

# Advances in Pancreatic Cancer



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20<sup>th</sup> Annual California Cancer Consortium  
The Langham Hotel, Pasadena, CA  
August 24, 2024

# Overview

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Scope of the problem

Progress in the treatment of pancreatic cancer

2024 ASCO Updates

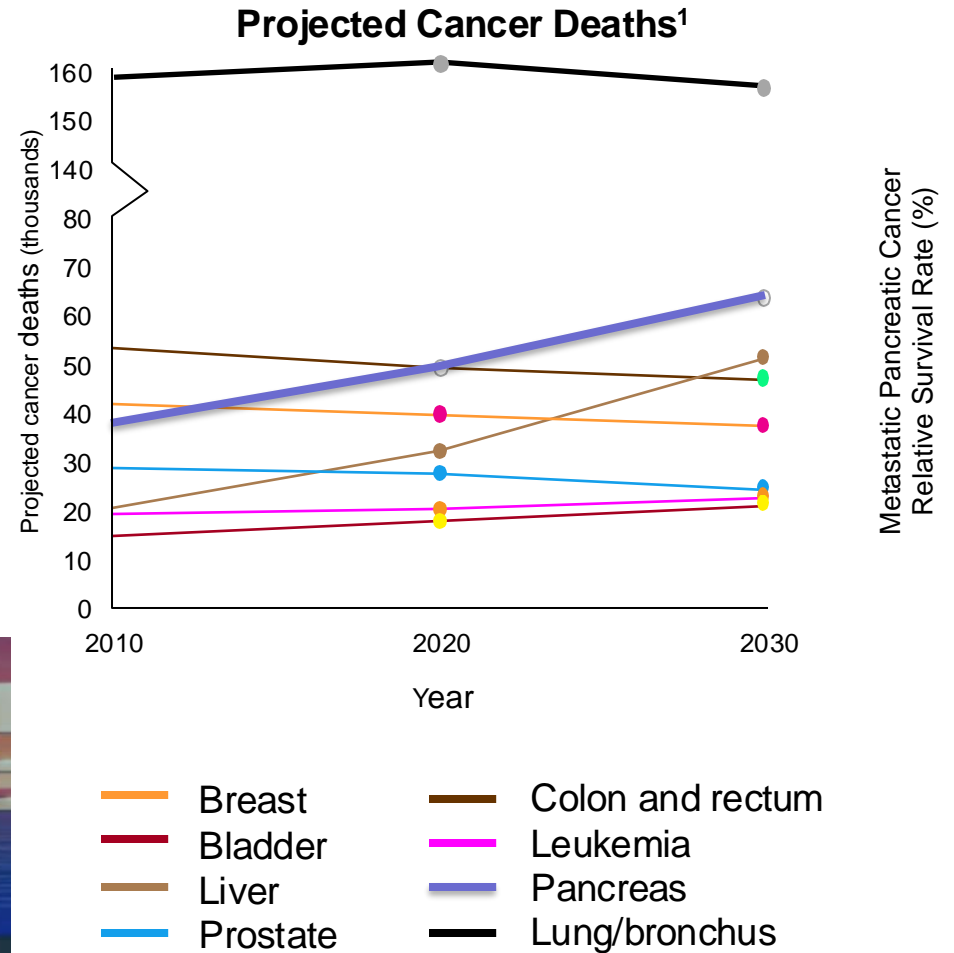
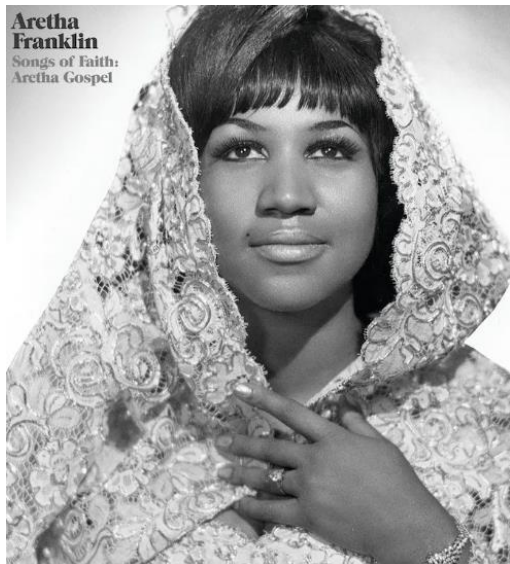
# Scope of the Problem



Worst survival of any solid tumor  
2024 US estimation

- 66,440 new cases
- 51,750 deaths

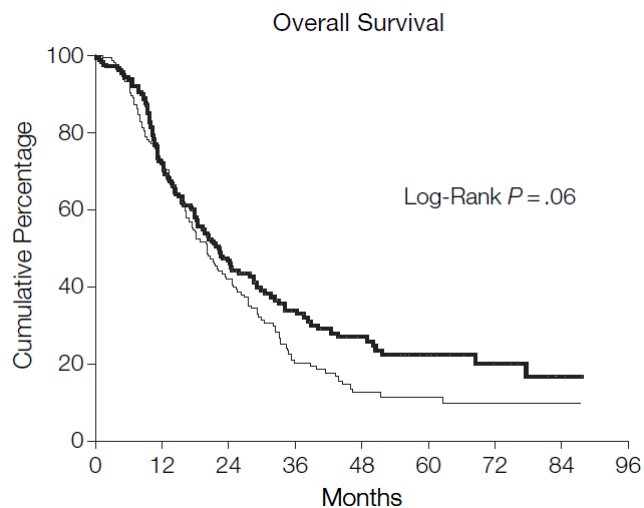
National Cancer Institute. SEER Stat Fact Sheets: Pancreas.



# Adjuvant Therapy for Pancreatic Cancer

## CONKO-01

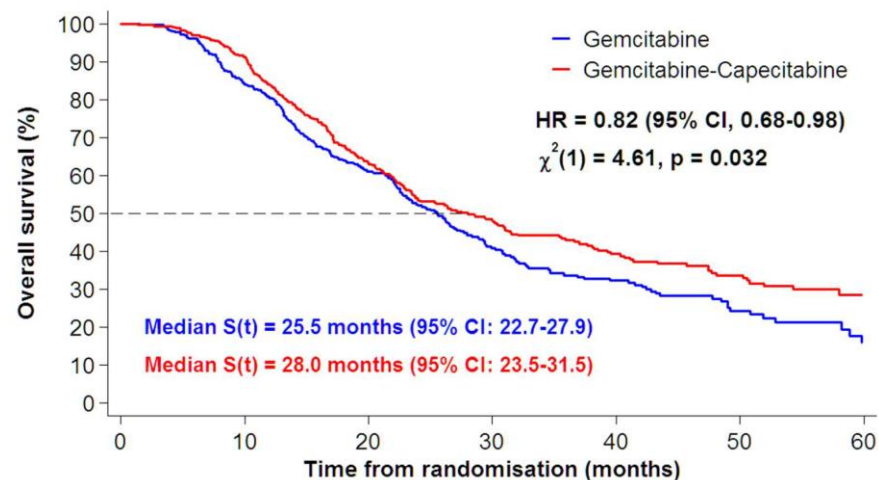
Gemcitabine



Median OS 20.2 vs **22.1** mo

## ESPAC4

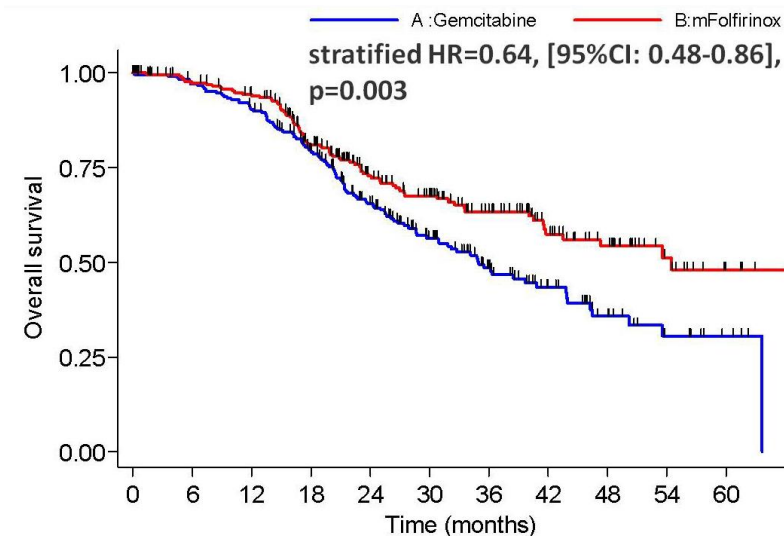
Gemcitabine + Capecitabine



Median OS 25.5 vs **28** mo

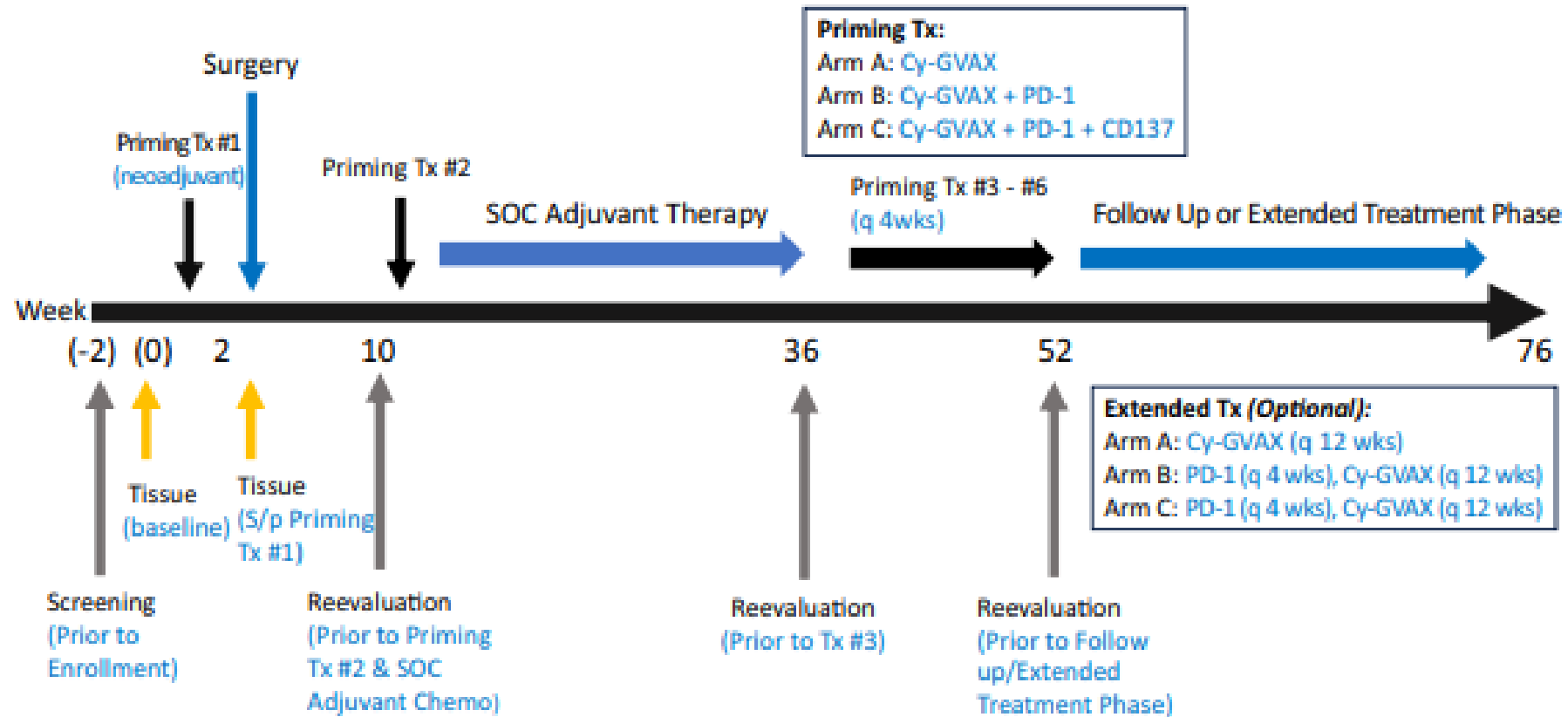
## PRODIGE 24

FOLFIRINOX

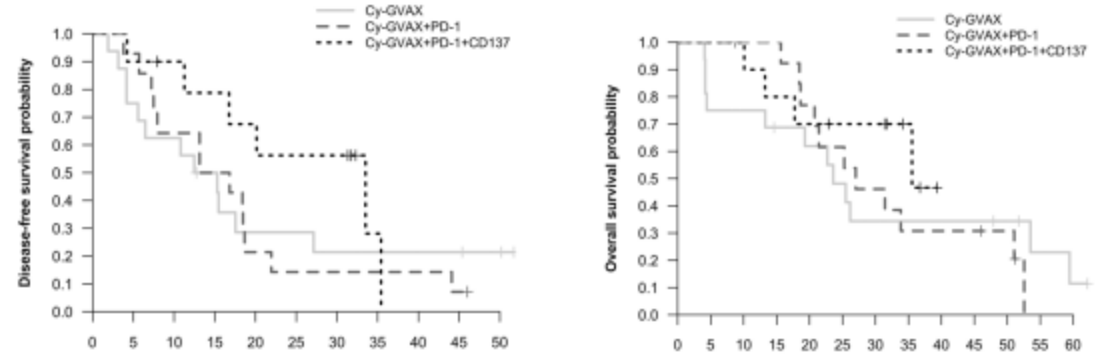
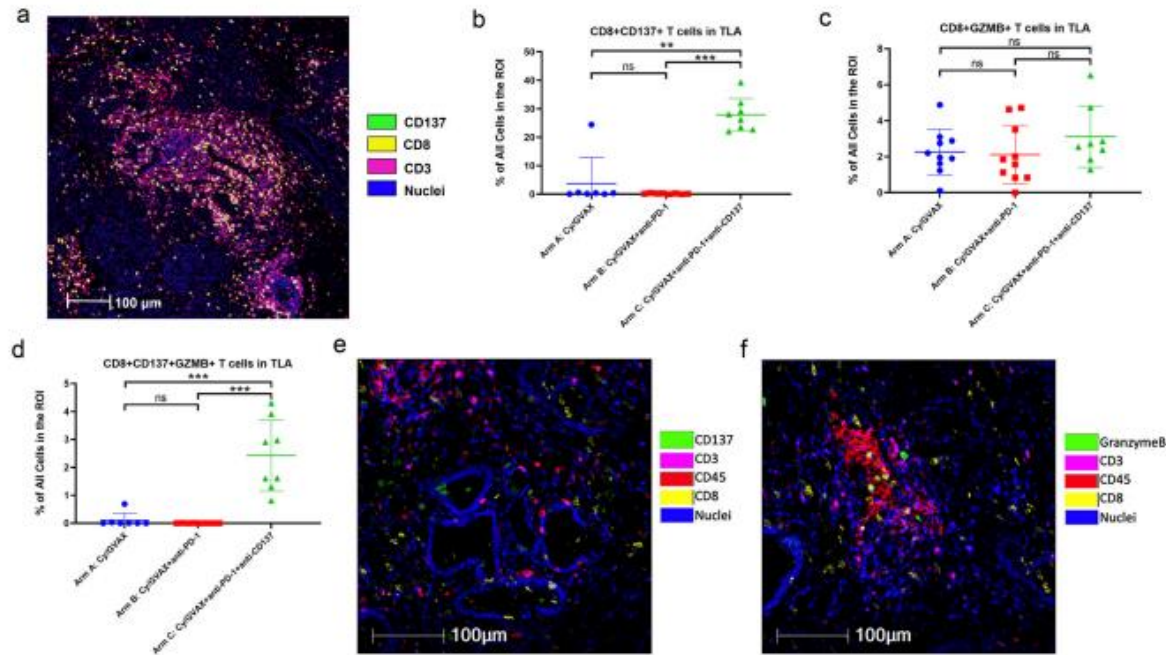


