City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Multimodal Management of Locally Advanced Pancreas Cancer: Role of Systemic Therapy

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City of Hope

Disclosures

- Consultant for Immuneering & Perthera
- Grant Research Support from Merck

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

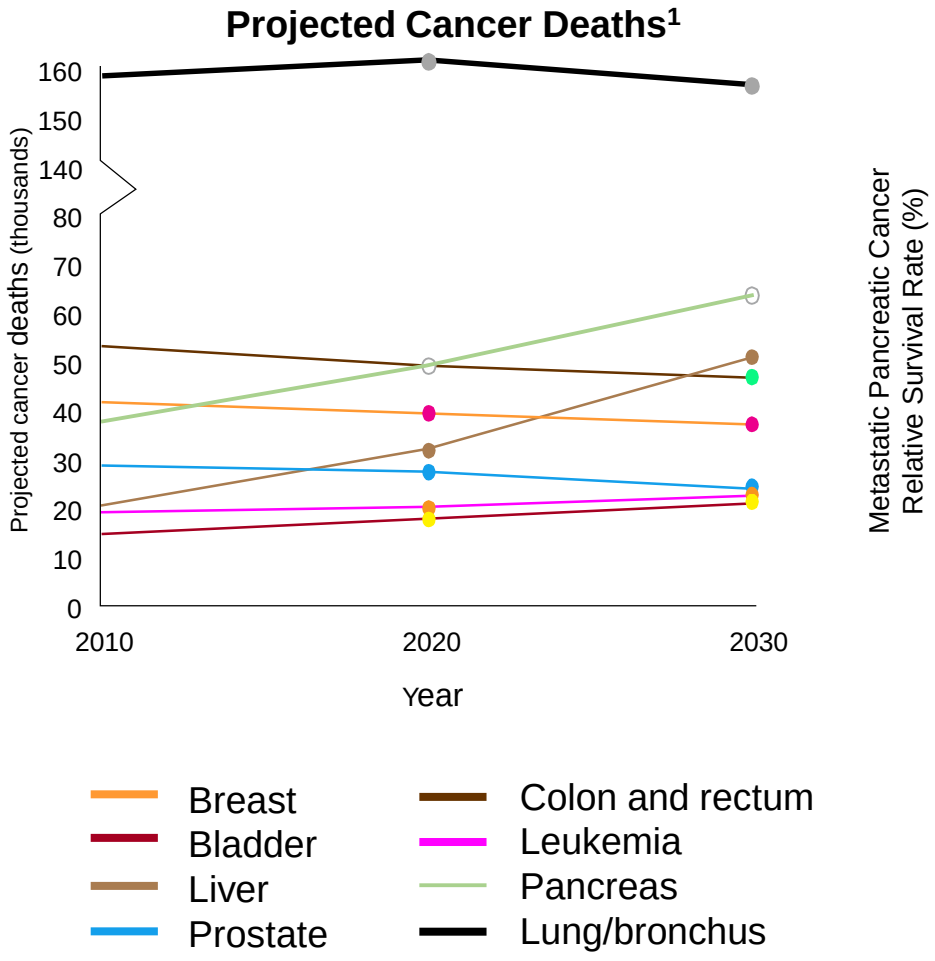
The following CLC & IB components will be addressed in this presentation:

- *Barries that may impact patient care.*
- *Factors contributing to level of care.*

Scope of the Problem

- Worst survival of any solid tumor
- 2025 US estimation
  - 67,440 new cases
  - 51,980 deaths

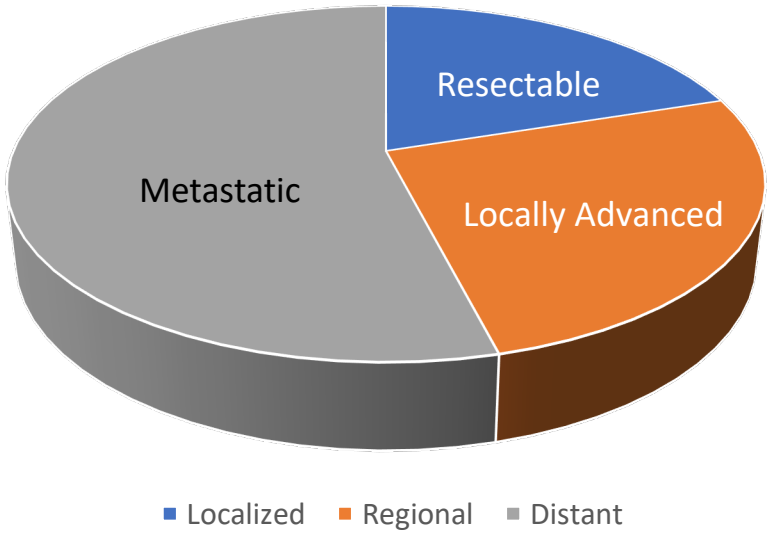
ACS Cancer Statistics.



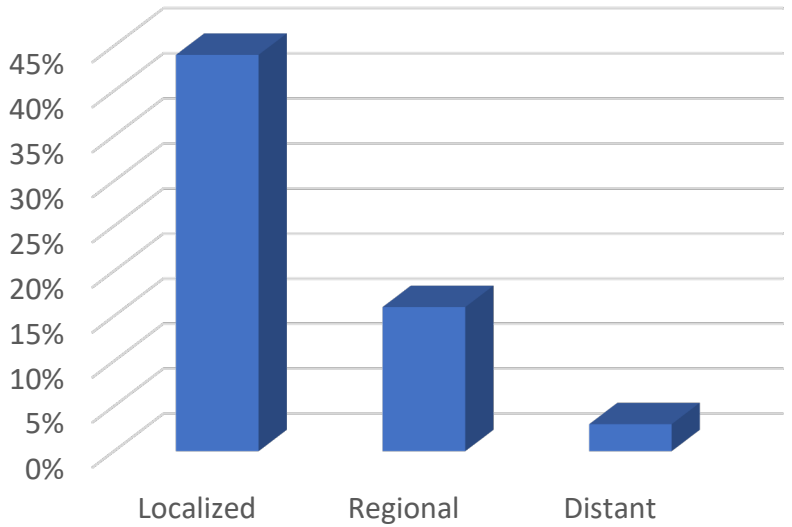
Rahib L, *et al. Cancer Res*. 2014;74(11):2913-2921.

