Pancreatic Cancer

FPON Webinar

Muhammad Zulfiqar, MD

Medical Oncologist, BC Cancer

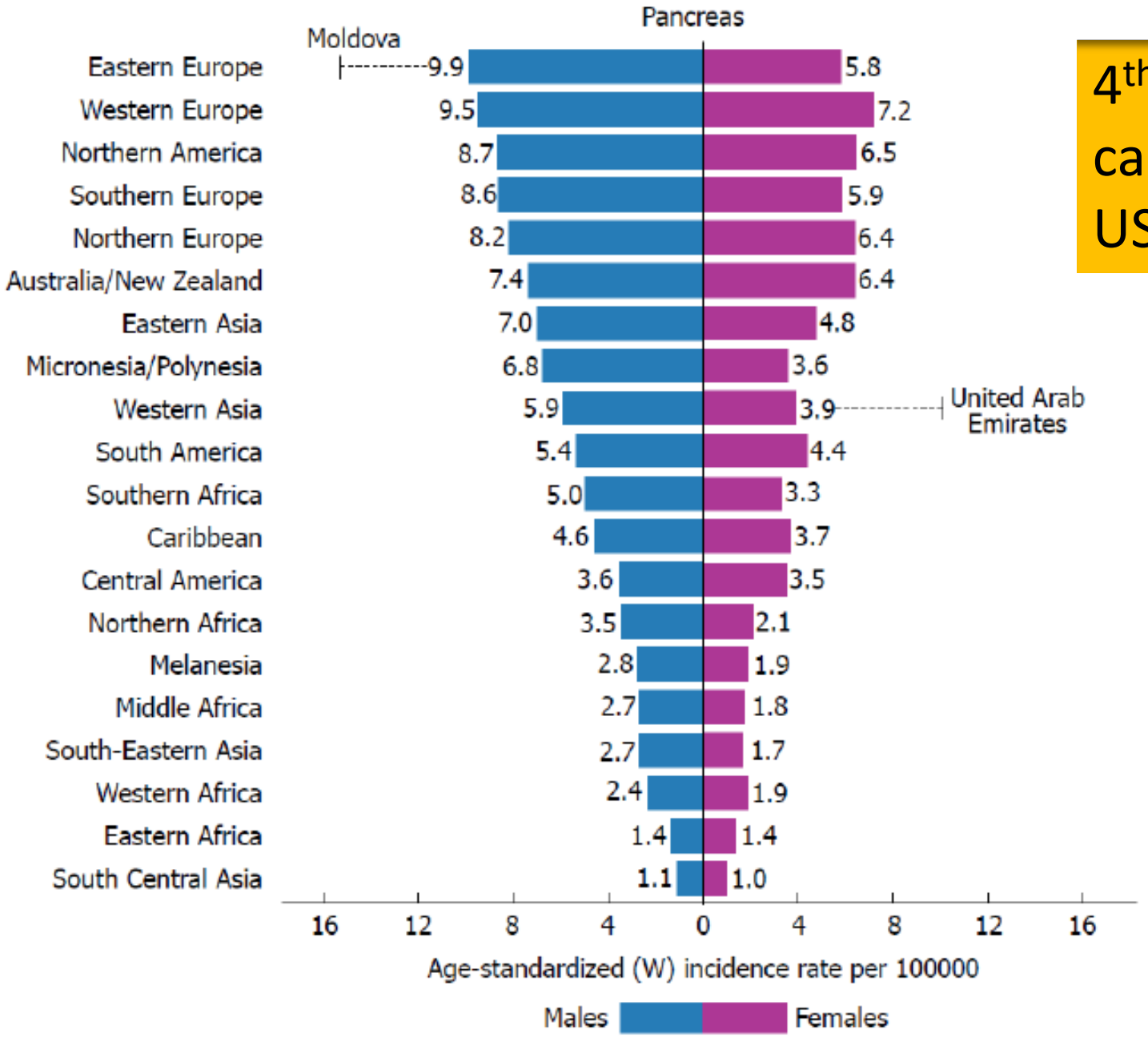
Disclosure

- I have served in advisory boards to Merck and Eisai.

Pancreatic Cancer

- Epidemiology
- Diagnosis
- Treatment
- Follow up

Epidemiology and Diagnosis



4th Leading cause of cancer related death in USA

In 2022

- 6,900 Canadians will be diagnosed with pancreatic cancer.
- 5,700 Canadians will die from pancreatic cancer.
- 3,800 men will be diagnosed with pancreatic cancer and 3,000 will die from it.
- 3,100 women will be diagnosed with pancreatic cancer and 2,800 will die from it.

Pancreatic adenocarcinoma

Smoking

Smoking may cause about 20-30% of all exocrine pancreatic cancer cases.

Family History

Risk increases if multiple first-degree relatives had the disease, or any were diagnosed under 50.

Obesity

Obese people have a 20% increased risk of developing the disease compared to people of a normal weight.

Pancreatitis

Chronic pancreatitis increases risk. Risk is even higher for people with hereditary pancreatitis.

Diabetes

Long standing (over 5 years) diabetes increases risk.