Median OS 35 vs **54.4** mo

# Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer



# Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer



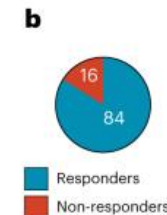
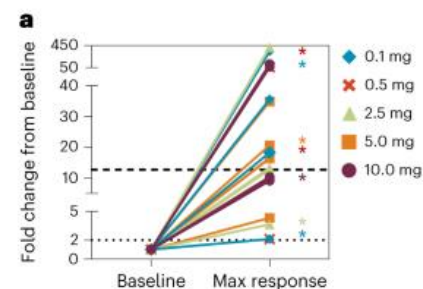
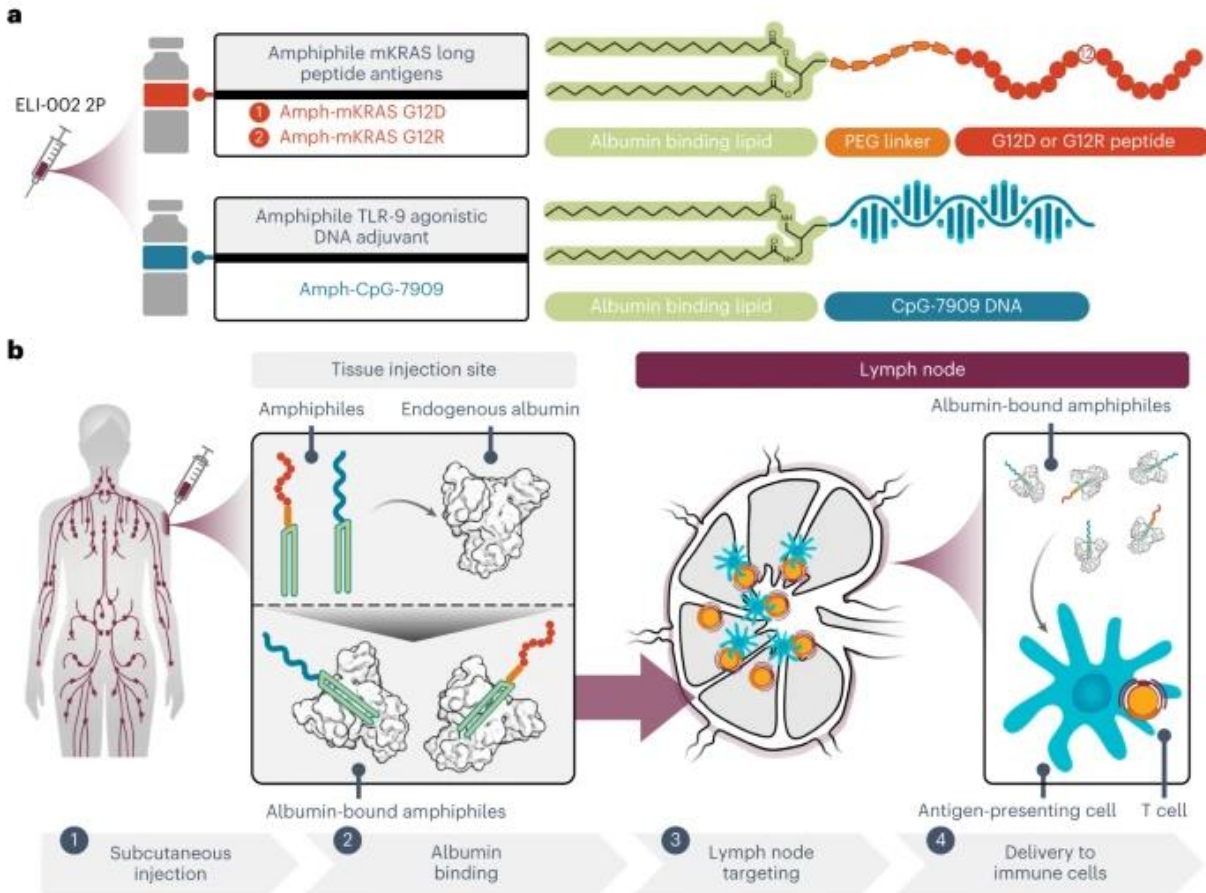
Median disease-free  
13.90/14.98/33.51 months

Overall survival  
23.59/27.01/35.55 months

GVAX+nivolumab+urelumab meets the primary endpoint by significantly increasing intratumoral CD8+ CD137+ cells

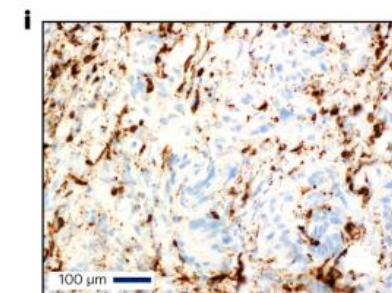
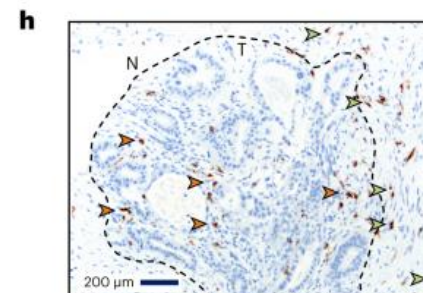
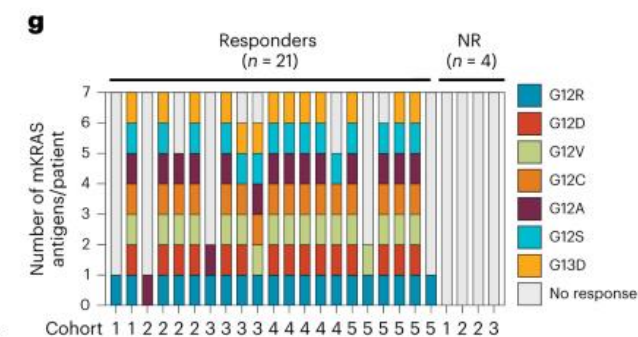
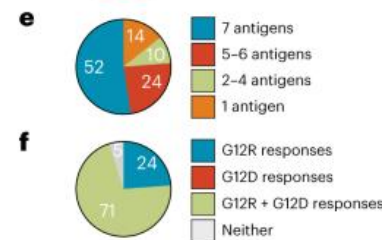
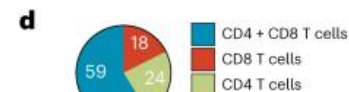


# Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: the phase 1 AMPLIFY-201 trial



**c**

Amph-CpG dose level	Ex vivo T cell response (n, %)	Average fold change
0.1 mg	2/3 (67%)	30
0.5 mg	4/6 (67%)	101
2.5 mg	4/5 (80%)	113
5.0 mg	5/5 (100%)	19
10.0 mg	6/6 (100%)	36
Total	21/25 (84%)	58



Pt. 2

N | Normal tissue

T | Tumor

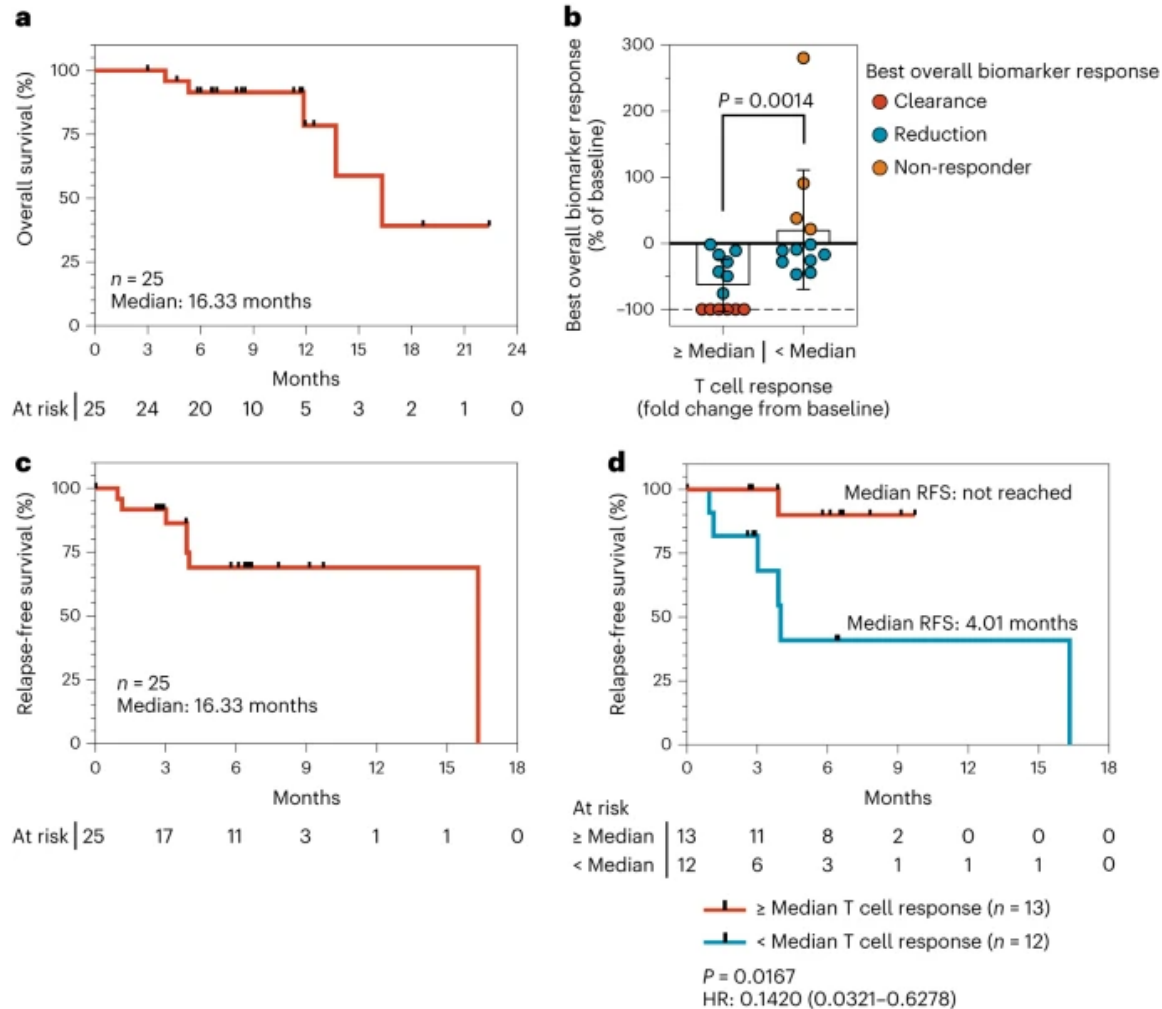
▶ Tumor infiltrating CD3<sup>+</sup>

▶ Tumor peripheral CD3<sup>+</sup>

Pt. 18

25 patients (20 pancreatic and five colorectal) who were positive for minimal residual mKRAS disease (ctDNA and/or serum tumor antigen)

# Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: the phase 1 AMPLIFY-201 trial



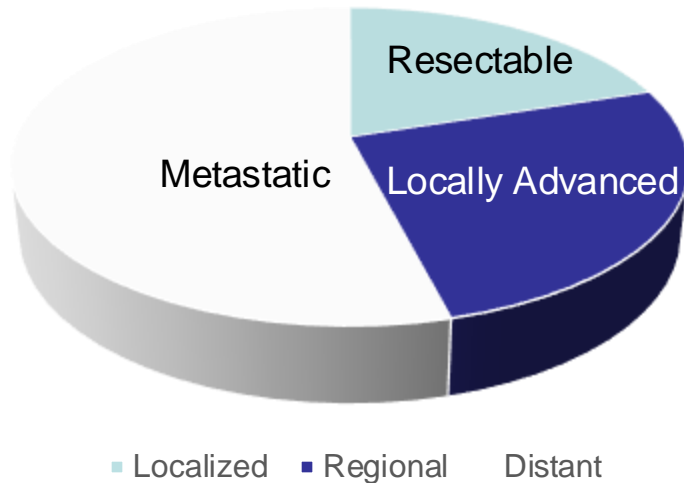
mKRAS T cell response correlates to tumor biomarker response and delayed tumor recurrence

We are currently testing a 7 KRAS lipid conjugated peptide variant in a randomized phase 2 study