Diagnosis of Pancreatic Cancer is Usually Late

Initial Presentation at Diagnosis

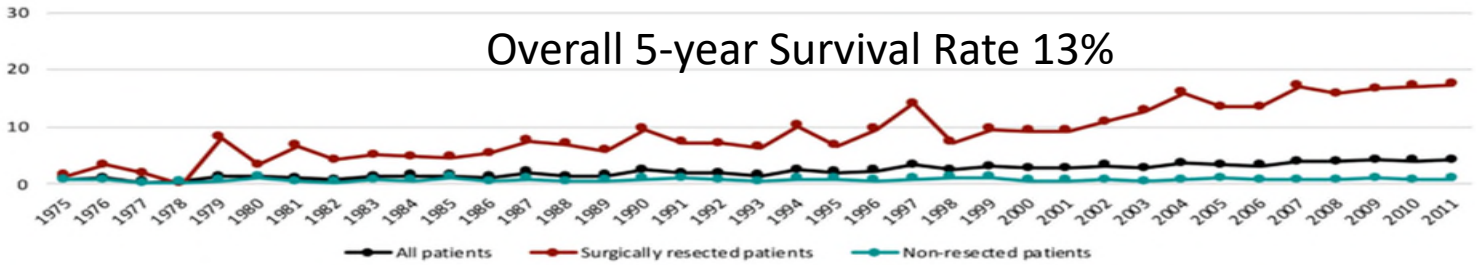


5-year Relative Survival Rates



Based on people diagnosed with pancreatic cancer between 2014 and 2020
Data from American Cancer Society

Overall 5-year Survival Rate 13%



Trends in the actual 5-year survival for 84,275 patients with pancreatic ductal adenocarcinoma diagnosed from 1975 to 2011. Follow-up cutoff date: December 31, 2016.

Bengtsson, A., Andersson, R. & Ansari, D. The actual 5-year survivors of pancreatic ductal adenocarcinoma based on real-world data. *Sci Rep* **10**, 16425 (2020)

NCCN Guidelines Version 2.2025
Pancreatic Adenocarcinoma

CRITERIA DEFINING RESECTABILITY STATUS AT DIAGNOSIS[a]

- Decisions about resectability status should be made in consensus at multidisciplinary meetings/discussions.

Resectability Status	Arterial	Venous
Resectable	• No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	• No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180°. • Solid tumor contact with variant arterial anatomy (eg, accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180°.	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Locally Advanced[b,c,d]	Head/uncinate process: • Solid tumor contact >180° with the SMA or CA. Pancreatic body/tail: • Solid tumor contact of >180° with the SMA or CA. • Solid tumor contact with the CA and aortic involvement.	• Not currently amenable to resection and primary reconstruction due to complete occlusion of SMV/PV

Table 1 | Radiographic criteria used to assess, classify and communicate PDAC resectability

Classification	AHPBA/SSAT/SSO[20]	MD Anderson[21]	Alliance[22]	NCCN[23]
Superior mesenteric vein–portal vein				
Resectable	No abutment, encasement or occlusion	Abutment or encasement without occlusion	Interface between tumour and vessel measuring <180°	No tumour contact or ≤180° contact without vein contour irregularity
Borderline-resectable	Abutment, encasement or occlusion	Occlusion	Interface between tumour and vessel measuring ≥180°, and/or reconstructable[a] occlusion	Solid tumour contact measuring >180°, or solid tumour contact ≤180° with contour irregularity or thrombosis
Locally advanced	Unreconstructable	Unreconstructable	Unreconstructable	Unreconstructable
Superior mesenteric artery				
Resectable	No abutment	No abutment	No interface between tumour and vessel	No solid tumour contact
Borderline-resectable	Abutment	Abutment	Interface between tumour and vessel measuring <180°	Solid tumour contact ≤180°
Locally advanced	Encasement	Encasement	Interface between tumour and vessel measuring ≥180°	Solid tumour contact >180°
Common hepatic artery or its first-order branches				
Resectable	No abutment or encasement	No abutment or encasement	No interface between tumour and vessel	No solid tumour contact
Borderline-resectable	Abutment or short-segment encasement	Abutment or short-segment encasement	Reconstructable[a], short-segment interface between tumour and vessel of any degree	Solid tumour contact without extension to the coeliac artery or hepatic artery bifurcation
Locally advanced	Unreconstructable	Unreconstructable	Unreconstructable	Unreconstructable
Coeliac trunk				
Resectable	No abutment or encasement	No abutment or encasement	No interface between tumour and vessel	No solid tumour contact
Borderline-resectable	No abutment or encasement	Abutment	Interface between tumour and vessel measuring <180°	Solid tumour contact ≤180°
Locally advanced	Abutment or encasement	Encasement	Interface between tumour and vessel measuring ≥180°	Solid tumour contact >180°

AHPBA, Americas Hepato-Pancreato-Biliary Association; Alliance, Alliance for Clinical Trials in Oncology; NCCN, National Comprehensive Cancer Network; SSAT, Society for Surgery of the Alimentary Tract; SSO, Society of Surgical Oncology. [a]Normal vein or artery proximal and distal to the site of suggested tumour, vessel involvement suitable for vascular reconstruction.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Pancreatic Adenocarcinoma

