
FOLFIRINOX: Survival Curve



Important Note

- Sometimes two drugs combine well and sometimes they don't
  - Gemcitabine + oxaliplatin is not better than gemcitabine alone
  - 5-FU + oxaliplatin is better than 5-FU alone
  - Similar story for irinotecan

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Are there trade-offs with these two new regimens?

Grading side effects

- Grade 1 = mild
- Grade 2 = moderate
- Grade 3 = Serious
- Grade 4 = life-threatening

- However, if it is happening every day, grade 2 can be very limiting:
  - E.g. grade 2 fatigue: not relieved by rest, interferes with activity

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Safety

Preferred Term	*nab*-P + Gem n = 421	Gem n = 402
Patients with at least 1 AE leading to death, %	4	4
Grade ≥ 3 hematologic AEs,[a] %		
Neutropenia	38	27
Leukopenia	31	16
Thrombocytopenia	13	9
Anemia	13	12
Patients who received growth factors, %	26	15
Febrile neutropenia,[b] %	3	1
Grade ≥ 3 nonhematologic AEs[b] in > 5% of patients, %		
Fatigue	17	7
Peripheral neuropathy[c]	17	< 1
Diarrhea	6	1
Grade ≥ 3 neuropathy		
Time to onset in days, median	140	113
Time to improvement by ≥ 1 grade in days, median	21	29
Time to improvement to grade ≤ 1 in days, median	29	--
Patients who resumed *nab*-P, %	44	--

[a] Based on lab values. [b] Based on investigator assessment of treatment-related events. [C] Grouped term.
AE, adverse event, Gem, gemcitabine; *nab*-P, *nab*-paclitaxel.
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CA.

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FOLFIRINOX: hematological AEs

AE, % per patient	Folfirinox N=167		Gemcitabine N=169		p
	All	Grade 3/4	All	Grade 3/4	Grade 3/4
Neutropenia	79.9	45.7	54.8	18.7	0.0001
Febrile Neutropenia	7.2	5.4	2.4	0.6	0.009
Anemia	90.4	7.8	94.6	5.4	NS
Thrombocytopenia	75.2	9.1	54.8	2.4	0.008

42.5 % of the pts received G-CSF in the F arm *vs* 5.3% in the G arm
One toxic death occurred in each arm
AE, adverse event

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FOLFIRINOX: main non-hematological AEs

AE, % per patient	Folfirinox N=167		Gemcitabine N=169		p
	All	Grade 3/4	All	Grade 3/4	
Infection without neutropenia	6	1.2	7.1	1.8	NS
Peripheral neuropathy	70.5	9	0.6	0	0.0001
Vomiting	61.4	14.5	43.2	4.7	0.002
Fatigue	87.3	23.2	78.7	14.2	0.036
Diarrhea	73.3	12.7	30.8	1.2	0.0001
Alopecia (grade 2)	32.5	(11.4)	3.0	(0.6)	0.0001
ALT	64.8	7.3	83.8	18.6	0.0022

Conroy et al, NEJM, 364:1817-1825, 2011

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Comparing gemcitabine + nab-paclitaxel to FOLFIRINOX

- Gemcitabine + nab-paclitaxel
  - Hazard ratio and median not as good as FOLFIRINOX
  - Some say side effects less than FOLFIRINOX
  - Studied around the globe, including Eastern Europe
  - Allowed slightly less healthy patients
- FOFLIRINOX
  - Numbness/tingling goes away more slowly than gemcitabine + nab-paclitaxel
  - Studied only in France
  - Restricted age to <75 years old

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Comparing key side effects

	***nab*-pacli + GEM**	**FOLFIRINOX**
Fatigue	17	23.6
Diarrhea	6	12.7
Neuropathy	17	9
Neutropenia	38	45.7
Neutropenic fever	3	5.4
Thrombocytopenia	13	9.1

Neuropathy appears to resolve faster with nab-paclitaxel

Conroy et al, NEJM, 364:1817-1825, 2011
Von Hoff, et al GI ASCO 2013 and ASCO 2013

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Which one is best?

- We don't know for certain
  - There are reasons to use each
- FOLFIRINOX has been modified which may reduce side effects (unlikely to reduce effectiveness)
- FOLFIRINOX has not been tested in people over 75 years old

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One last note

- Performance status
  - The ability of a person to conduct the activities of life
    - Karnofsky 0-100%, 100% is normal
    - ECOG: 0-4, 0 is normal
    - ECOG 1 = 90 and 80% on Karnofsky
    - ECOG 2 = 60 and 70% on Karnofsky
  - FOLFIRINOX has only been tested in ECOG 0-1
  - Gemcitabine + nab-paclitaxel was tested in Karnofsky 70-100%

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My doctor is using something other than what you mentioned