# Detecting pancreatic cancer early can save lives

## Initial Presentation at Diagnosis

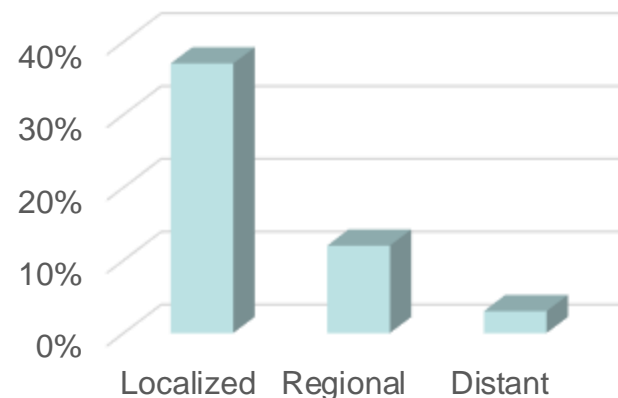


Ajay Goel, PhD

## • Pancreatic Cancer Detection Consortium U01

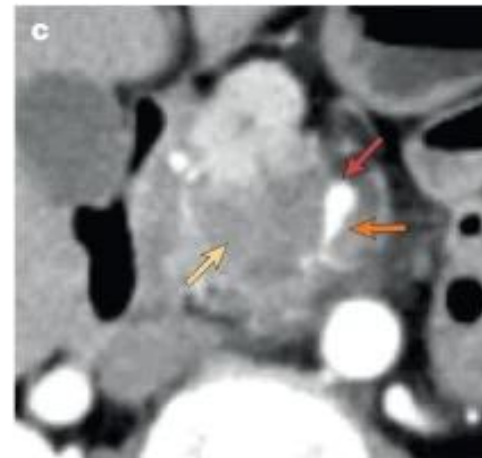
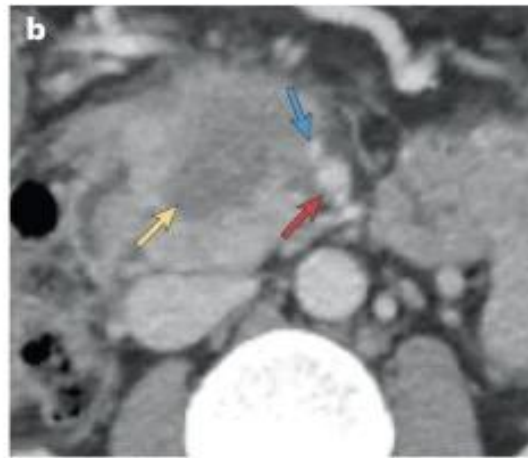
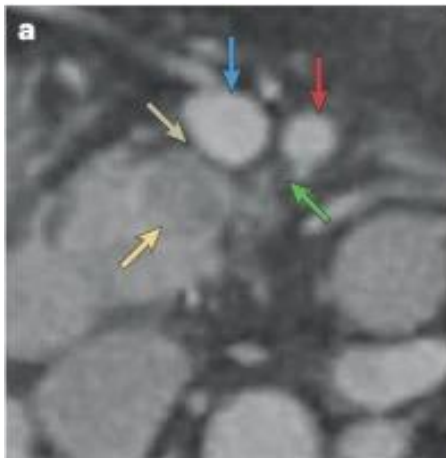
- International collaboration
- Blood test for early detection
- Free-floating and exosome-packaged microRNAs
- Exosomes from each organ are stamped with a unique mark, like a ZIP code, allowing researchers to zero in on exosomes made by the pancreas.
- High risk individuals: chronic pancreatitis or new-onset diabetes
- Early results showed that combining the blood test with CA19-9 accurately identified 97% of the people with early stage pancreatic cancer (presented at AACR 2024)

## 5-year Relative Survival Rates

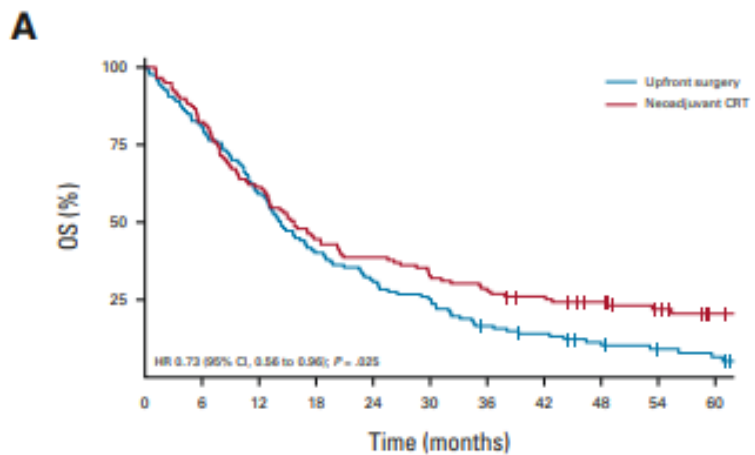
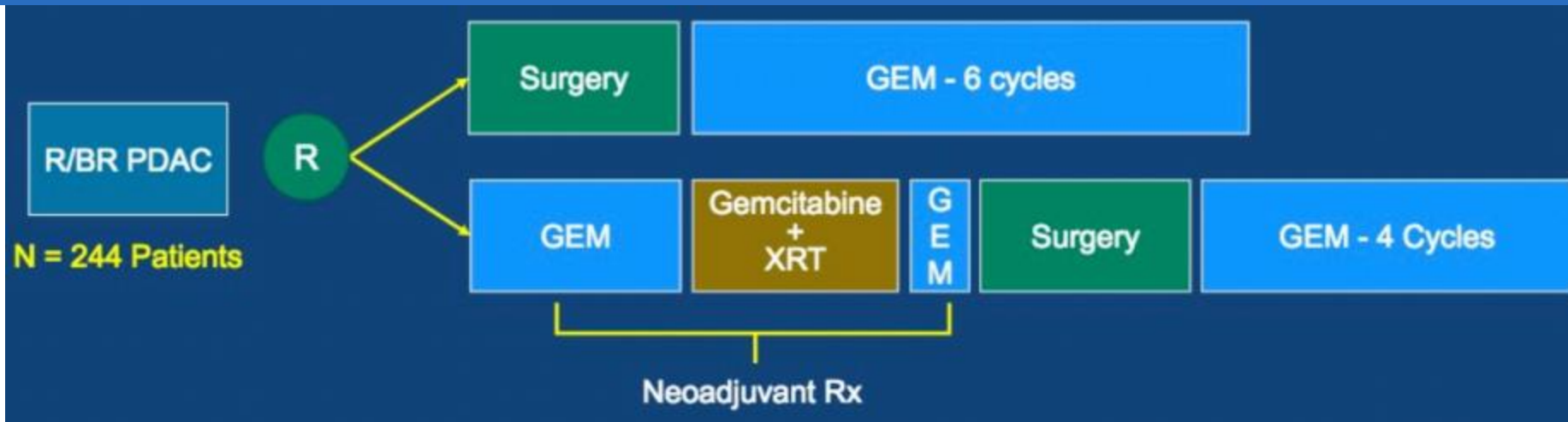


# Neoadjuvant Treatment

- Provides early treatment of micrometastatic disease
- Opportunity to downstage tumors to make them resectable
- Avoids surgery in patients with rapidly progressive disease
- Challenges
  - Chemotherapy is toxic and some patients are unable to tolerate
  - Resectable disease can become unresectable if complications from chemotherapy prevent treatment

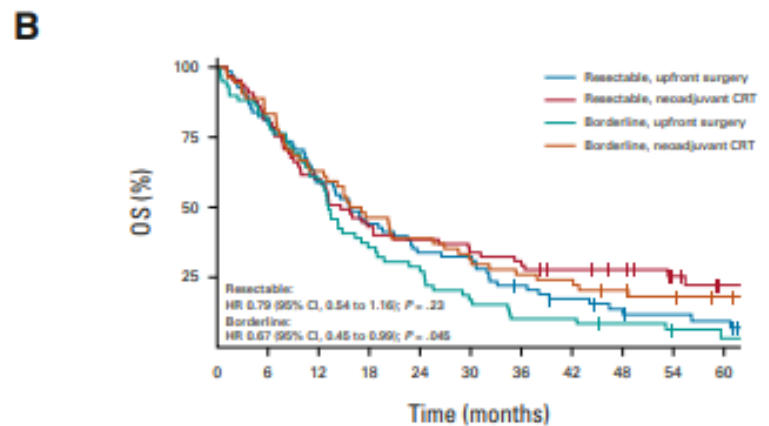


# Neoadjuvant Chemoradiotherapy Versus Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Long-Term Results of the Dutch Randomized PREOPANC Trial



No. at risk:

	0	6	12	18	24	30	36	42	48	54	60
Upfront surgery	127 (0)	103 (0)	75 (0)	51 (0)	40 (0)	32 (0)	20 (1)	16 (2)	11 (4)	7 (6)	5 (6)
Neoadjuvant CRT	119 (0)	98 (0)	73 (0)	53 (0)	46 (0)	39 (0)	34 (0)	29 (2)	24 (5)	17 (10)	11 (10)

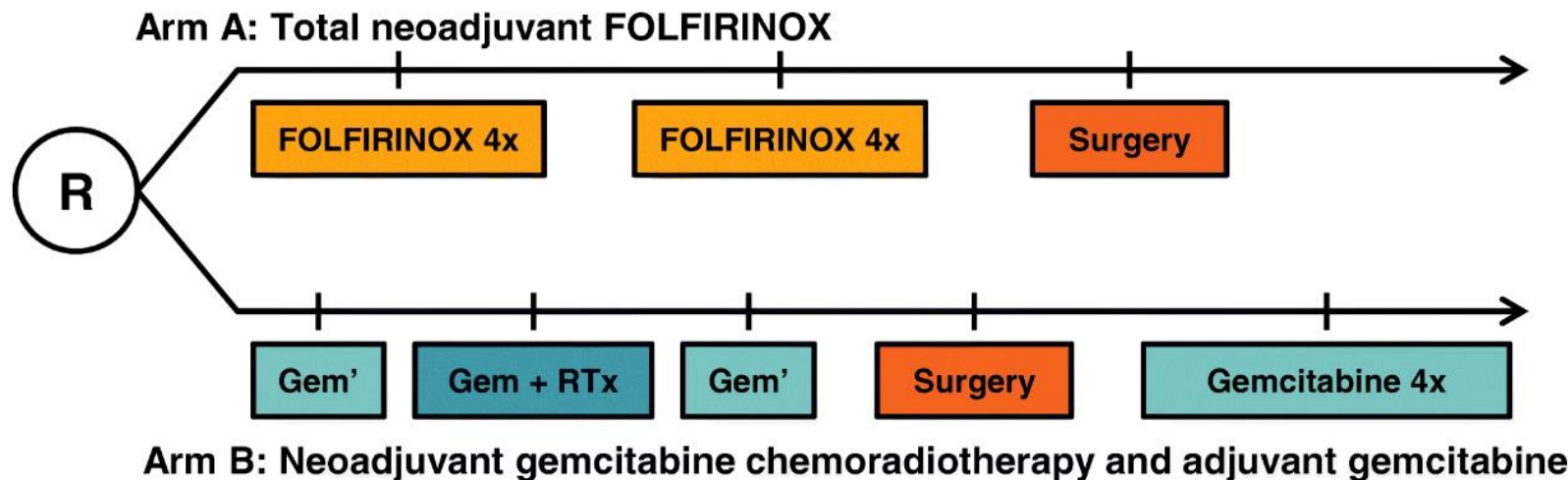


No. at risk:

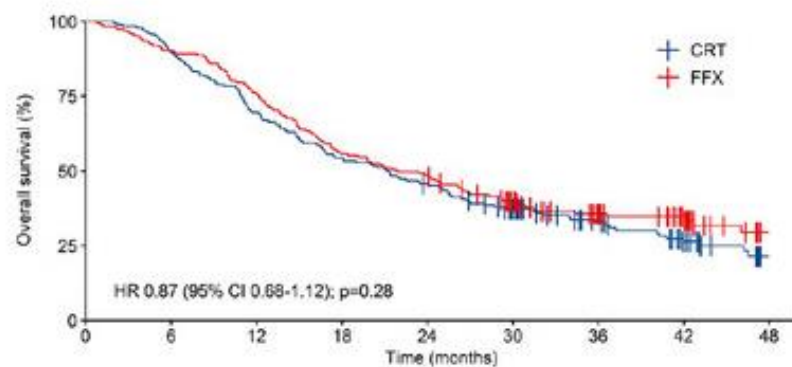
	0	6	12	18	24	30	36	42	48	54	60
Resectable, upfront surgery	68 (0)	55 (0)	40 (0)	30 (0)	23 (0)	22 (0)	14 (1)	10 (2)	7 (3)	5 (4)	4 (4)
Resectable, neoadjuvant CRT	65 (0)	53 (0)	39 (0)	28 (0)	25 (0)	22 (0)	20 (0)	16 (2)	14 (4)	9 (8)	5 (11)
Borderline, upfront surgery	59 (0)	48 (0)	35 (0)	21 (0)	17 (0)	10 (0)	6 (0)	6 (0)	4 (1)	2 (2)	1 (2)
Borderline, neoadjuvant CRT	54 (0)	45 (0)	34 (0)	25 (0)	21 (0)	17 (0)	14 (0)	13 (0)	10 (1)	8 (2)	6 (4)

- April 2013 and July 2017
- 246 eligible patients
- Median overall survival by ITT was 16.0 months with preoperative chemoradiotherapy and 14.3 months with immediate surgery
- More benefit in borderline resectable patients

# Neoadjuvant FOLFIRINOX versus gemcitabine-based chemoradiotherapy in the PREOPANC-2 trial (ESMO Congress 2023, LBA83)



## Overall Survival



Median OS	
FFX	21.9 (17.7-27.0)
CRT	21.3 (16.8-25.5)