Risk Factors

Main modifiable risk factors:

Chronic pancreatitis
Tobacco use
Obesity
Chronic diabetes
Diet (low fibre)
Alcohol abuse

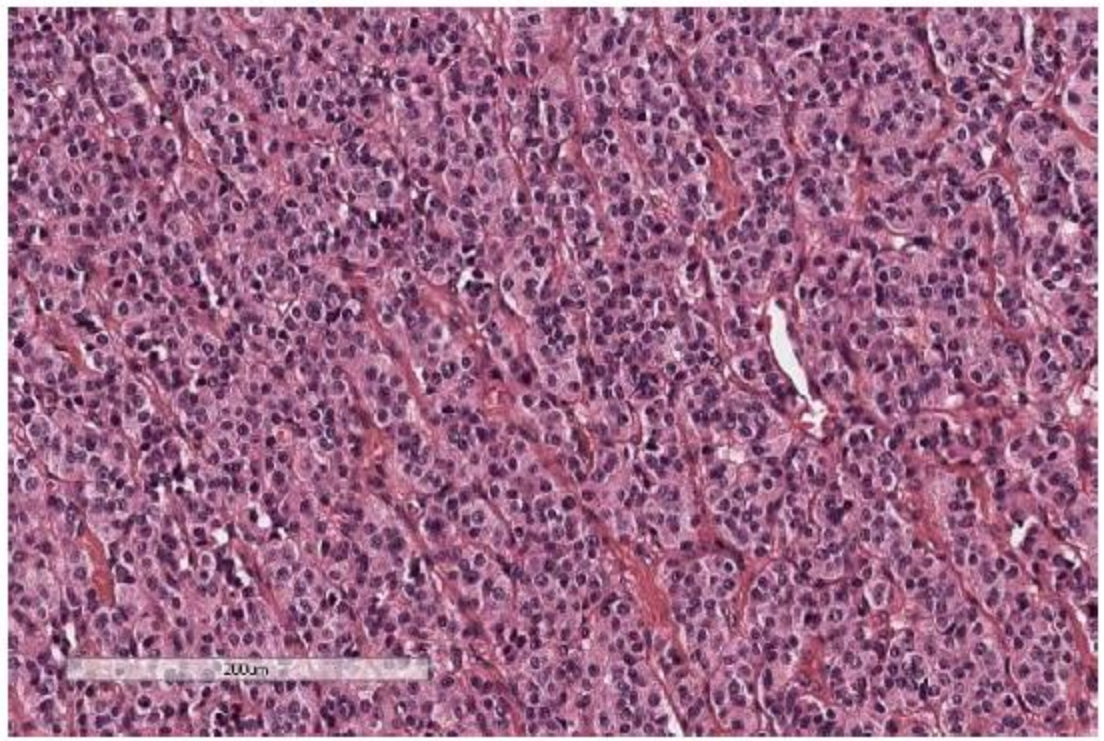
Main genetic risk factors:

Lynch syndrome
Breast and ovarian cancer syndrome
Peutz Jeghers syndrome
Familial adenomatous polyposis
Hereditary pancreatitis
Cystic fibrosis
Ataxia telangiectasia

Polling Question:

- 50 years old gentleman presented with jaundice and ongoing mid-epigastric dull pain with decreased appetite and weight loss of 10 lb in last two month. US showed pancreatic head mass. CT guided biopsy was done. It was non-conclusive. ERCP was done but cytology and brushing only showed atypical cells. CA19-9 was normal. BC Cancer declined referral stating lack of tissue diagnosis. What is appropriate next step.
- 1- Refer to hepatobiliary surgeon for therapeutic considerations.
- 2-BC Cancer re-referral as it appears like a malignancy and should be handled by BC Cancer
- 3-CA19-9 and staging CT scan chest, abdomen and pelvis and re-referral to BC cancer if there is metastatic disease.

Adenocarcinoma (90%)



Neuroendocrine lesions

Rare lesions: Acinar cell carcinomas….

Sarcoma
Lymphoma

Completely different morphology, biology, treatment

Therapeutic considerations

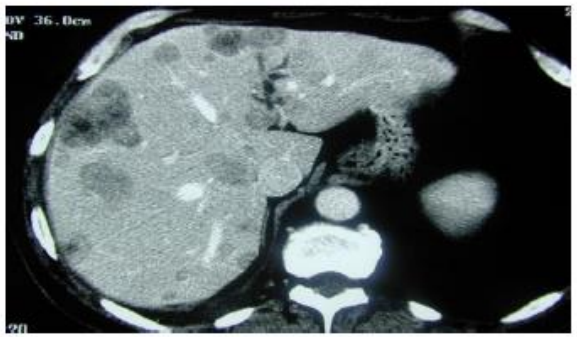
- New and emerging targeted treatments require specific knowledge of driver mutations to customize systemic treatments.
  - BRCA1/BRCA2- PARP inhibitors, platinum sensitivity
  - NTRK gene fusion – Larotrectinib, Entrectinib
  - MSI status – check point inhibitors
  - RET fusion-positive tumors — Selpercatinib
  - RAS G12C-mutated tumors — sotorasib

Polling Question

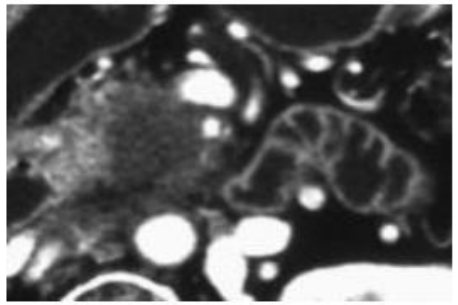
- What percentage of patients with pancreatic adenocarcinoma has localized resectable disease at the time of presentation.
- 1-15%
- 2-5%
- 3-35%