- Many doctors use a regimen that they have had good experiences with
  - They are neither right nor wrong
  - Everybody is trying to do their best for their patients
  - These regimens are just not proven in large trials to be better or worse than gemcitabine alone
  - But small trials or individual experiences can be tricky and sometimes misleading
    - That is why other docs might not be using your doctor's favorite regimen

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Bisket

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Locally Advanced, Unresectable

- A lot less is known here
  - We have official definitions, but to some extent we are not entirely sure who si convertible to surgery and who isn't
  - Options include: chemotherapy and radiation
    - FOLFIRINOX and gemcitabine + nab-paclitaxel have not been studied here yet
  - Early studies all combined chemotherapy + radiation together, called chemoradiation

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Locally advanced, unresectable

- One key study: LAP-07
  - Randomization of chemotherapy (gemcitabine or gemcitabine + erlotinib) to chemotherapy followed by chemoradiation
  - No difference in survival between arms
  - However, control of disease in the area of the pancreas was better with radiation
  - Current question is whether or not chemoradiation would have done better with better chemo

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Other things being done

- Stereotactic radiation
  - Highly focused, intense radiation to a small area
    - Names include SBRT, gamma knife, cyberknife, proton beam
    - None are absolutely proven.
    - Differences are subtle
- Surgery on the SMA
  - If this goes wrong, and it does, the side effects can be horrible

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They are not friends

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Borderline Resectable Disease

- Goal here is to try to improve the likelihood the surgeon can remove the whole tumor with negative margins
  - R0: no tumor at any of the cut edges of the pathology specimen
- Chemotherapy and chemoradiation have both been used
- No randomized trials

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Borderline Resectable

- No standard of care
- Trial preferred
- Most common these days, based on intergroup trial is:
  - Chemo first
  - Followed by chemoradiation
  - Followed by surgery

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Layla

Resectable Disease

- Head of pancreas (80%)
  - Whipple is most common
  - Pylorus preserving pancreaticoduodenectomy
    - Variation on Whipple
- Body, tail (20%)
  - Partial pancreatectomy
  - Distal pancreatectomy
    - Spleen usually has to come out with this one

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Early Detection

- Even when we catch this disease early, surgery alone only cures 10-12% of people
  - Chemotherapy, either gemcitabine or 5FU, improves this
  - The US has used chemoradiation also, but this is not proven to be better
    - Current study randomly assigning people who have had resection to chemo alone or chemo followed by chemoradiation

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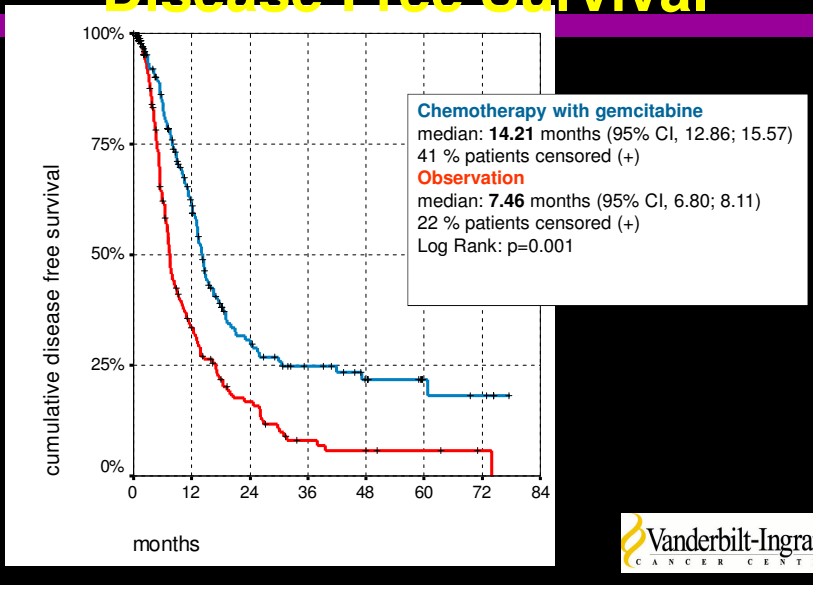
CONKO-001 Kaplan Meier Disease Free Survival