1-year OS	
FFX	75.7%
CRT	69.6%

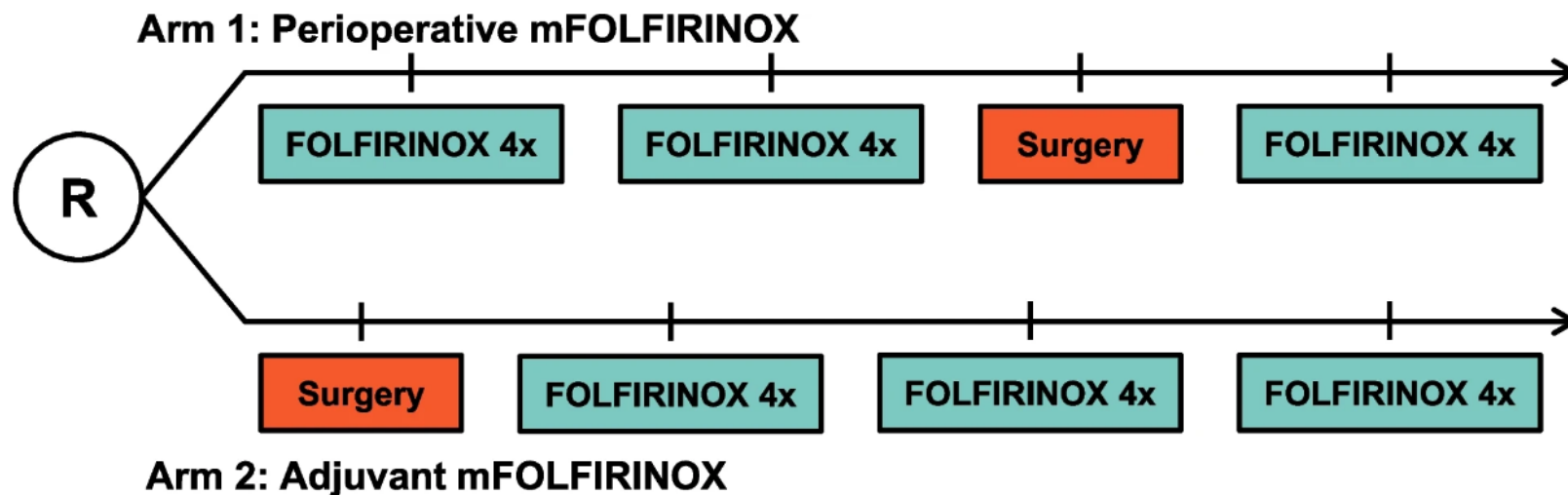
2-year OS	
FFX	48.6%
CRT	45.7%

3-year OS	
FFX	35.6%
CRT	32.8%

Number at risk	
CRT	184 165 128 100 83 61 39 24 7
FFX	185 167 140 103 90 64 43 28 9

- No overall (OS) benefit
- Median OS was 21.9% versus 21.3%
- Resection rates 77% versus 75%
- Serious adverse rates (49% versus 43%, respectively; p=0.26) were also similar between treatment arms

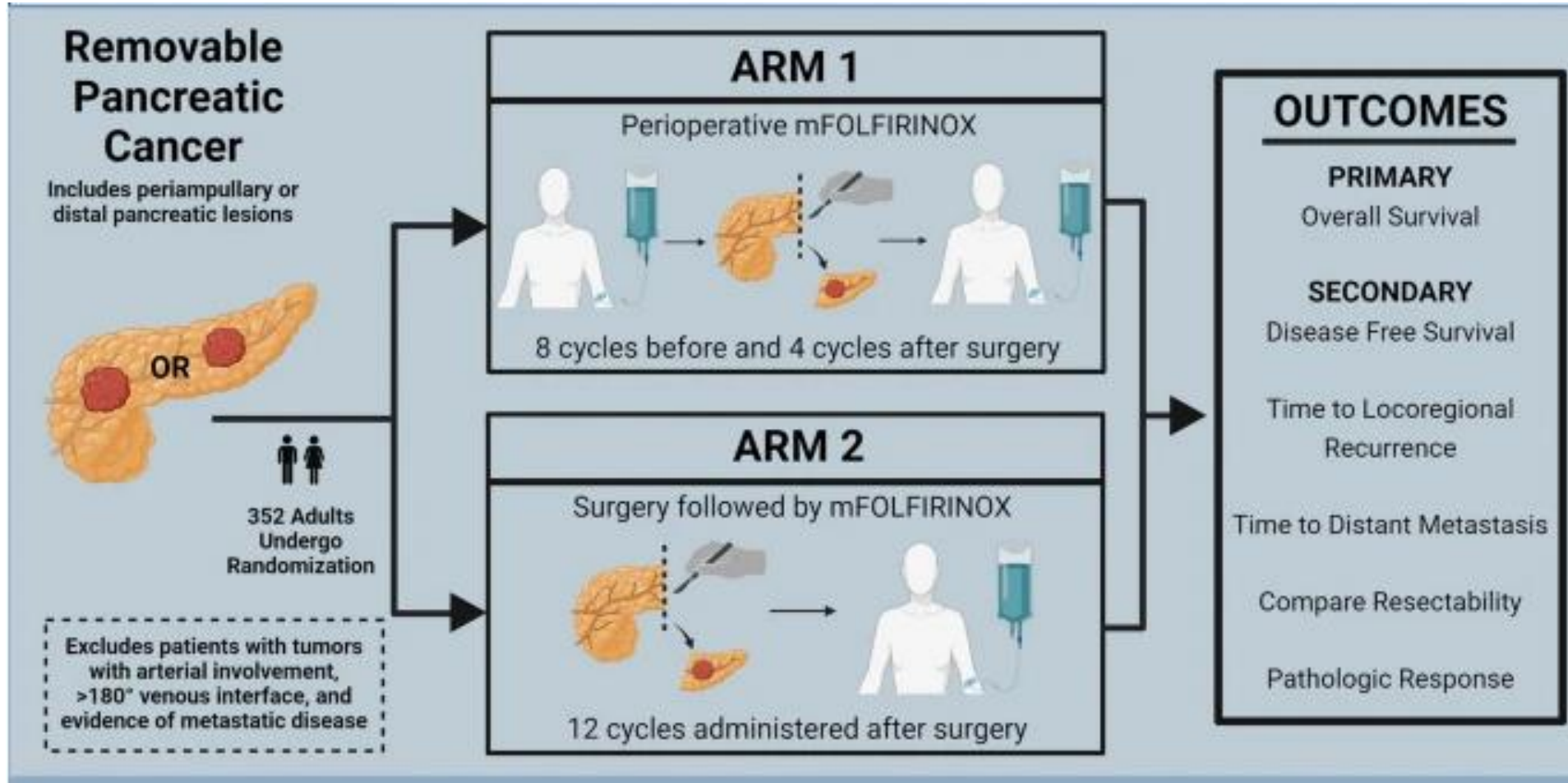
# Perioperative or adjuvant mFOLFIRINOX for resectable pancreatic cancer (PREOPANC-3): study protocol for a multicenter randomized controlled trial



	<b>Celiac axis</b>	<b>Superior mesenteric artery</b>	<b>Common hepatic artery</b>	<b>Superior mesenteric vein / portal vein</b>
Resectable (all four required)	no contact	no contact	no contact	≤ 90° contact
Borderline Resectable (minimally one required)	≤ 90° contact	≤ 90° contact	≤ 90° contact	> 90–270° contact and no occlusion
Locally Advanced (minimally one required)	contact > 90°	contact > 90°	contact > 90°	contact > 270° or occlusion



# Alliance A021806: A phase III trial evaluating perioperative versus adjuvant therapy for resectable pancreatic cancer



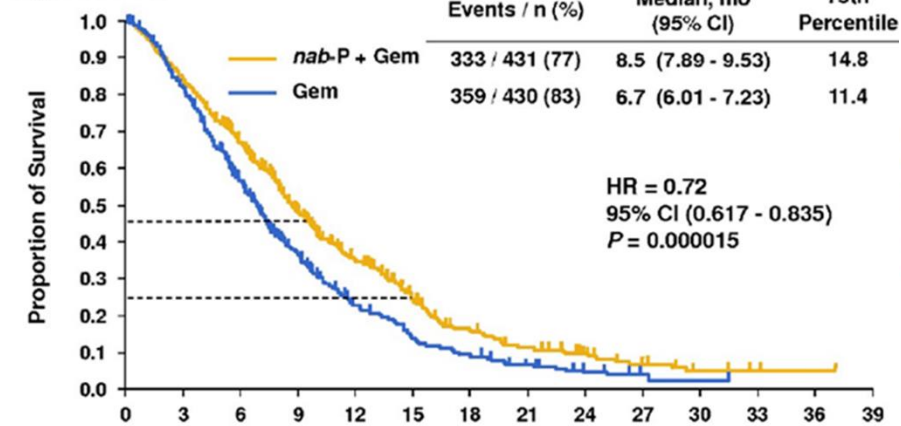
- Answer the question of chemotherapy timing for patients with resectable PDAC
- Consider accruing to this trial