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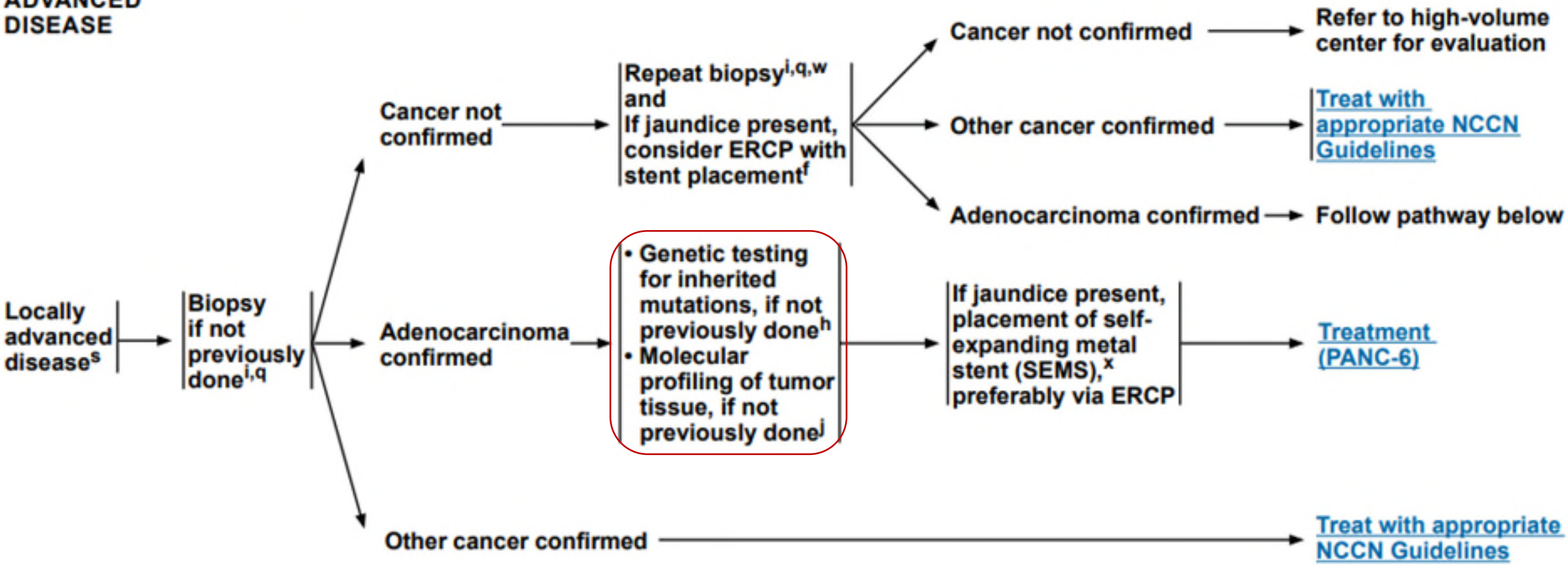
Discussion