Diagnosis

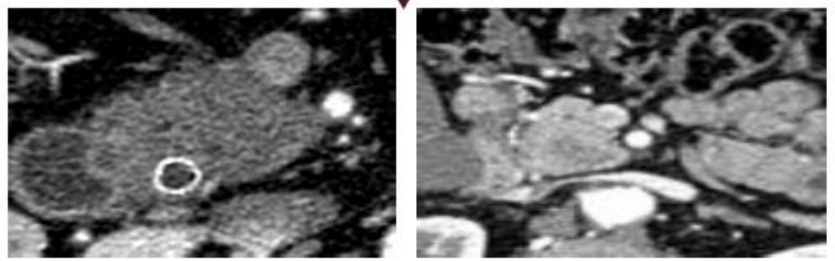
Metastatic disease 60%



Locally advanced disease 25%



Resectable disease 15%



Borderline

R0 surgery

Presentation

- Asthenia – 86 percent
- Weight loss – 85 percent
- Anorexia – 83 percent
- Abdominal pain – 79 percent
- Epigastric pain – 71 percent
- Dark urine – 59 percent
- Jaundice – 56 percent
- Nausea – 51 percent
- Back pain – 49 percent
- Diarrhea – 44 percent
- Vomiting – 33 percent
- Steatorrhea – 25 percent
- Thrombophlebitis – 3 percent

- **Signs**
- Jaundice – 55 percent
- Hepatomegaly – 39 percent
- Right upper quadrant mass – 15 percent
- Cachexia – 13 percent
- Courvoisier's sign (nontender but palpable distended gallbladder at the right costal margin) – 13 percent
- Epigastric mass – 9 percent
- Ascites – 5 percent

Value of Tumor Marker Testing in Diagnosis

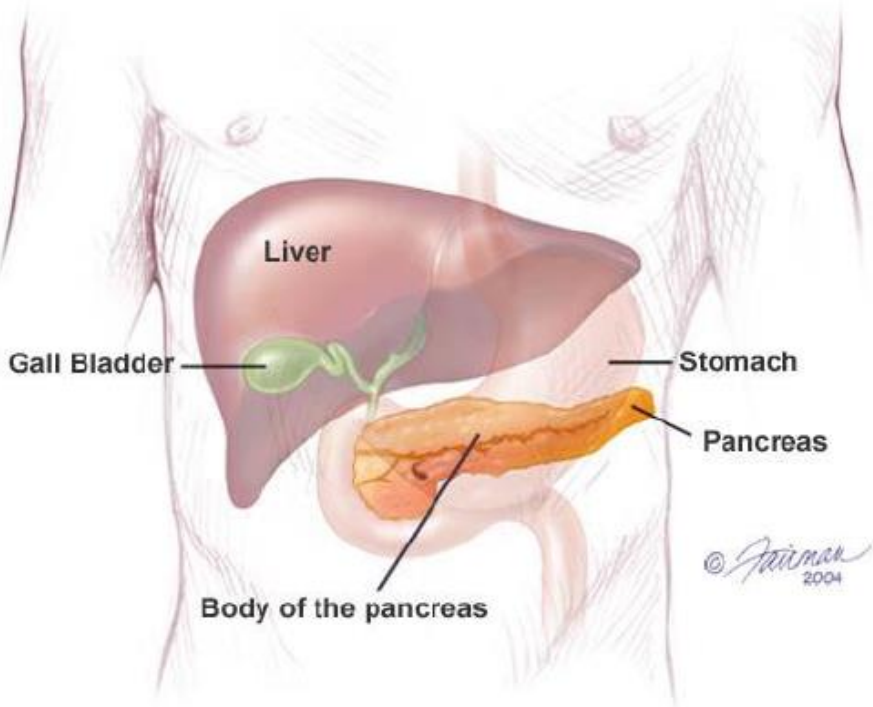
- CA19-9
  - sensitivity and specificity rates of CA 19-9 for pancreatic cancer range from 70 to 92, and 68 to 92 percent, respectively
  - Sensitivity closely related to tumor size
  - Lewis-negative phenotype (an estimated 5 to 10 percent of the population)
  - Bile duct obstructing jaundice
  - Various benign pancreaticobiliary disorders