# Management of Advanced Pancreatic Cancer

## MPACT

### Gemcitabine and nab-paclitaxel

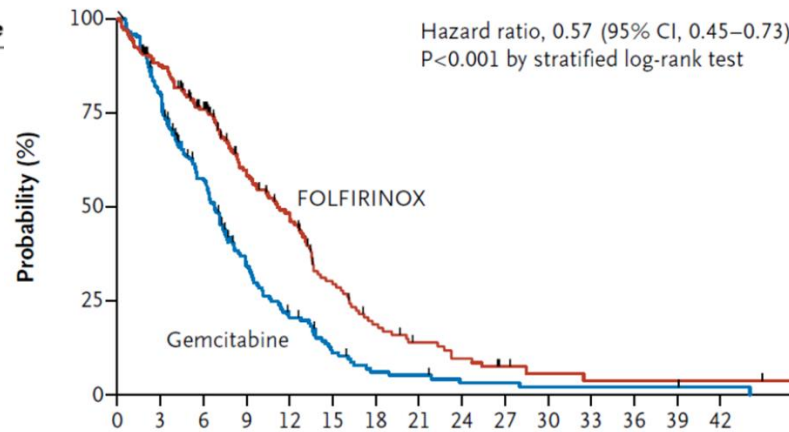
Figure 2. OS



Median OS **8.5** vs 6.7 mo

## PRODIGE 4 / ACCORD 11

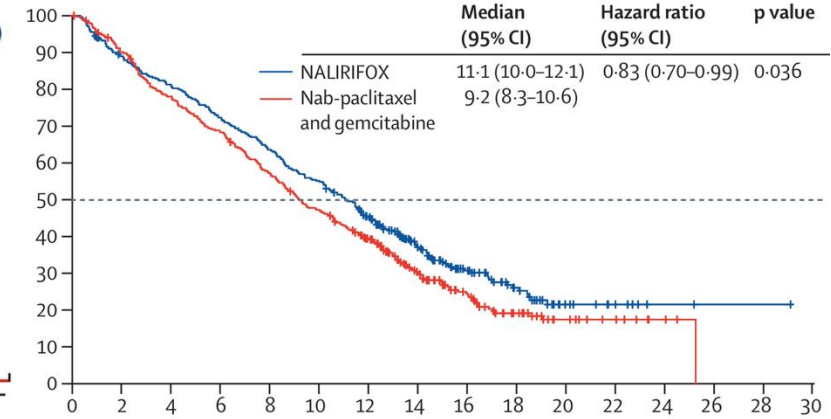
### FOLFIRINOX



Median OS **11.1** vs 6.8 mo

## NAPOLI-3

### NALIRIFOX



Median OS **11.1** vs 9.2 mo

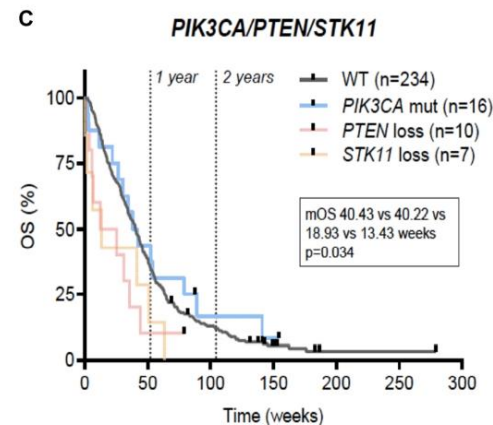
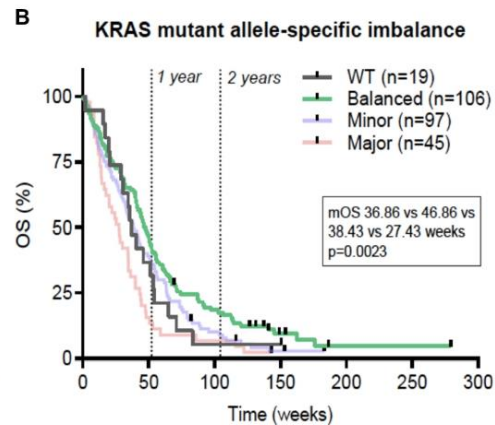
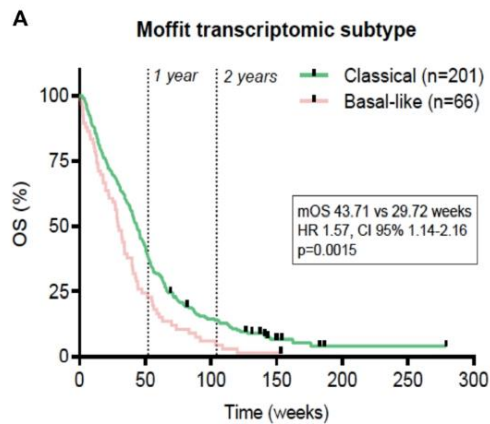
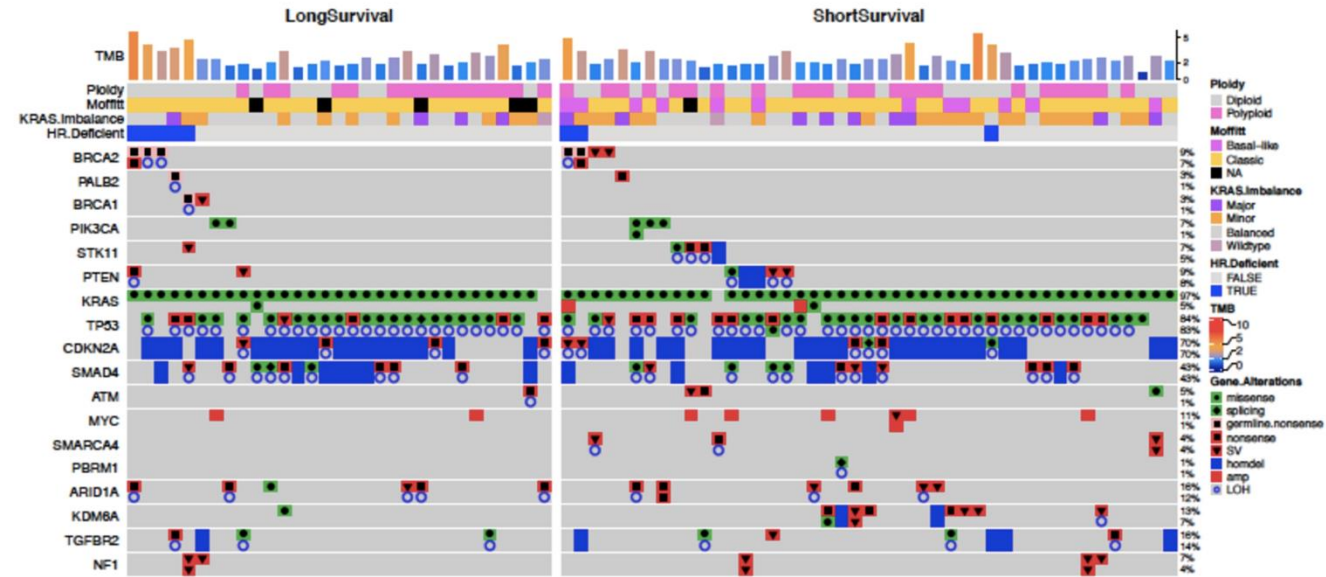
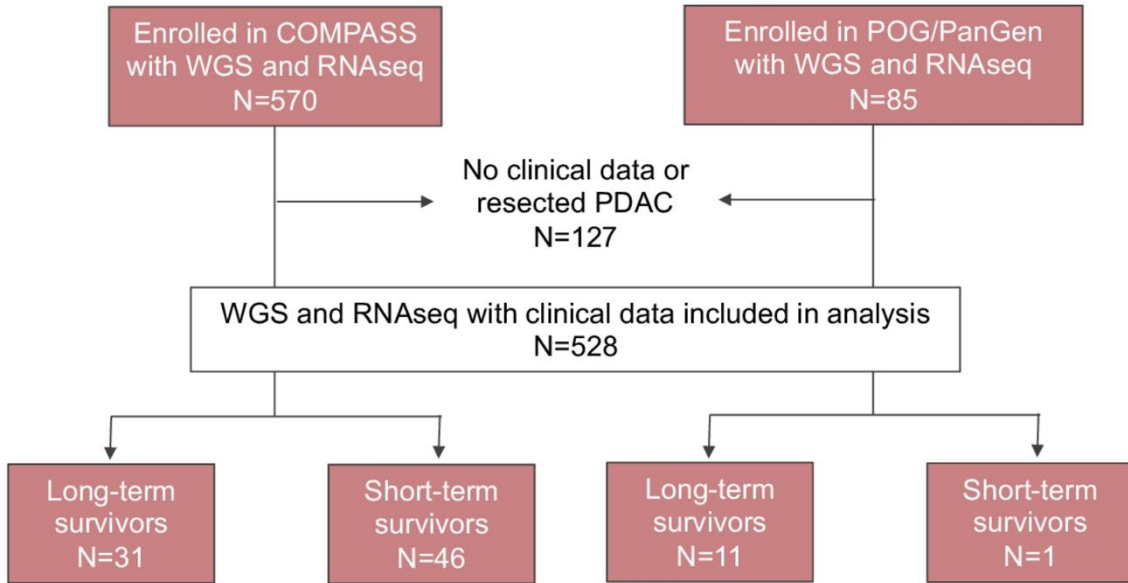
4-drug chemotherapy regimen is better than a 2-drug regimen

# Toxicity Profile

Grade 3/4 toxicity	Neutropenia	Fatigue	Diarrhea	Neuropathy
Gemcitabine + nab-paclitaxel	38%(25%)	17%(5%)	6%(5%)	17%(6%)
FOLFIRINOX (not modified)	45.7%	23.6%	12.7%	9%
NALIRIFOX	14%	6%	20%	3%

- mFOLFIRINOX, NALIRIFOX or gemcitabine + nab-paclitaxel are appropriate first line treatments for patients with metastatic disease
- Gemcitabine still standard for poor performance status pts

# COMPASS: Comprehensive Molecular Characterization of Advanced Pancreatic Ductal Adenocarcinoma for Better Treatment Selection



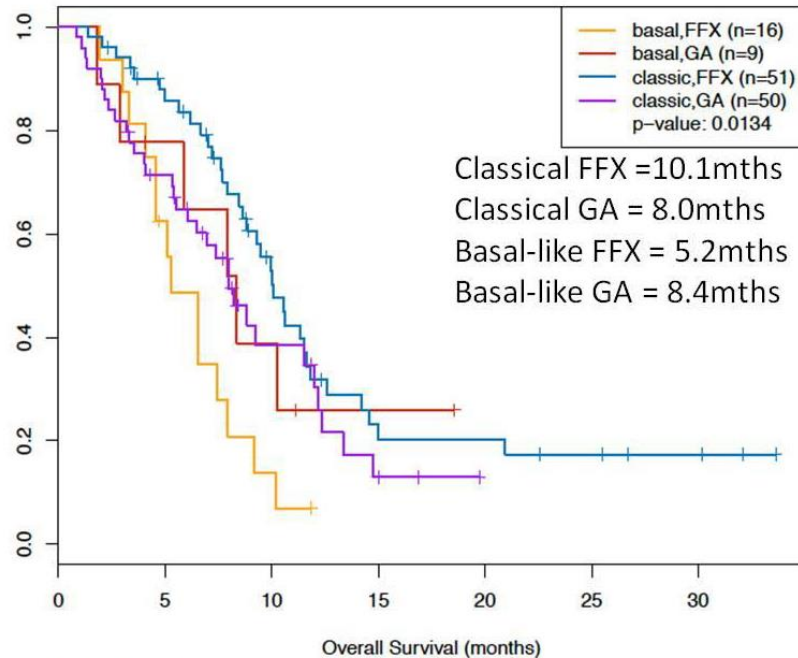
Survival  $\leq 3$  mo

- Enhanced RAS signaling
- Deregulation of the PI3K/AKT/mTOR pathway
- Basal-like transcriptomic subtype.



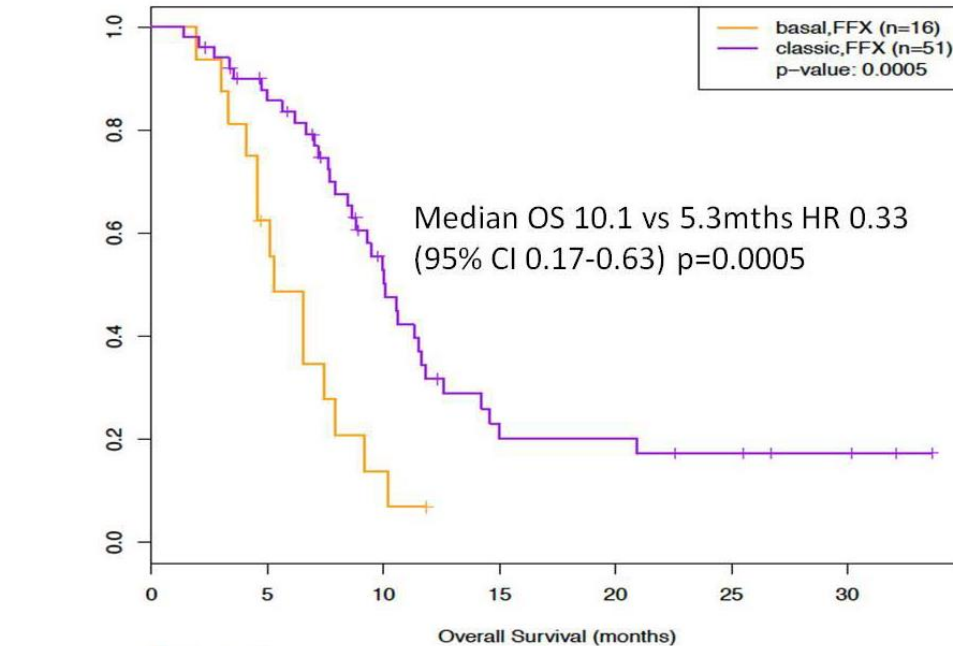
# Basal subtype overall worse prognosis compared to classical subtype

All patients  $\geq 1$  dose chemo n=126



	Number at risk						
	0	5	10	15	20	25	30
basal, FFX 16	16	9	2				
basal, GA 9	9	6	3	1			
classic, FFX 51	51	40	19	7	7	5	3
classic, GA 50	50	33	10	3			

OS mFFX only n=67

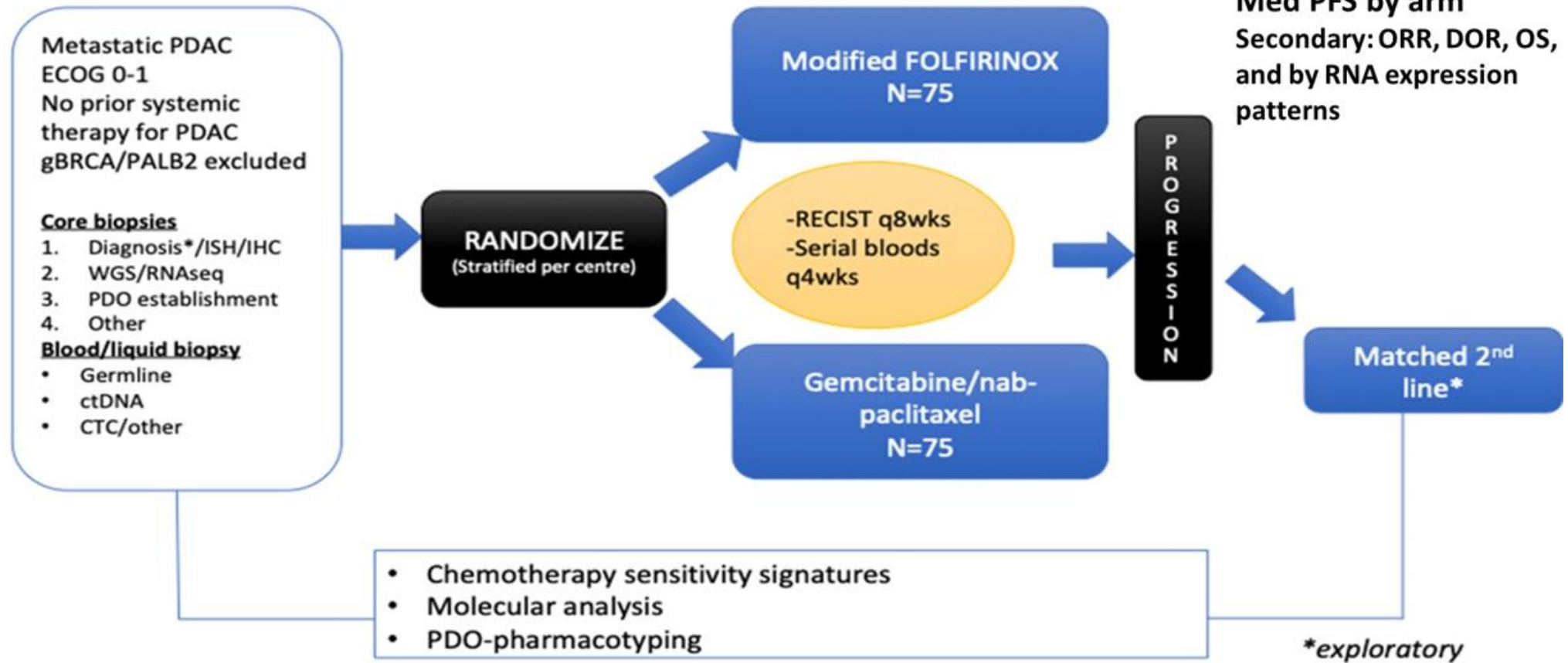


	Number at risk						
	0	5	10	15	20	25	30
basal, FFX 16	16	9	2				
classic, FFX 51	51	40	19	7	7	5	3