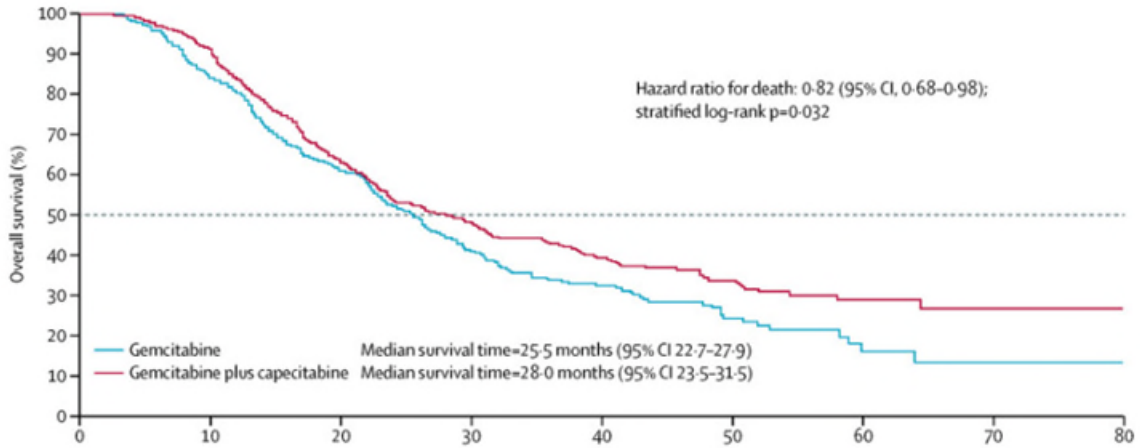
LOCALLY ADVANCED DISEASE **WORKUP**



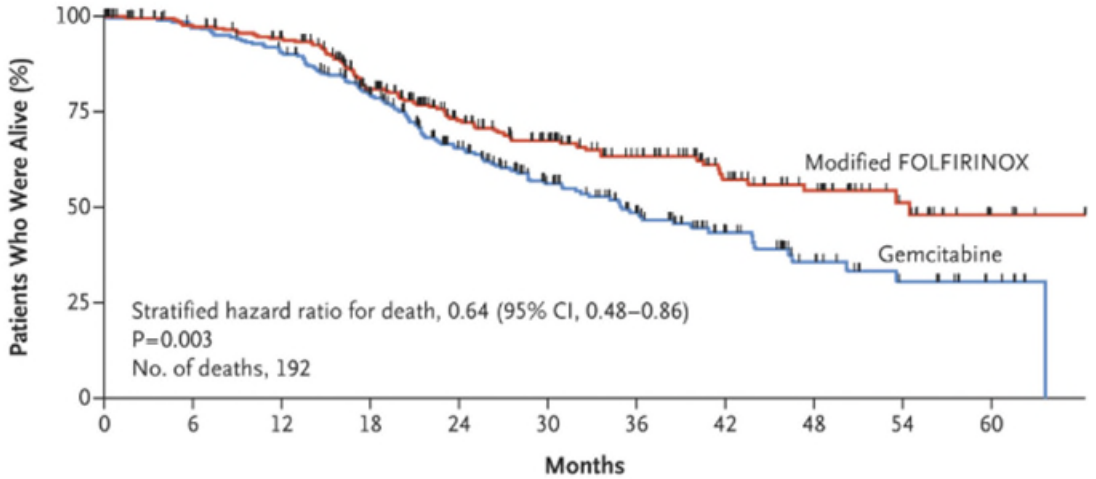
Systemic therapy is the most important treatment for locally advanced PC

Results for resectable pancreatic cancer

ESPAC-4 Adjuvant Gemcitabine and Capecitabine



PRODIGE Adjuvant FOLFIRINOX



Majority of patients still die from cancer

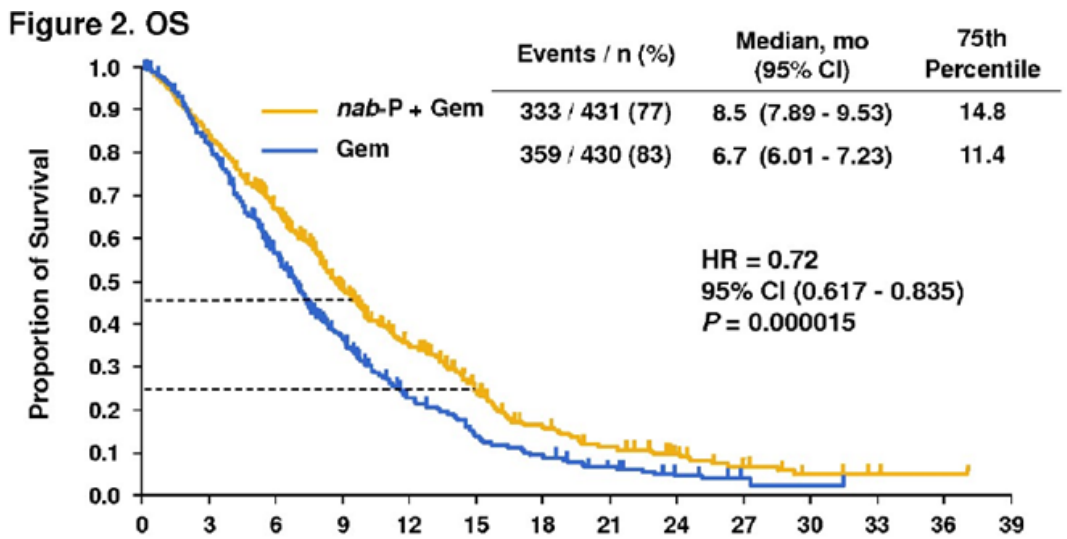
Pancreatic cancer is a systemic disease

Gemcitabine plus nab-paclitaxel versus Gemcitabine in Patients with Metastatic Pancreatic Cancer (MPACT)

Metastatic Pancreas Cancer (861 Pts)

- **Gemcitabine +**
  1000 mg/m^2
  Nab-paclitaxel
  125 mg/m^2
  weekly for 3 of 4 weeks
- **Gemcitabine**
  1000 mg/m^2 weekly for 7 of 8 weeks then weekly for 3 of 4 weeks

Primary endpoint: Overall survival



Median OS 8.5 vs 6.7 mo HR 0.72 p=0.000015
Median PFS 5.5 vs 3.7 mo HR 0.69 p=0.000024

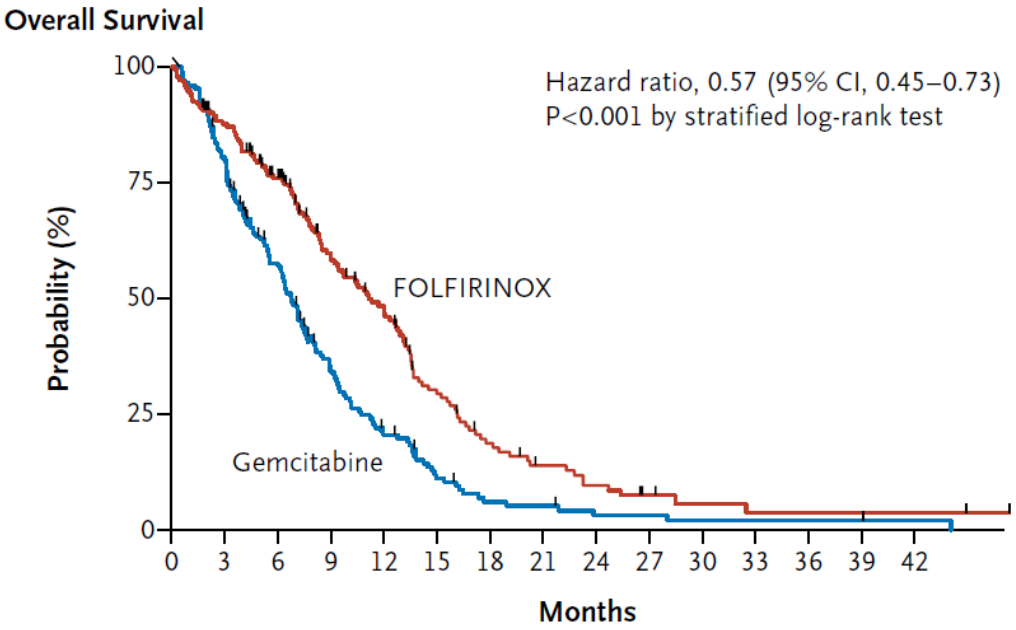
Von Hoff D, et al. NEJM 2013.