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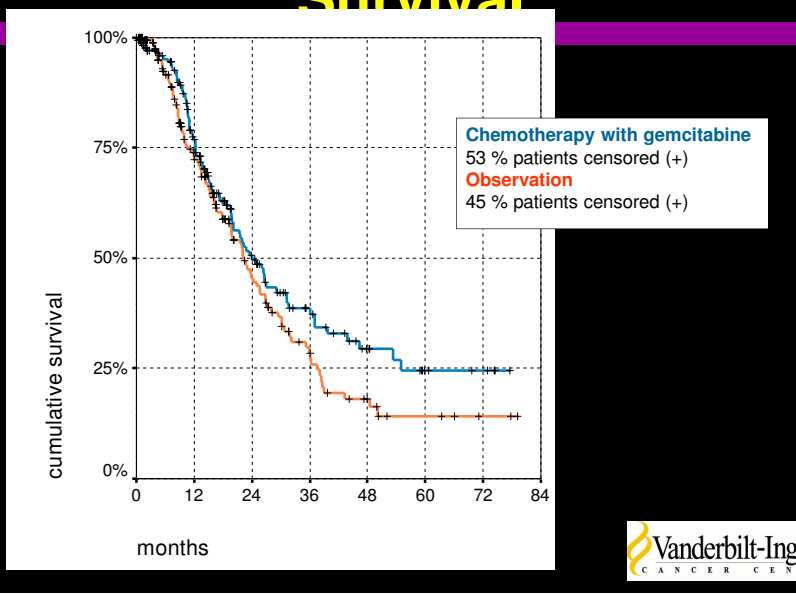
CONKO-001 Kaplan Meier Survival



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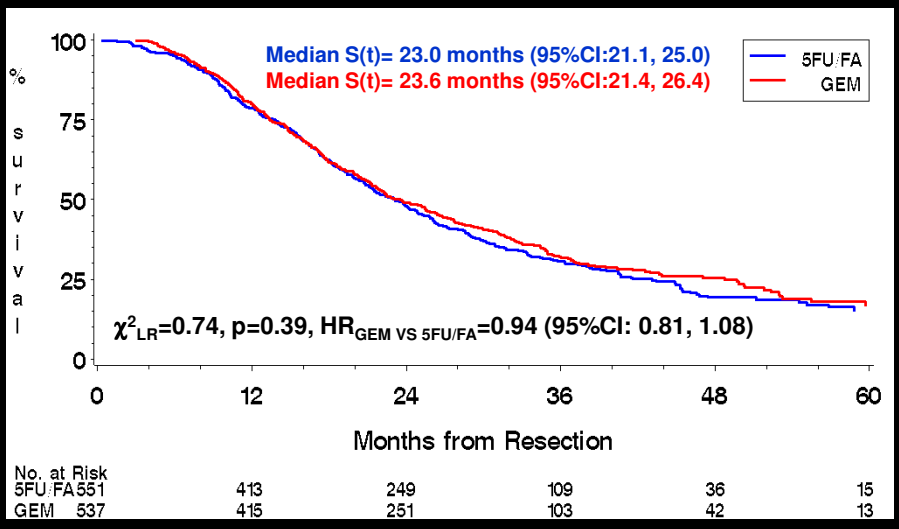
ESPAC 3: Gemcitabine vs 5FU



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R1 Resection

- While it looked like everything was removed, when the pathologist looked at it under the microscope
  - Microscopic cells came right up to the edge where the knife cut
- Almost every trial has shown this group also benefits from chemotherapy
- Similarly, this group may benefit from chemoradiation more than R0

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CONKO-001 Disease Free Survival

		Chemotherapy median (months)	Observation median (months)	P – value (log rank)
N	Negative	19.3	11.2	< 0.05
	Positive	13.1	7.0	< 0.05
R	R0	14.0	7.9	< 0.05
	R1	14.5	5.5	< 0.05

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Resectable Disease

- Standard of care is surgery first
- Chemotherapy with either gemcitabine or 5FU
- Clinical trials are focusing on 3 areas
  - New regimens:
    - APACT compares gemcitabine + nab-paclitaxel to gemcitabine alone
    - French are looking at modified FOLFIRINOX
  - Giving chemo or chemoradiation before surgery
  - Looking at the value of post-surgery radiation

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Before You fall completely asleep

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Other therapies

- Targeted agents
  - Still looking for ones that work in pancreas
  - Trying to target Ras mutations
- Immune therapies
  - Vaccines are in trials (GVAX is furthest ahead)
  - Immune modulators: free the immune system to attack—also in trials

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Special situations

- BRCA mutations, PALB2 mutations, Fanconi anemia
  - Inherited in most cases
  - May be more susceptible to:
    - Platinums
    - Mitomycin
    - PARP inhibitors (experimental)

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Palliative Care

- Never forget this whether we are giving anticancer therapy or not
  - Making a person feel better can make them live longer
    - Pain control has been shown to extend the life of people with pancreas cancer
    - Timely initiation of hospice has been shown to extend the life of people with pancreas cancer
- SYMPTOMS MATTER!!!

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Last Thing

- There are a lot of myths out there
  - PET scan is better than CT:
    - No, it is just different. Different scans are needed in different situations
  - If you turn your body alkaline, you will kill the cancer
    - Your pH is 7.4. You can make your urine alkaline, but unless your kidneys have failed you can't turn you alkaline. Your body can't survive in a more alkaline environment either
  - Chemotherapy kills the immune system
    - It reduces the neutrophil counts for short periods which can increase the risk of bacterial infections. The rest of the immune system is intact

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Happy Father's Day

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