# Pancreatic adenocarcinoma signature stratification for treatment-01

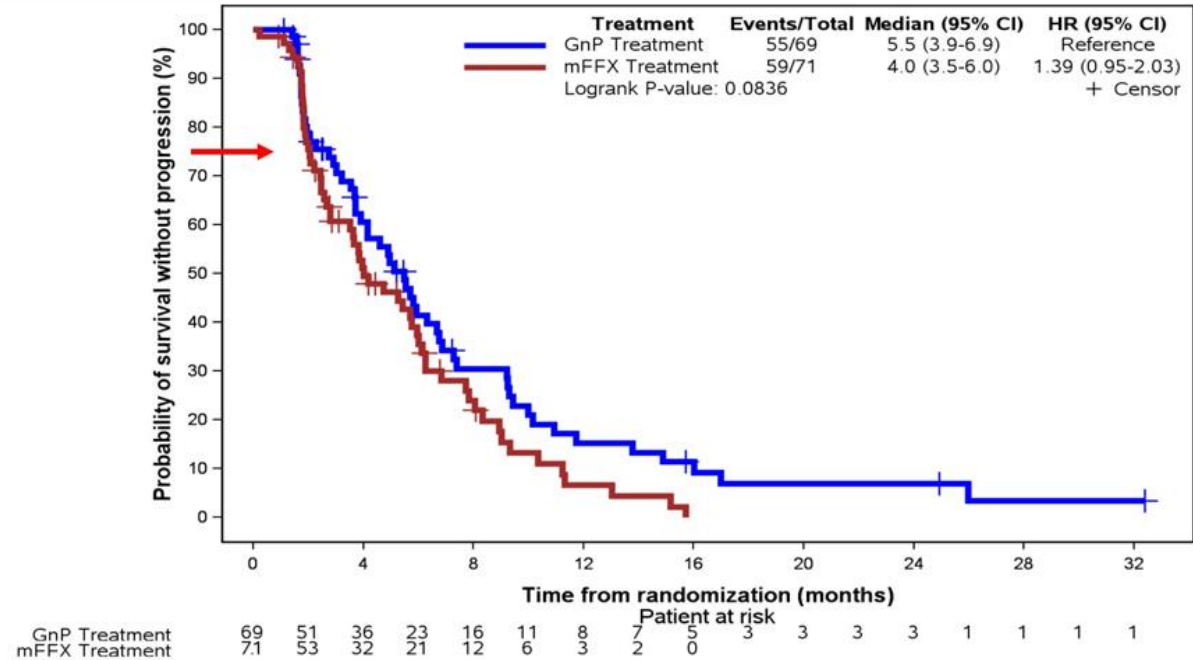
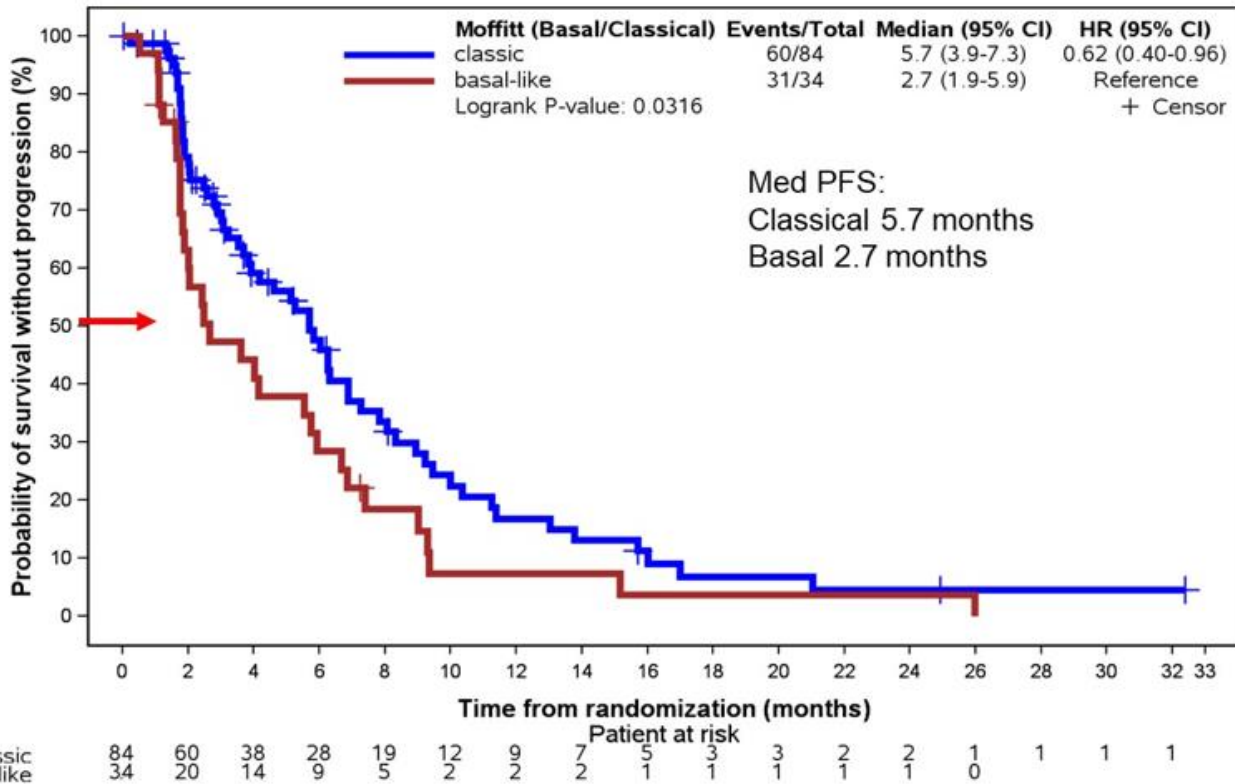
## PASS-01 Schema: Randomized phase II trial (n = 150)



+Eligible histological variants to also include mucinous adenocarcinoma or adenosquamous carcinoma

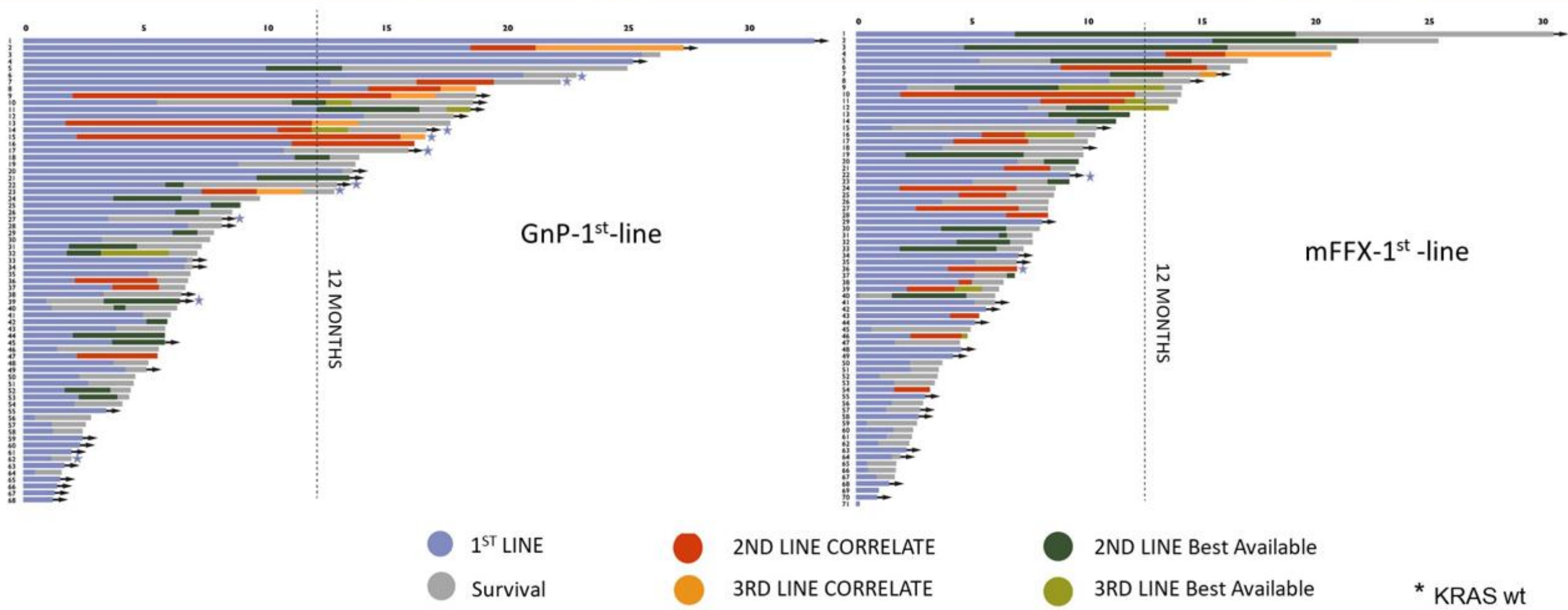
# PASS-01 PFS (Primary Endpoint)

- Basal subtype associated with poor prognosis



- Higher % KRAS wt in the Gem Nab arm (14% vs 4%)
- More basal subtype in the FFX arm

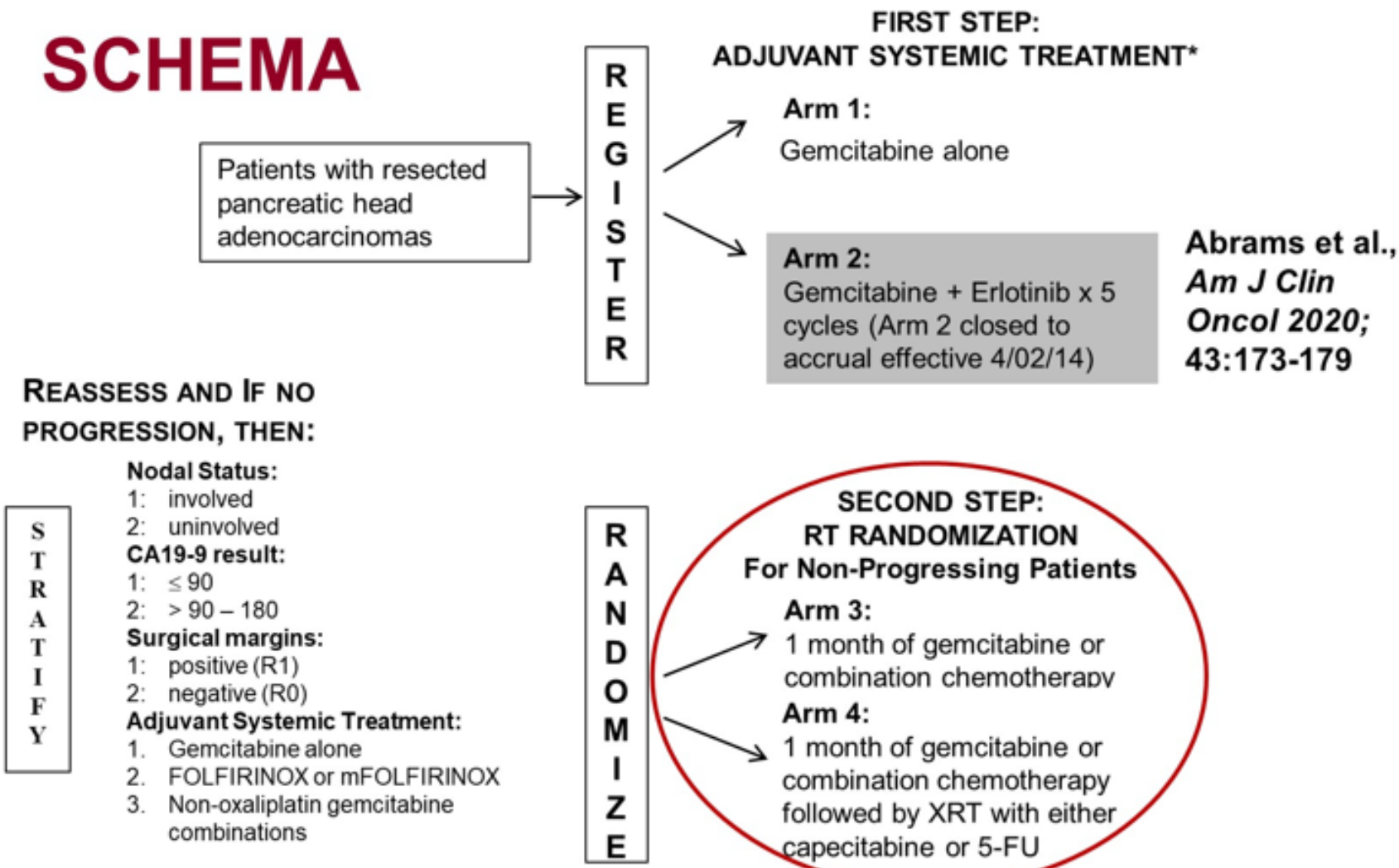
# 56% (64/114) patients were able to receive 2nd-line treatment: a correlate-guided approach was delivered in 50% (32/64)



**Correlate-guided Therapy (20 by genomics, 12 by PDOs over 28 Molecular Tumor Boards)**

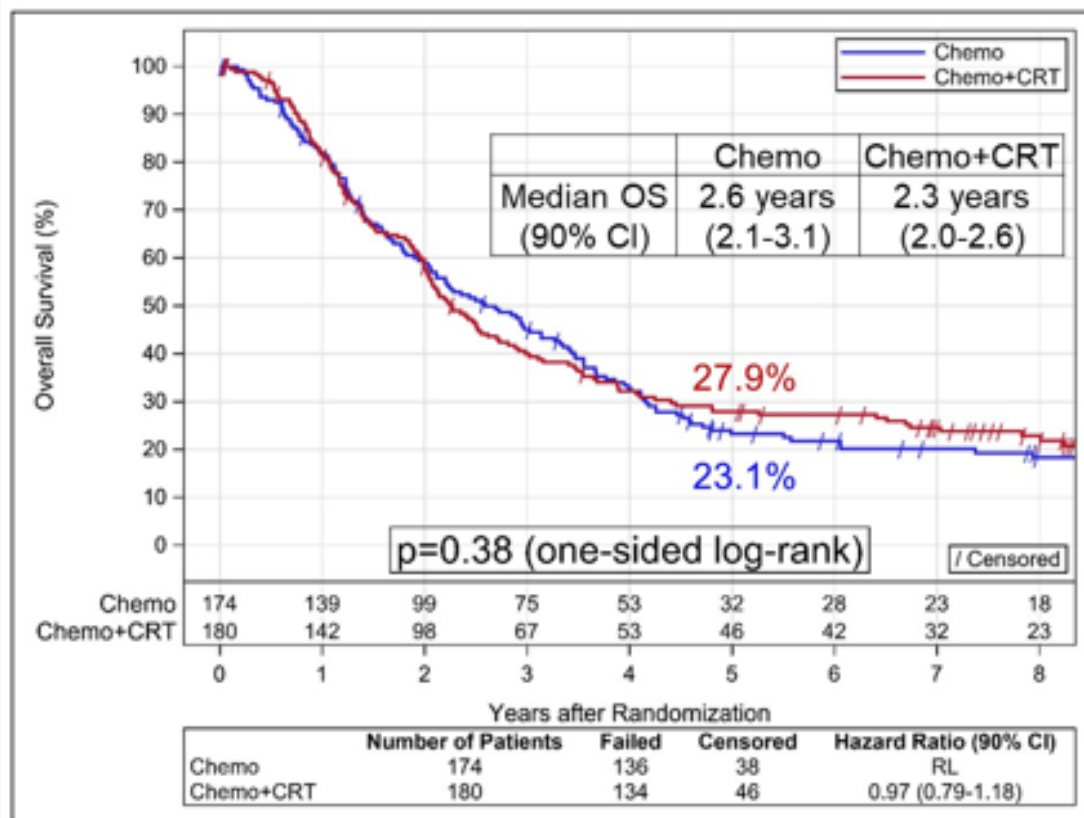
# NRG Oncology/RTOG 0848: Adjuvant chemotherapy +/- chemoradiation for patients with resected periampullary pancreatic adenocarcinoma