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer (PRODIGE 4 / ACCORD 11)

Metastatic Pancreas Cancer (342 Pts)

FOLFIRINOX
Oxaliplatin 85 mg/m^2, 5FU bolus 400 mg/m^2, LV 400 mg/m^2, Irinotecan 180 mg/m^2, 5FU CIV 2.4 g/m^2 over 46 hrs

Gemcitabine
1000 mg/m^2 weekly for 7 of 8 weeks then weekly for 3 of 4 weeks



Median OS 11.1 vs 6.8 mo HR 0.57 p<0.001
Median PFS 6.4 vs 3.3 mo HR 0.47 p<0.001

Primary endpoint – overall survival

mFOLFIRINOX removes bolus 5FU and
Reduces dose of irinotecan

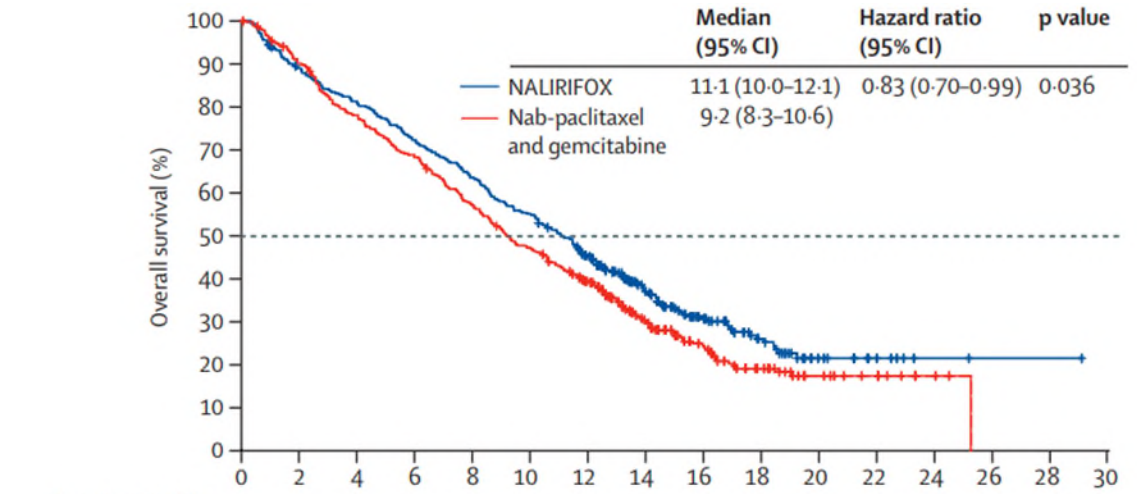
Conroy T, et al. NEJM 2011.

NALIRIFOX versus Gemcitabine and nab-paclitaxel for Metastatic Pancreatic Cancer (NAPOLI-3)

Metastatic Pancreas Cancer (770 Pts)

NALIRIFOX
Liposomal Irinotecan 50 mg/m^2,
Oxaliplatin 60 mg/m^2,
Leucovorin 400 mg/m^2,
5FU CIV 2.4 g/m^2 over 46 hrs
Days 1 and 15

Gemcitabine 1000 mg/m^2
Nab-paclitaxel 125 mg/m^2
Days 1, 8 and 15



Median OS 11.1 vs 9.2 mo HR 0.83 p<0.036
Median PFS 7.4 vs 5.6 mo HR 0.69 p<0.0001

Primary endpoint – overall survival

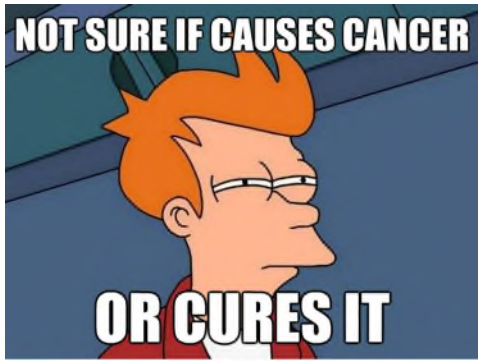
Wainberg Z, et al. The Lancet 2023.