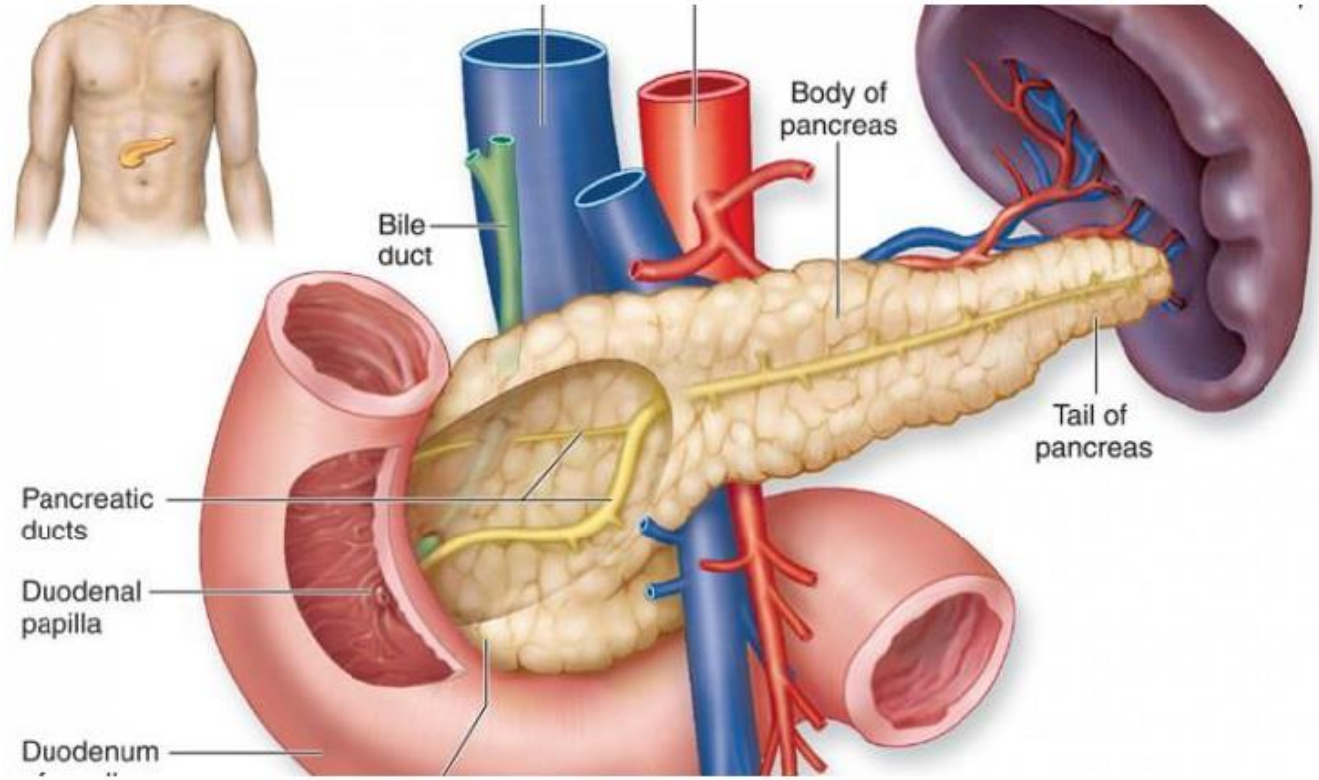
Polling Question 2

- What percentage of patients survive for 5 years after successful complete surgical resection with node negative status.
- 1- 70%
- 2-30%
- 3-50%
- 4-10%

Treatment of Early Disease

Non Metastatic


Liver
Gall Bladder
Stomach
Pancreas
Body of the pancreas
2004

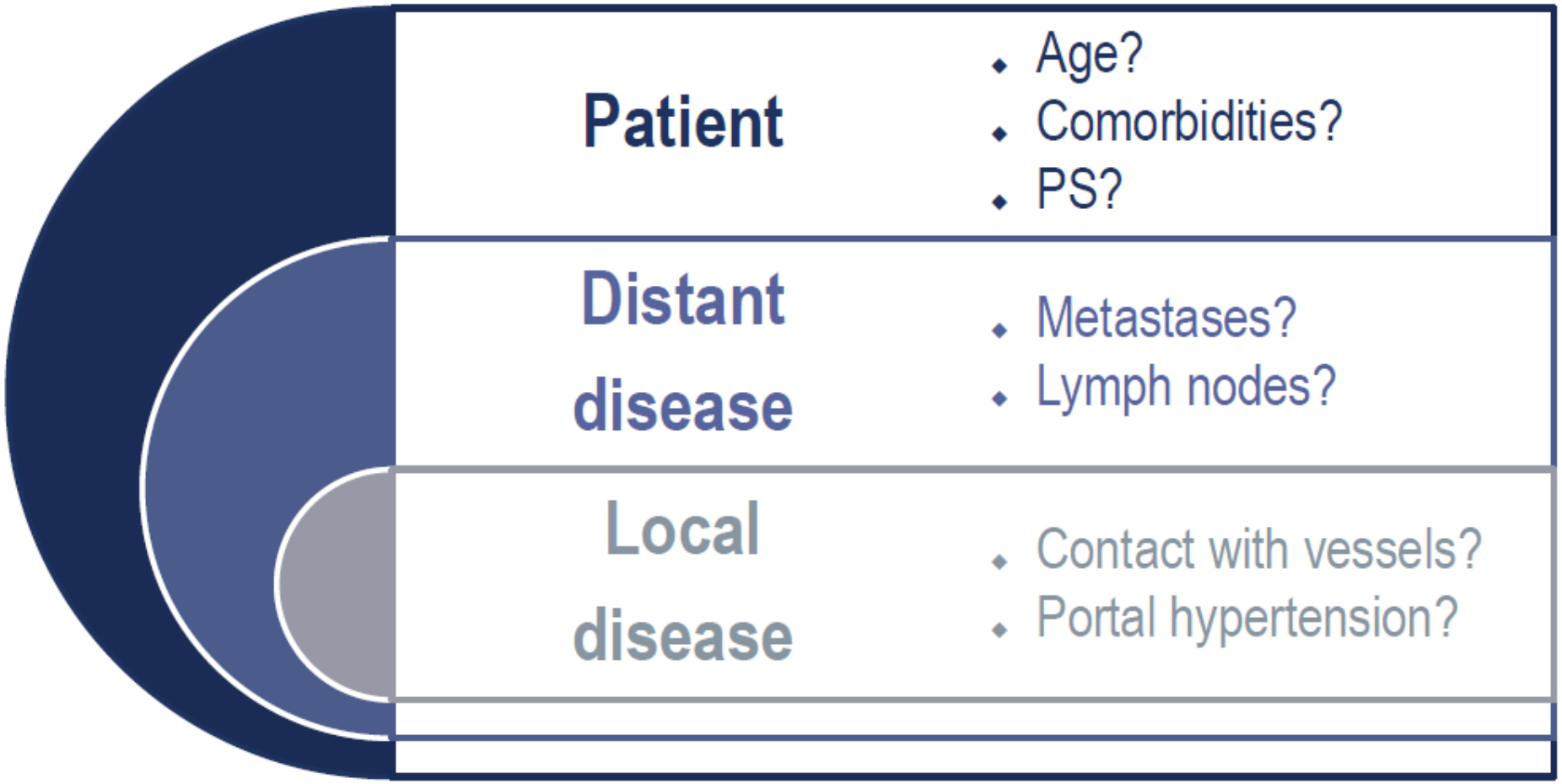

Body of pancreas
Bile duct
Tail of pancreas
Pancreatic ducts
Duodenal papilla
Duodenum