## SCHEMA

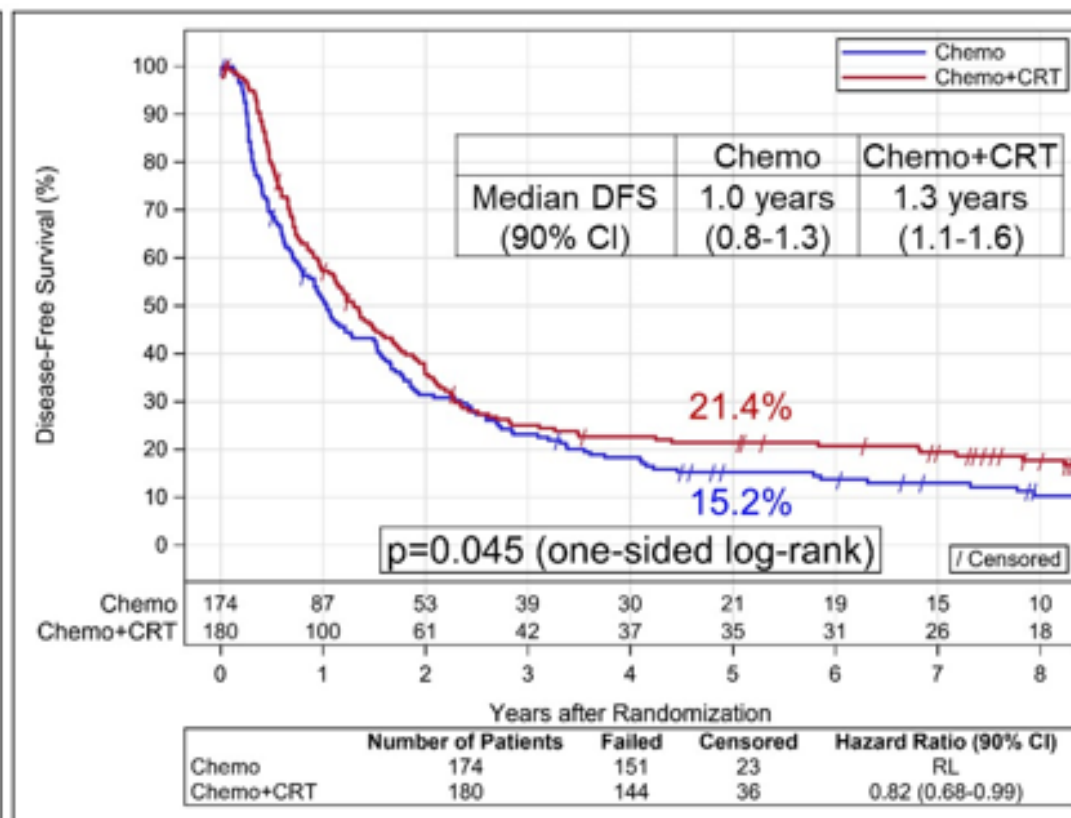




# NRG Oncology/RTOG 0848: Adjuvant chemotherapy +/- chemoradiation for patients with resected periampullary pancreatic adenocarcinoma



**Overall Survival**

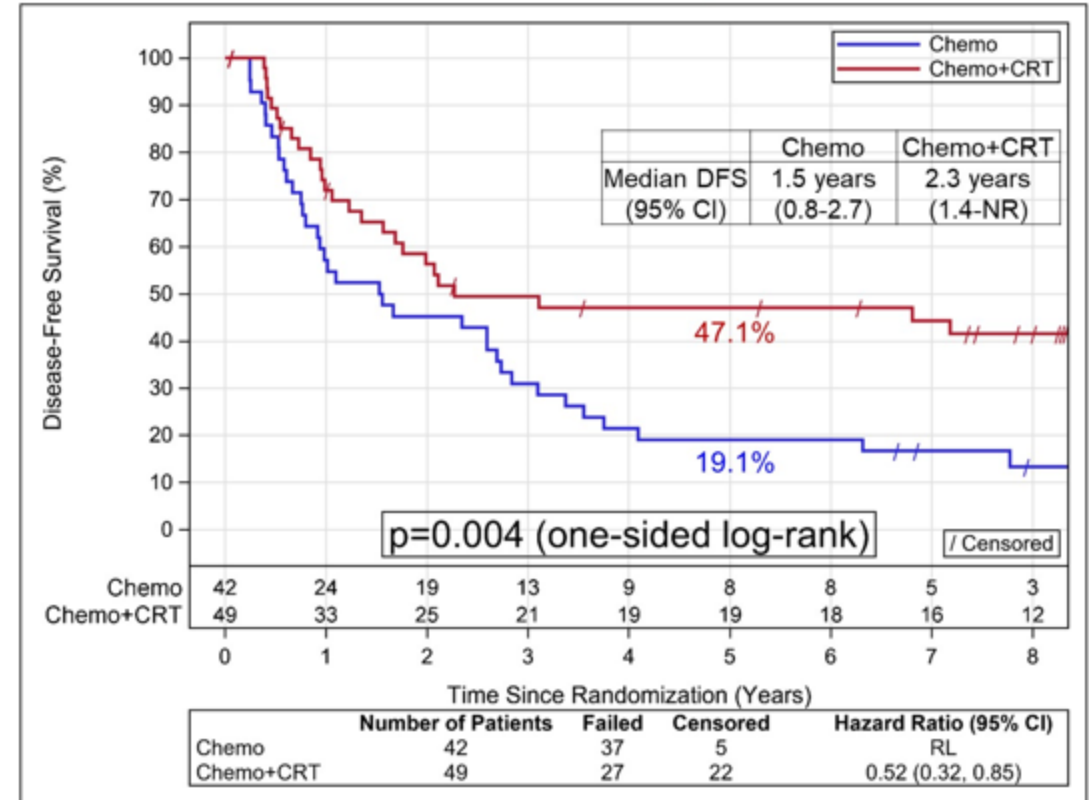
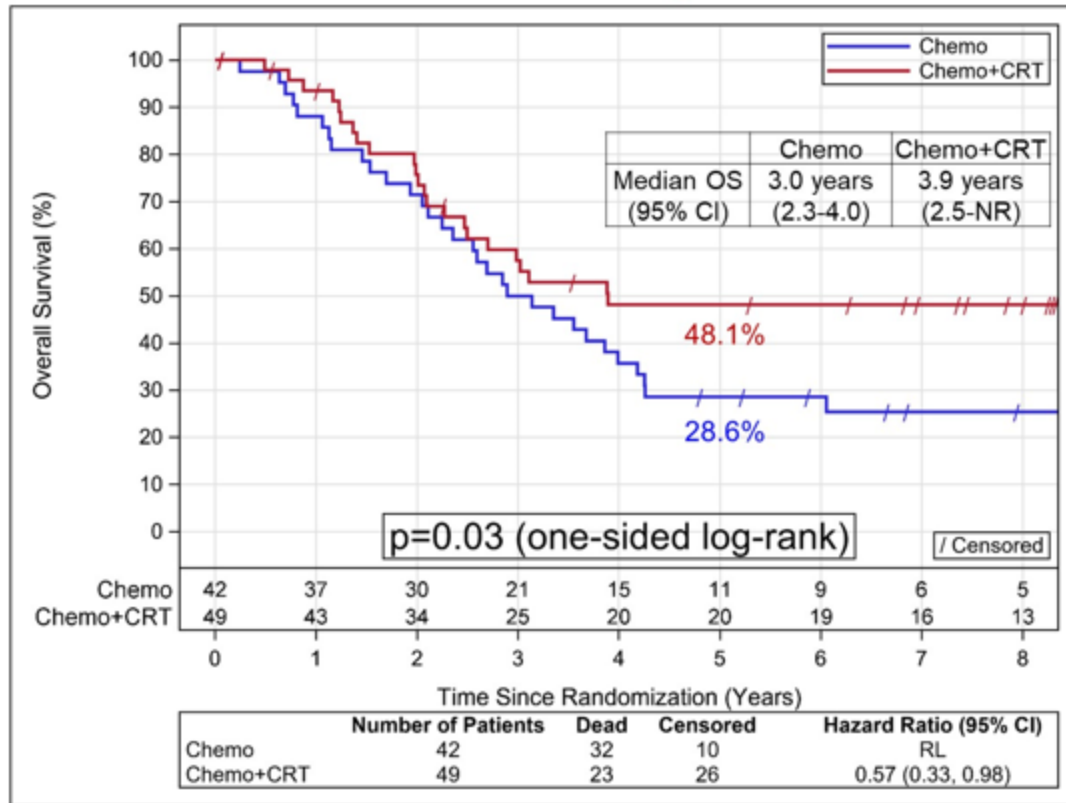


**Disease-Free Survival**

No difference in OS and DFS

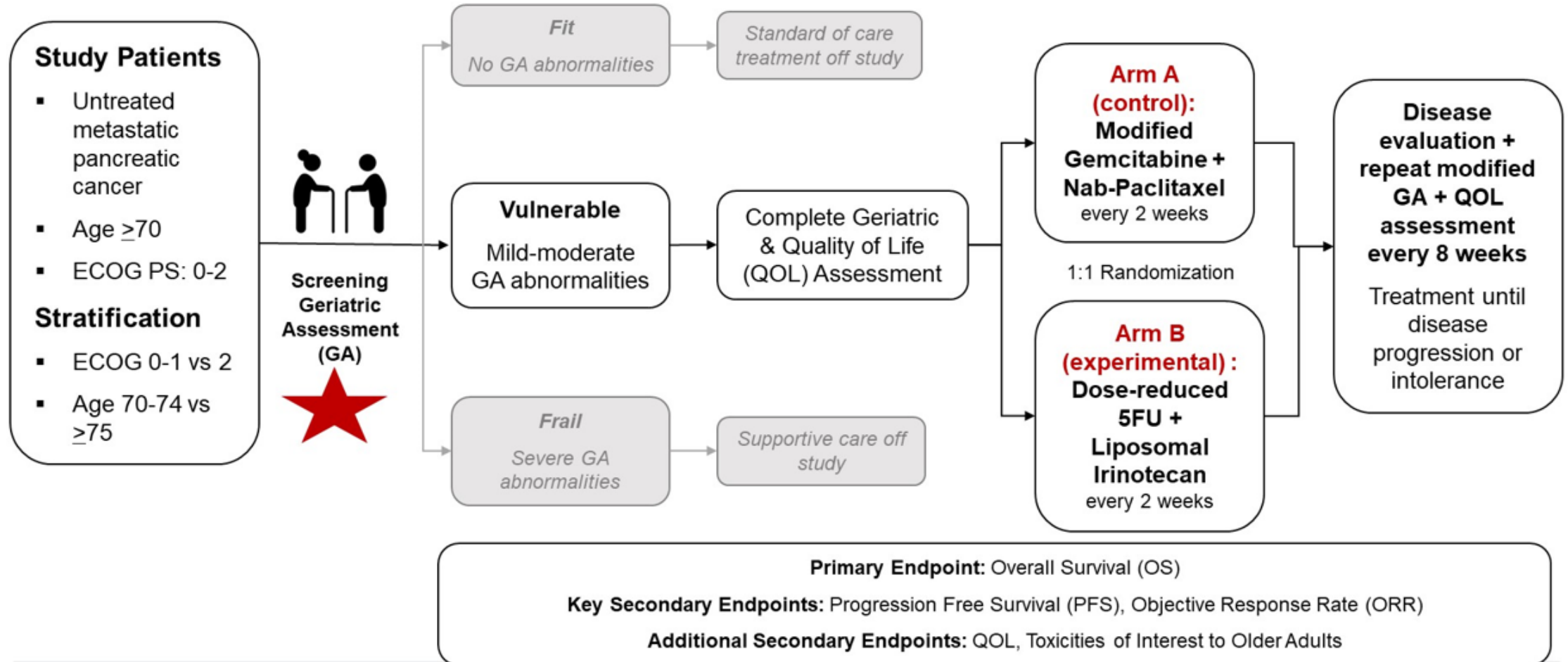


# NRG Oncology/RTOG 0848: Adjuvant chemotherapy +/- chemoradiation for patients with resected periampullary pancreatic adenocarcinoma