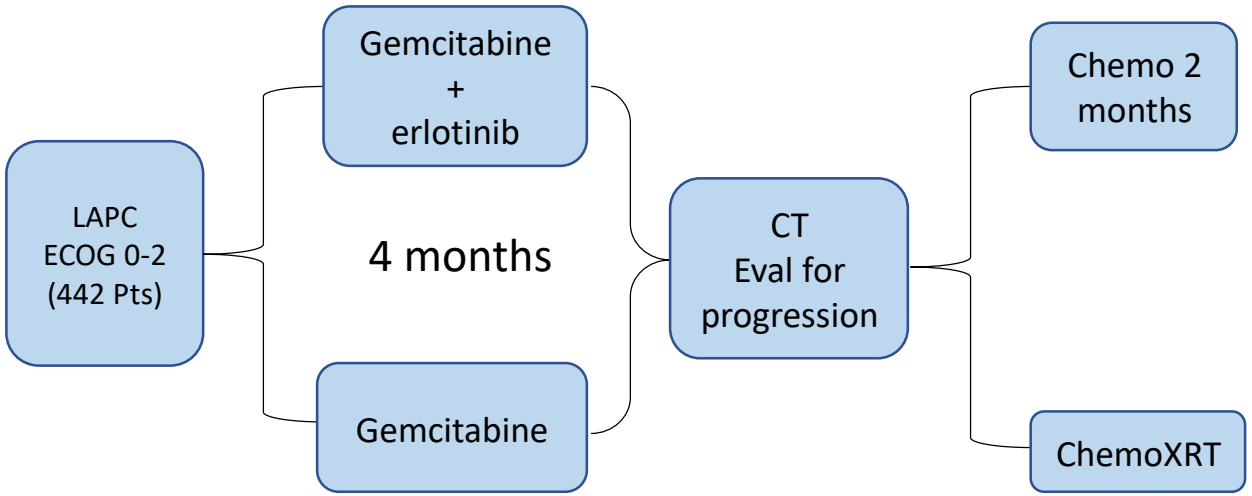
Systemic Therapy for Pancreatic Cancer

- Chemotherapy regimens have improved with better success in downstaging tumors at the cost of toxicity

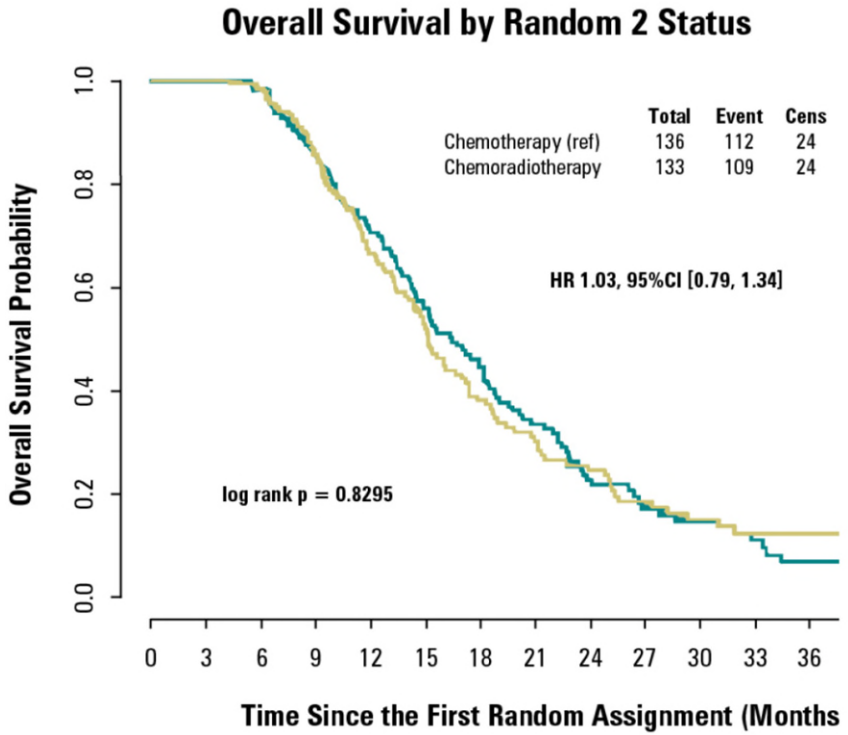
Grade 3/4 toxicity	Neutropenia	Fatigue	Diarrhea	Neuropathy	Response Rate
Gemcitabine + nab-paclitaxel	38%	17%	6%	17%	23%
FOLFIRINOX	45.7%	23.6%	12.7%	9%	31%
NALIRIFOX	14%	6%	20%	3%	42%

Radiation Therapy for Locally Advanced Pancreatic Cancer (LAP-07 Trial)



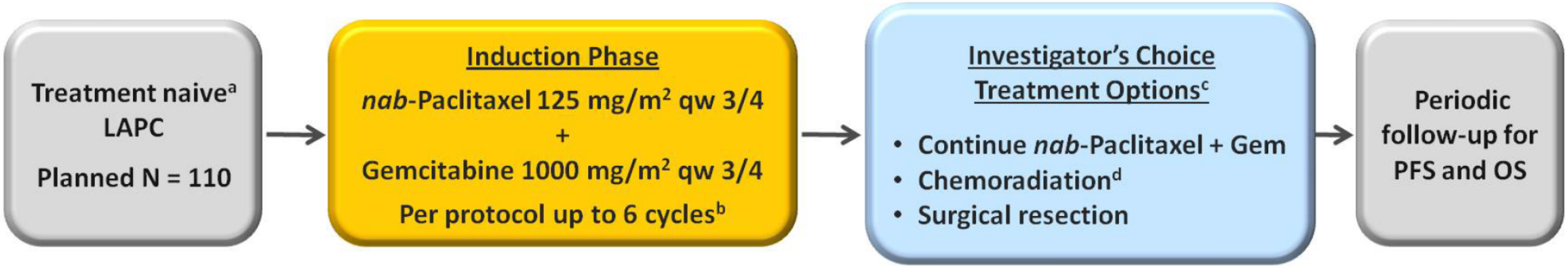


Median overall survival
16.4 vs 15.2 months (CT vs CRT group)
[HR] 1.03, 95% CI [0.79, 1.34], p = 0.8295