TNM Staging

T1	Tumour 2 cm or less
	T1a Tumour 0.5 cm or less
	T1b Tumour greater than 0.5 cm but no more than 1 cm
	T1c Tumour greater than 1 cm but no more than 2 cm
T2	Tumour more than 2 cm but no more than 4 cm
T3	Tumour more than 4 cm in greatest dimension
T4	Tumour involves coeliac axis, superior mesenteric artery and /or common hepatic artery
N1	Metastases in 1 to 3 nodes
N2	Metastases in 4 or more nodes

M category unchanged			
Stage			
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Initial Assessment for therapeutic considerations



Locally advanced borderline resectable

- mFOLFIRINOX
- Gemcitabine

Successful Surgical Resection

With surgery alone relapse rates are reported to be 85 to 95% within 5 years

Adjuvant therapy to kill residual tumour cells seems fundamental to improve patients outcome

Studies: ESPAC-1[1]:
5FU > observation

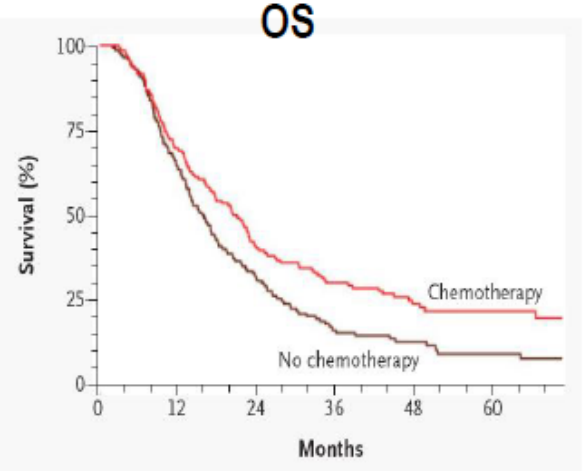
CONKO-001[2]:
Gemcitabine > obs

ESPAC-3[3]:
Gemcitabine = 5FU

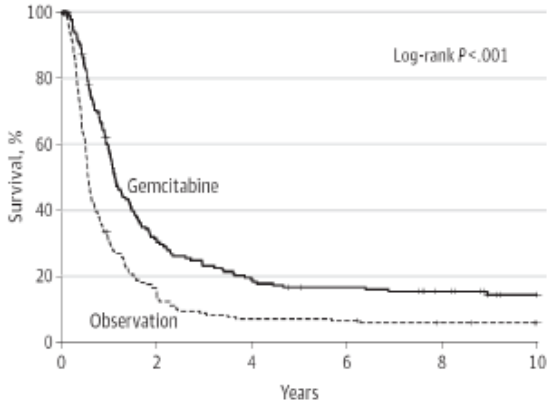
ESPAC-4[4]:
Gem+Capecitabine > Gem

2001 — 2004 — 2007 — 2010 — 2013 — 2016

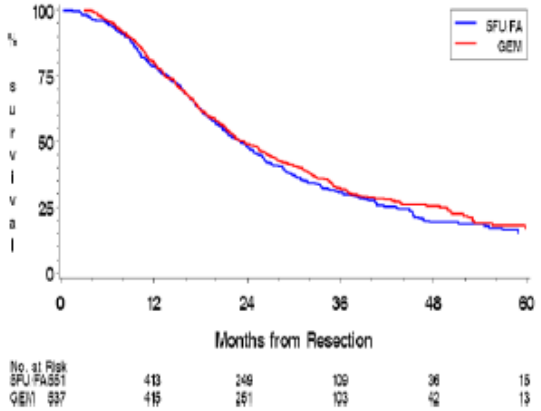
OS



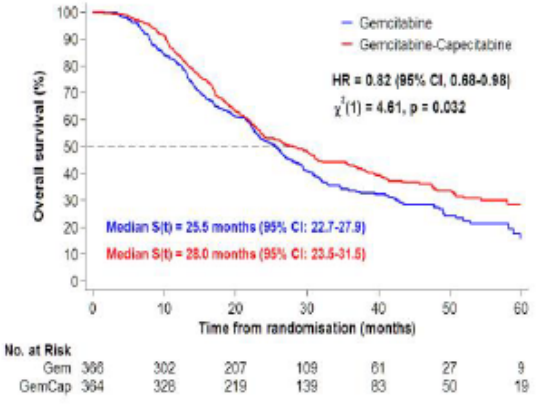
DFS



OS

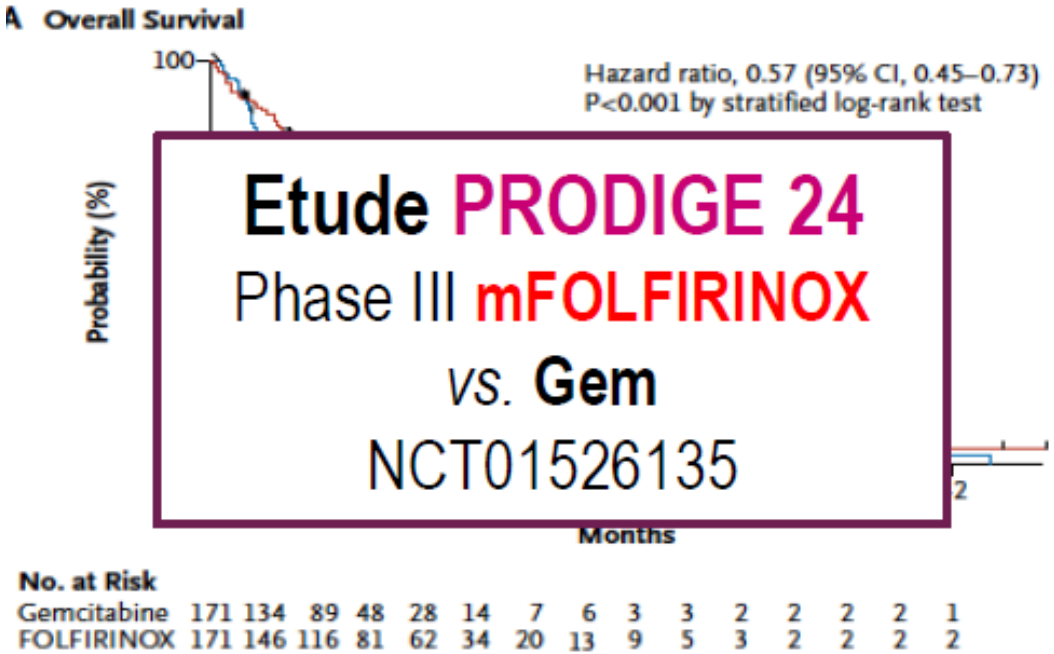


OS



ORIGINAL ARTICLE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

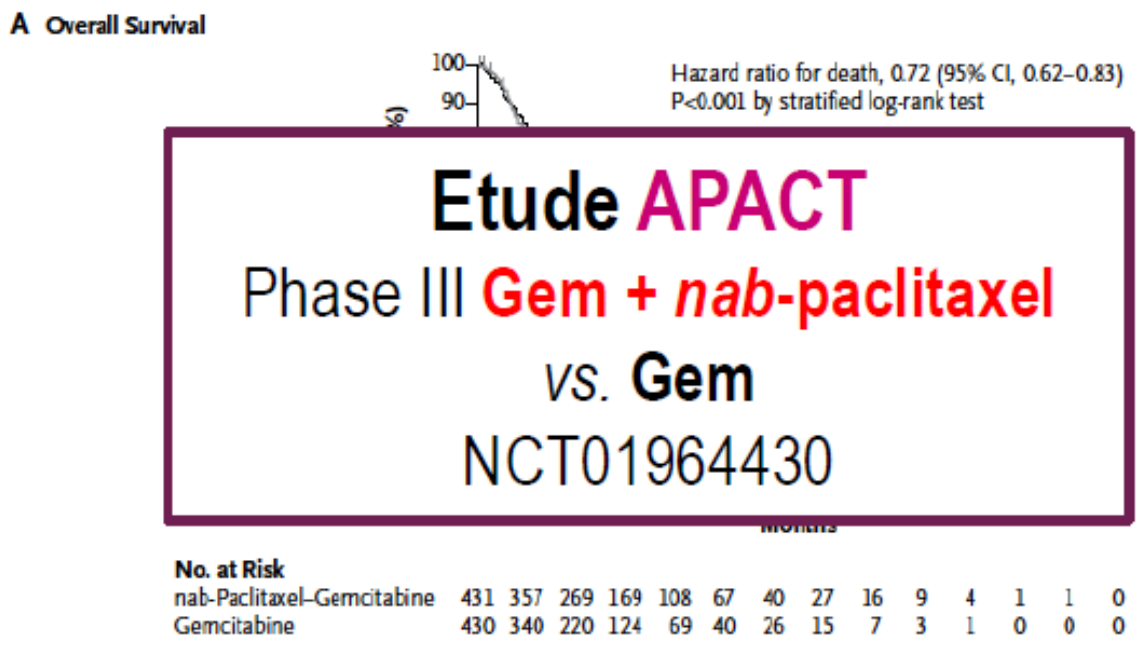


From N Engl J Med, Conroy T, *et al.*, FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer, 364(19), 1817–25. Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