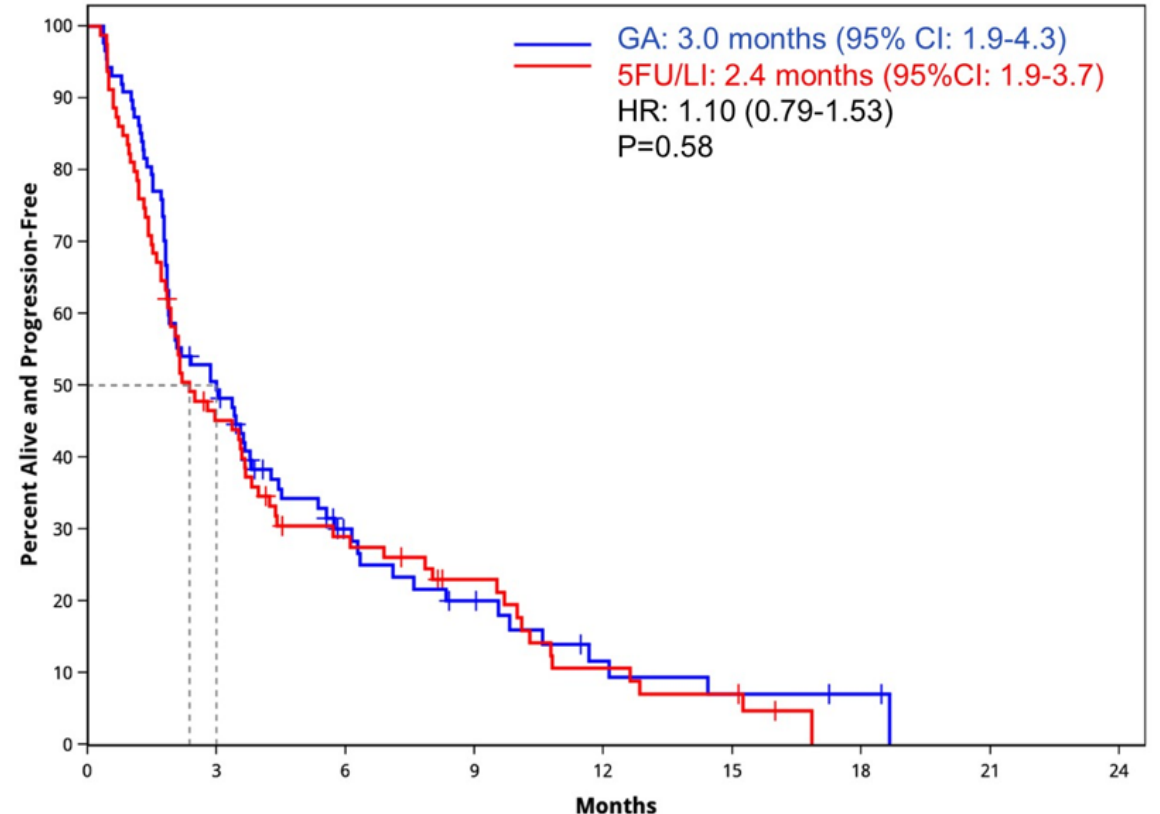
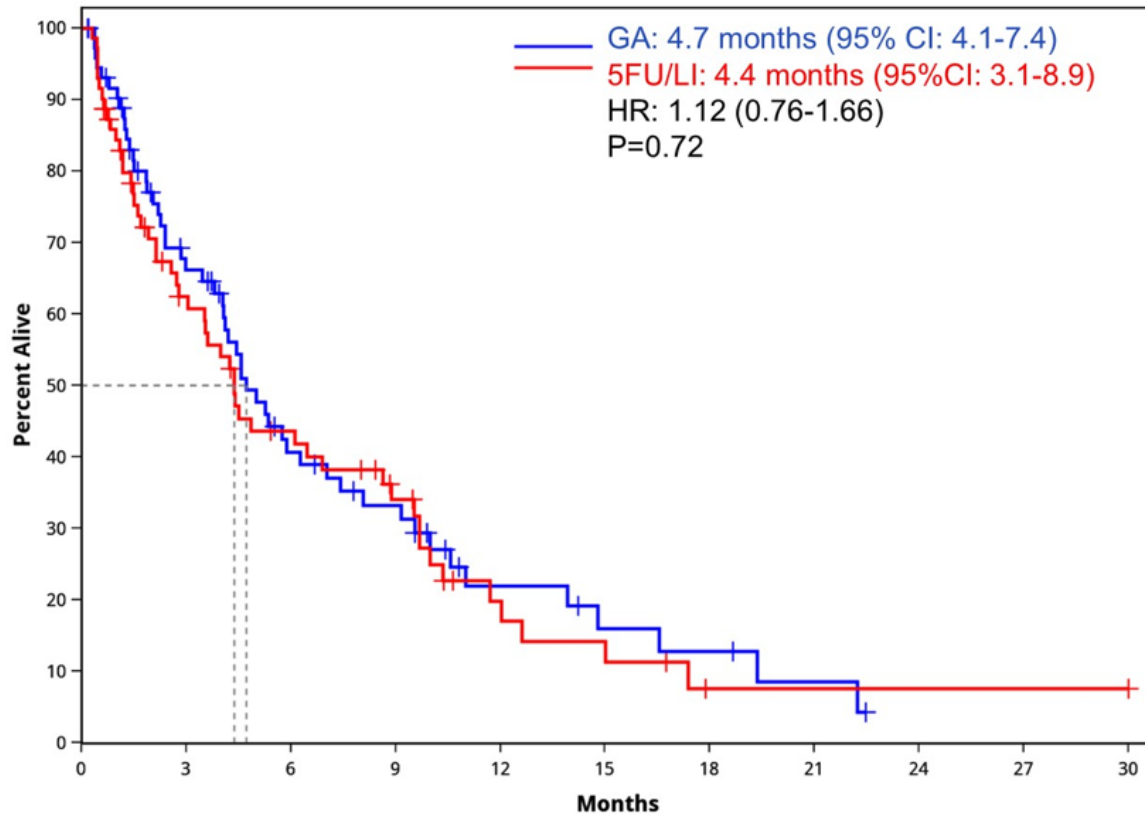


Chemo CRT improved OS and DFS in the node-negative patients  
 Limitations: Gemcitabine is an inferior adjuvant therapy

# ECOG-ACRIN EA2186 (GIANT Trial)



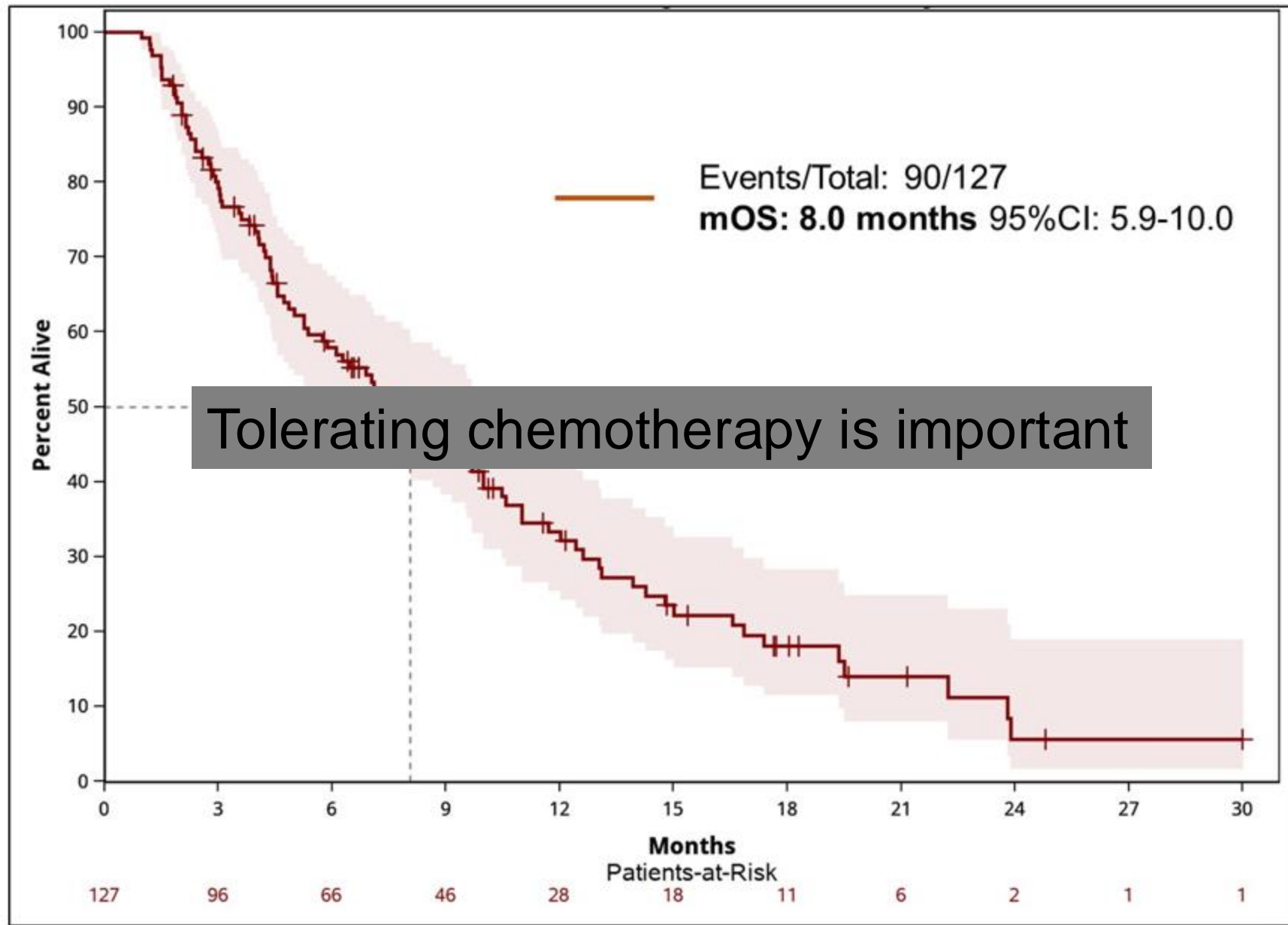
# ECOG-ACRIN EA2186 (GIANT Trial)



No difference in OS and PFS  
OS of 4.7 and 4.4 months is worse than expected in this  
population of vulnerable older adults

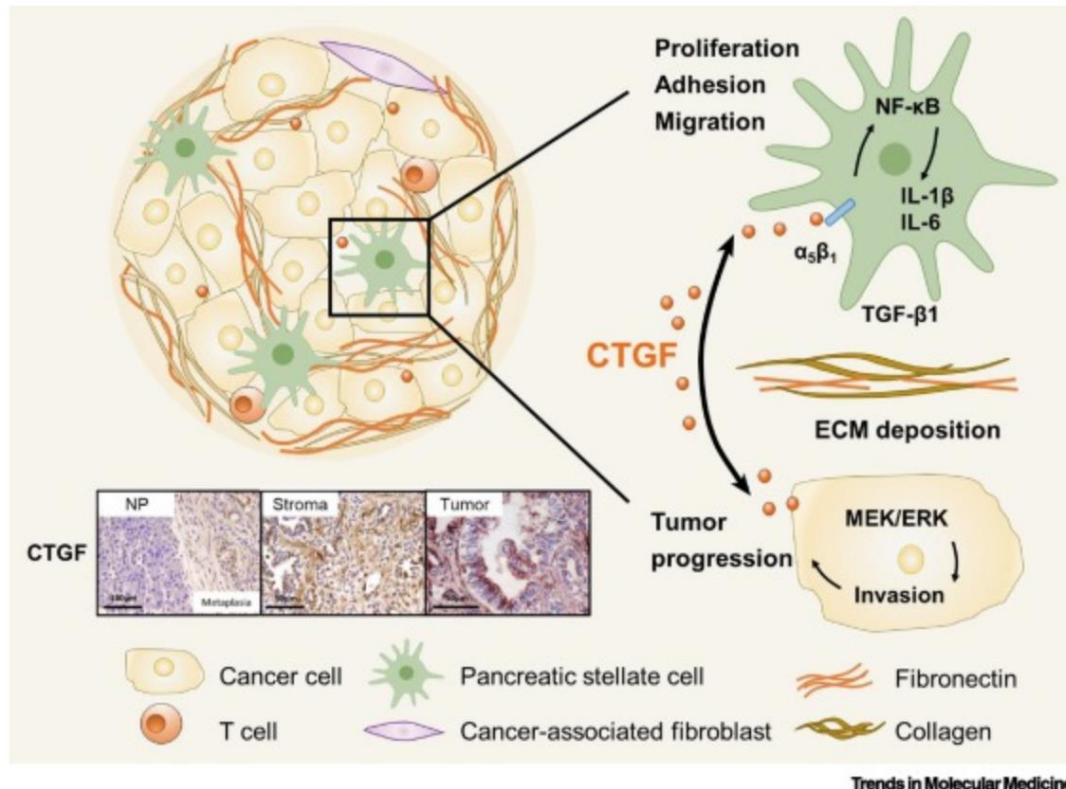
# OS analysis of patients who received $\geq 4$ weeks of treatment

Number of chemotherapy doses	N (%)
0	22 (12.5%)
1	22 (14.3%)
$\geq 2$	127 (72%)



# Topline Results from Two Late-Stage Pamrevlumab Pancreatic Cancer Studies Were Announced in Press Release July 31, 2024

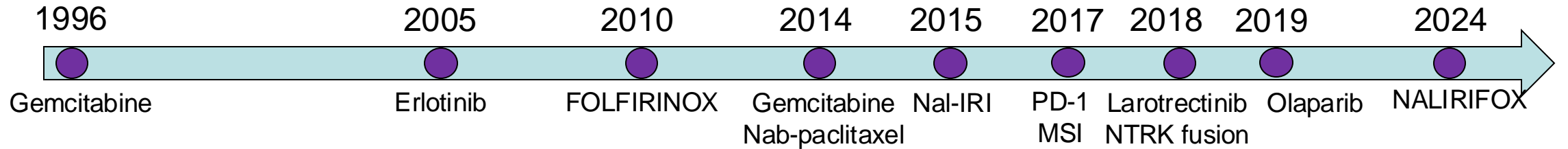
- Pamrevlumab - human monoclonal antibody targeting connective tissue growth factor (CTGF) with potential anti-fibrotic and antineoplastic activities.



- LAPIS (284 pt):** Gemcitabine and nab-paclitaxel or oxaliplatin, folinic acid, irinotecan, and fluorouracil (FOLFIRINOX) with and without pamrevlumab. Median OS was 17.3 months in the pamrevlumab arm vs 17.9 months in the comparator arm (HR, 1.08; 95% CI, 0.83-1.41; stratified log-rank P =.55).
- Precision Promise (825 pt):** Pamrevlumab plus gemcitabine and nab-paclitaxel vs gemcitabine and nab-paclitaxel alone in first- and second-line metastatic pancreatic ductal adenocarcinoma (PDAC). No improvement in OS (HR, 1.170; 95% CI, 0.882-1.563; P =.13977)



# Final Thoughts



- Accelerating progress in pancreatic cancer research
- Molecular subtypes of pancreatic cancer have different biologies
- Targeted treatments improve overall survival
- Novel trial designs will help accelerate drug development in pancreatic cancer