Hammel, et al. JAMA. 2016;315(17):1844-1853

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



nab-P + Gem	Chemoradiation	Surgery
12 pts	17 pts	16 pts

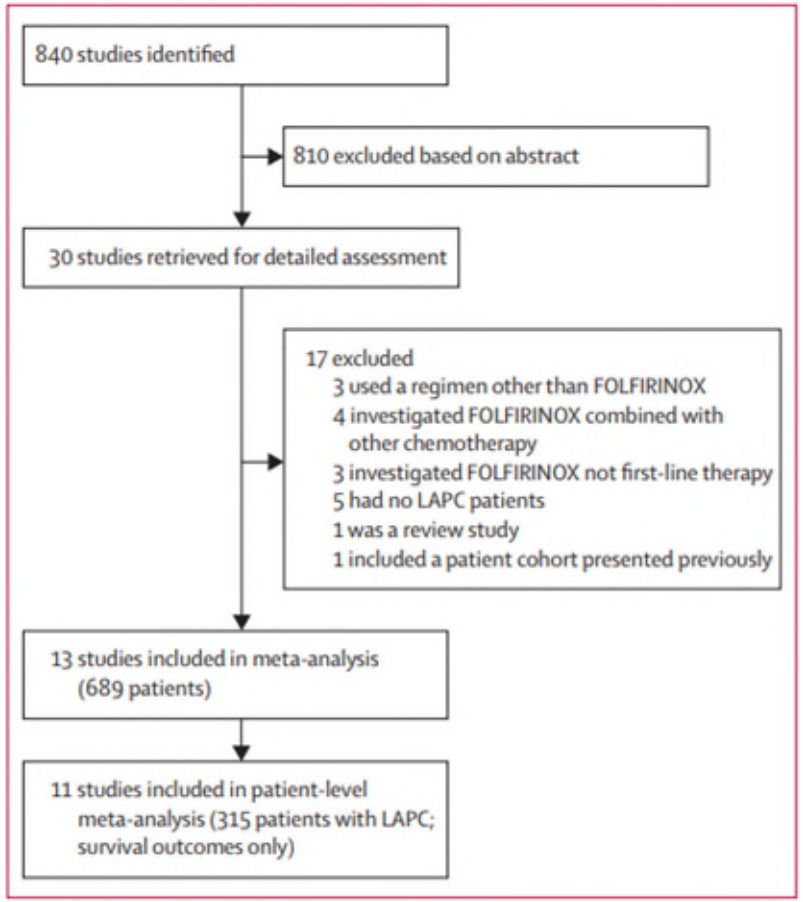
- Objective: To assess the safety and efficacy of 6 cycles of induction therapy.
- Primary Endpoint: Time to Treatment Failure

- Median TTF 8.8 months (90% CI, 6.67-9.82)
- ORR 33% and DCR 78%
- Nab-Paclitaxel plus gemcitabine induction allowed conversion from unresectable to resectable in 15% of the patients

Median overall survival was 18·8 months (90% CI 15·0–24·0)

Presented By Pascal Hammel at 2018 Gastrointestinal Cancers Symposium

Meta-analysis FOLFIRINOX for Locally Advanced Pancreatic Cancer



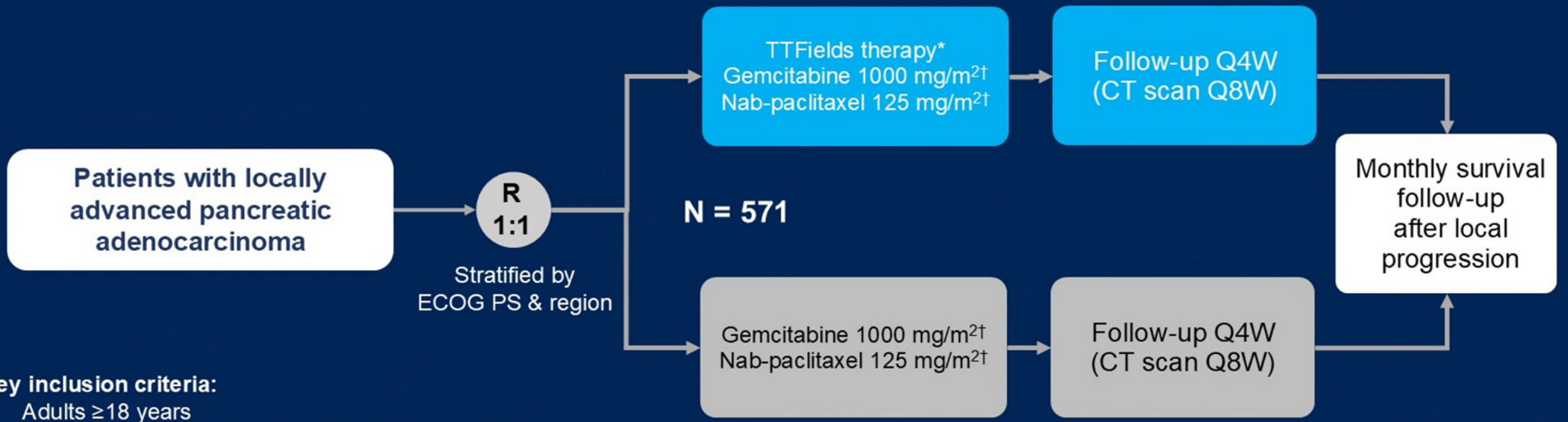
- 11 studies with 315 patients

- Primary outcome: Overall survival
- Pooled proportion of patients who received any radiotherapy treatment was 63·5%
- Pooled proportion of patients who had resection was 25·9%
- R0 resection was reported in 60 (74%) of 81 patients.

- Pooled patient-level median overall survival of 24·2 months

Suker, Mustafa et al. The Lancet Oncology, Volume 17, Issue 6, 801 – 810, 2016.