The NEW ENGLAND JOURNAL of MEDICINE

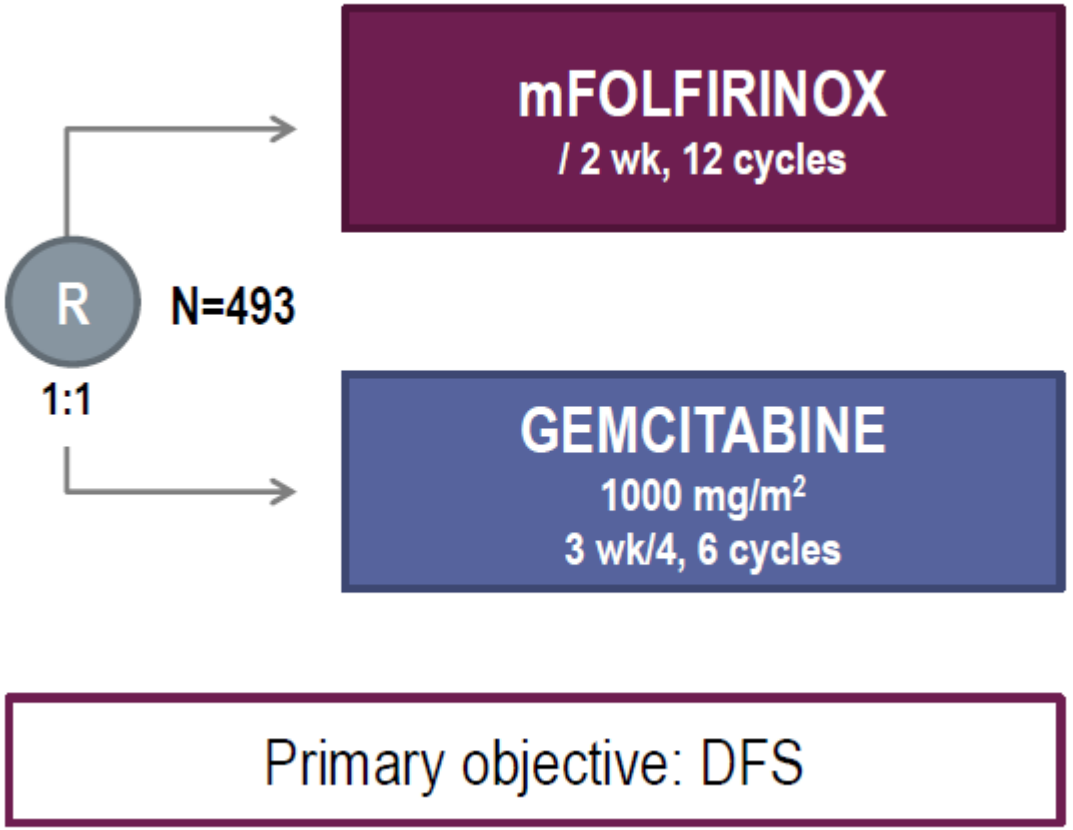
ORIGINAL ARTICLE

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine



From N Engl J Med, Von Hoff DD, Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine, 369:1691-1703. Copyright © 2013. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Adjuvant FOLFIRINOX

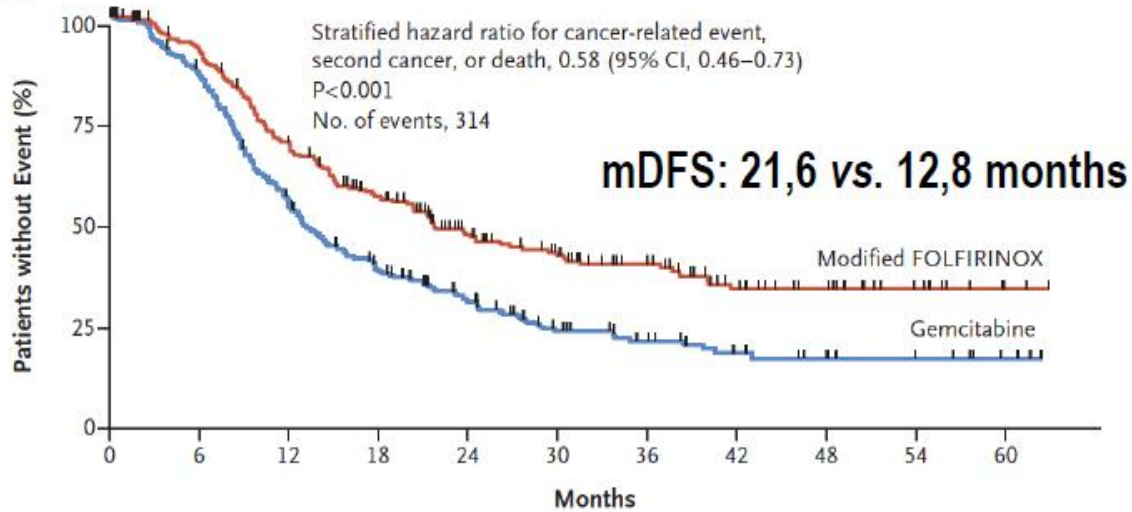


PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

FFCD GERCOR UNICANCER

Phase III RCT
N=493 pts

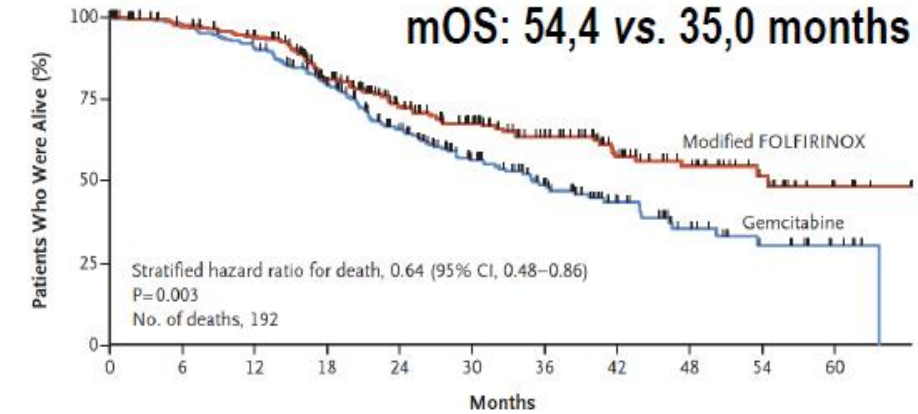
A Disease-free Survival



mDFS: 21,6 *vs.* 12,8 months

No. at Risk											
Modified FOLFIRINOX	247	210	156	118	80	60	46	29	21	11	2
Gemcitabine	246	205	127	85	59	34	24	15	10	7	3