Tumor Treating Fields With Gemcitabine and Nab-Paclitaxel for Locally Advanced Pancreatic Adenocarcinoma: Randomized, Open-Label, Pivotal Phase III PANOVA-3 Study



Key inclusion criteria:

- Adults ≥18 years
- Previously untreated, biopsy confirmed disease
- Life expectancy ≥3 months
- ECOG PS 0-2

Key exclusion criteria:

- Prior palliative treatment to the tumor
- Implanted electronic medical device in torso
- Known allergies to medical adhesives, hydrogel or chemotherapies

Study sites: 198 across 20 countries (North and South America, Europe, Asia)‡
Enrollment: March 2018 – March 2023

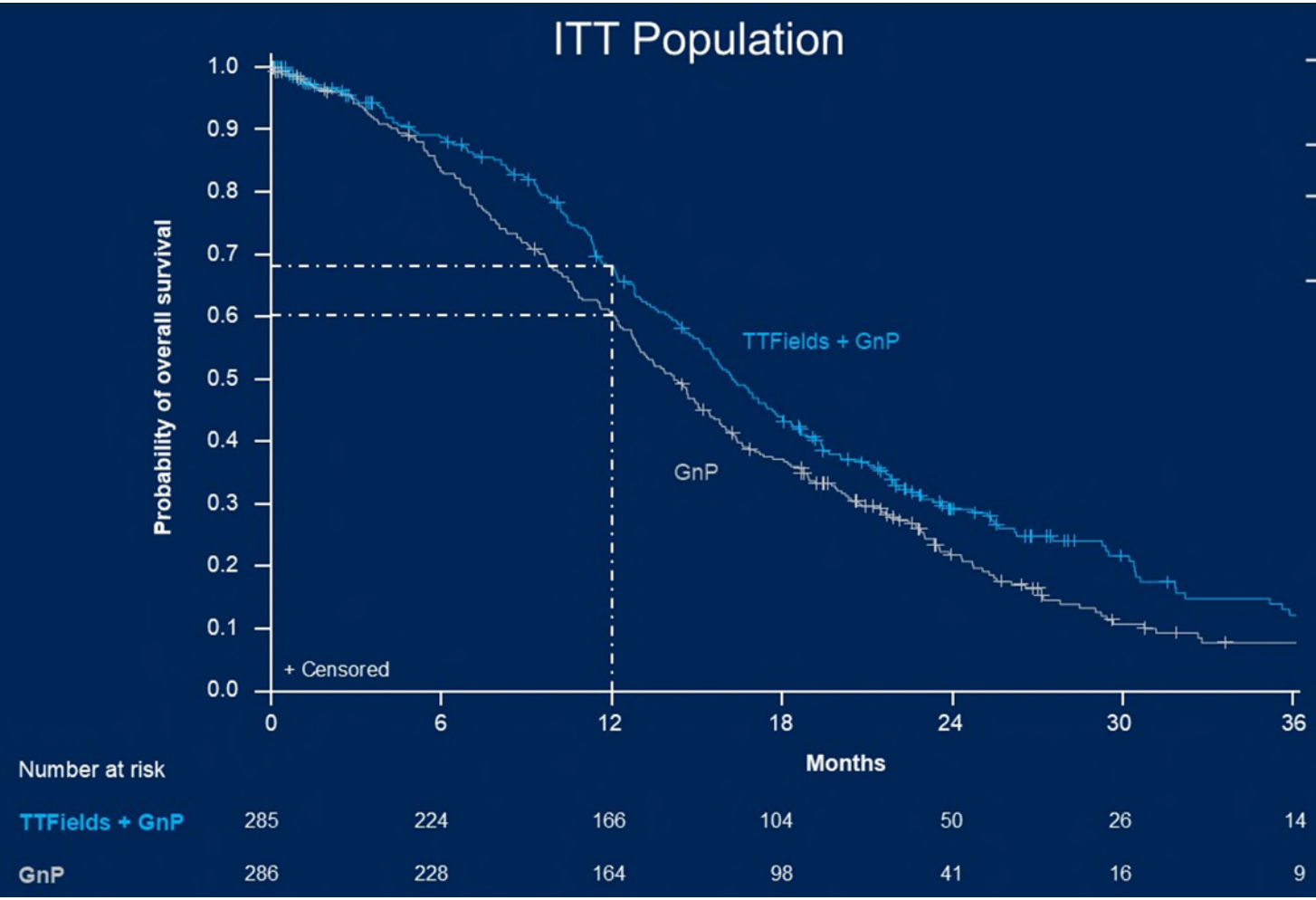
Data cut-off: October 16, 2024
Registration number: NCT03377491

PRESENTED BY: Dr Vincent Picozzi

Tumor Treating Fields With Gemcitabine and Nab-Paclitaxel for Locally Advanced Pancreatic Adenocarcinoma: Randomized, Open-Label, Pivotal Phase III PANOVA-3 Study

PRESENTED BY: Dr Vincent Picozzi

Primary Endpoint Overall Survival: PANOVA-3 Study



ITT	TTFields + GnP	GnP	P-value
Median OS (95% CI)	16.2 (15.0, 18.0)	14.2 (12.8, 15.4)	**0.039**
Events	201	230	
	HR = 0.82 (95% CI: 0.68, 0.99)		
1-year survival rate, Median (95% CI)	68.1 (62.0, 73.5)	60.2 (54.2, 65.7)	**0.029**

mITT	TTFields + GnP	GnP	P-value
Median OS (95% CI)	18.3 (16.1, 20.0)	15.1 (13.4, 17.0)	**0.023**
Events	151	169	
	HR = 0.77 (95% CI: 0.62, 0.97)		
1-year survival rate, Median (95% CI)	75.1 (68.3, 80.6)	65.9 (59.0, 72.0)	**0.022**

TTFields		
Median daily device usage, % (range)	62.1 (0, 99.0)	NA
Median duration of exposure, weeks (range)	27.6 (0.1, 234.4)	NA

PRESENTED BY: Dr Vincent Picozzi

Conclusions

- Pancreatic cancer is a systemic disease and upfront systemic therapy improves survival
- Urgent need for regimens with higher response rates and less toxicity (targeted therapies?)
- Radiation therapy and surgery only benefit select patients with locally advanced pancreatic cancer
- Multidisciplinary management is key to obtaining the best outcomes