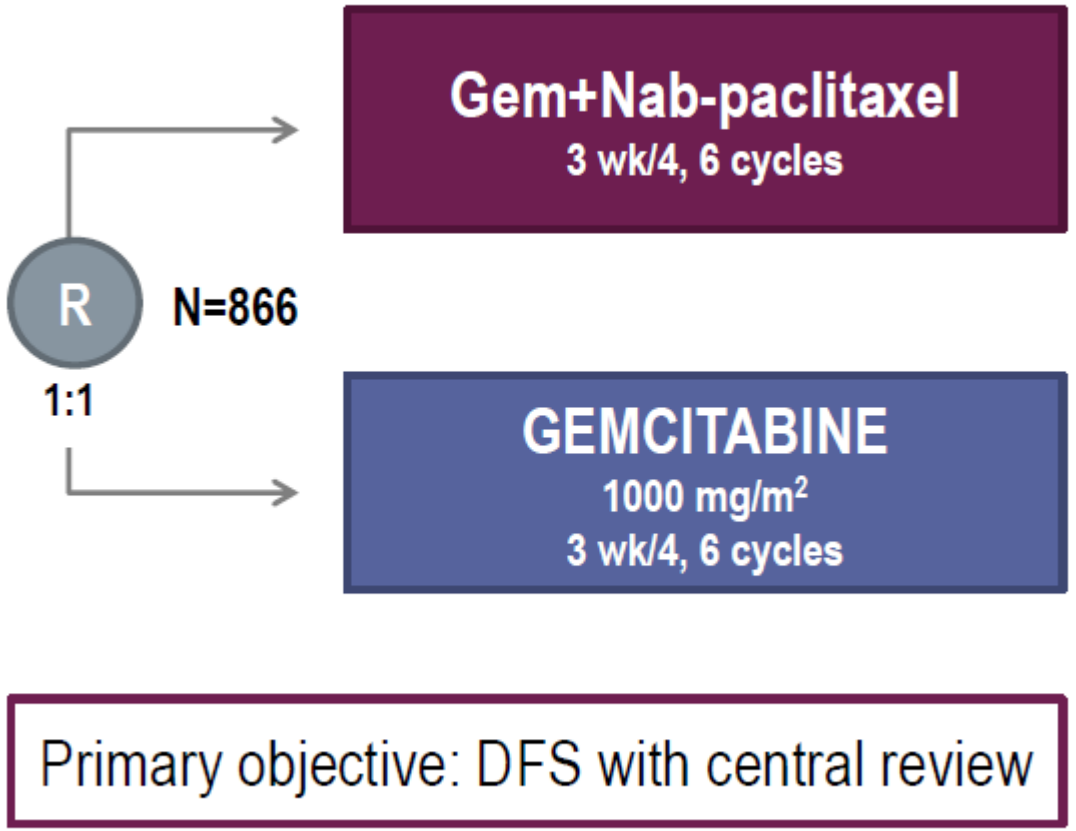
B Overall Survival

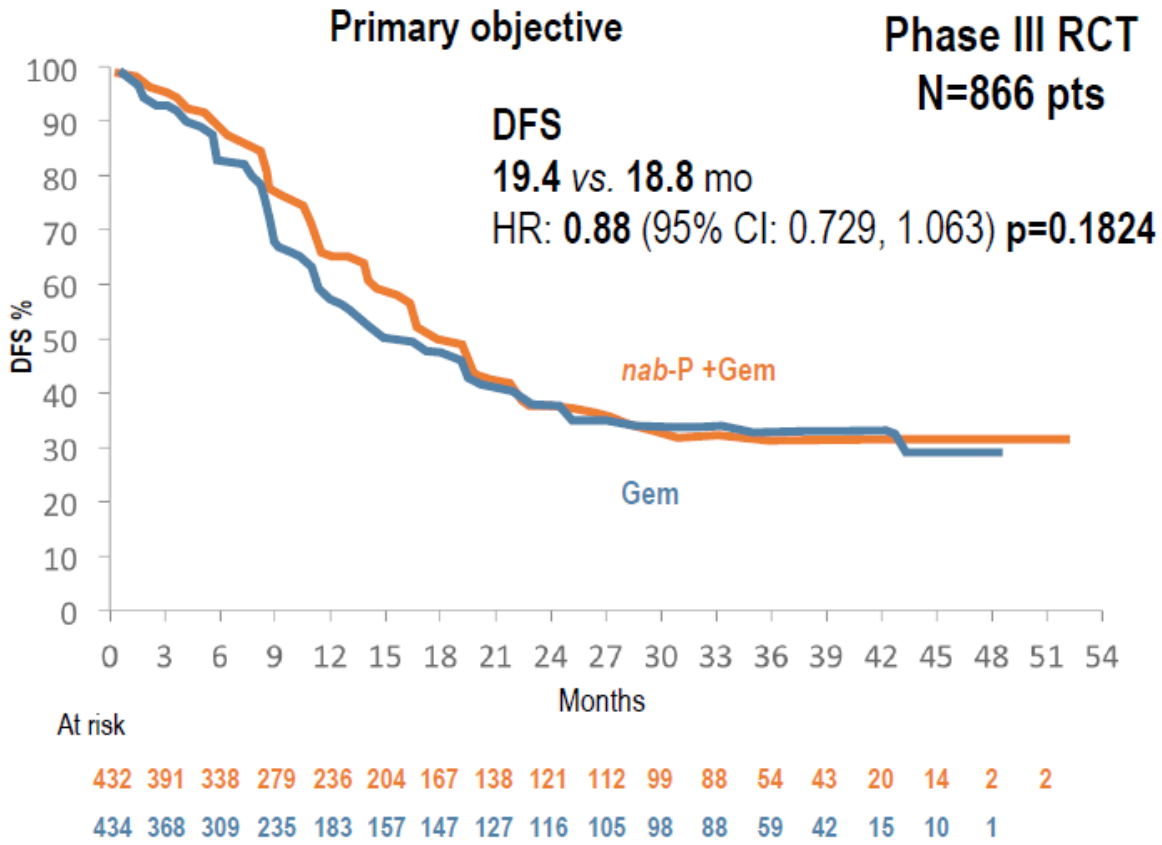


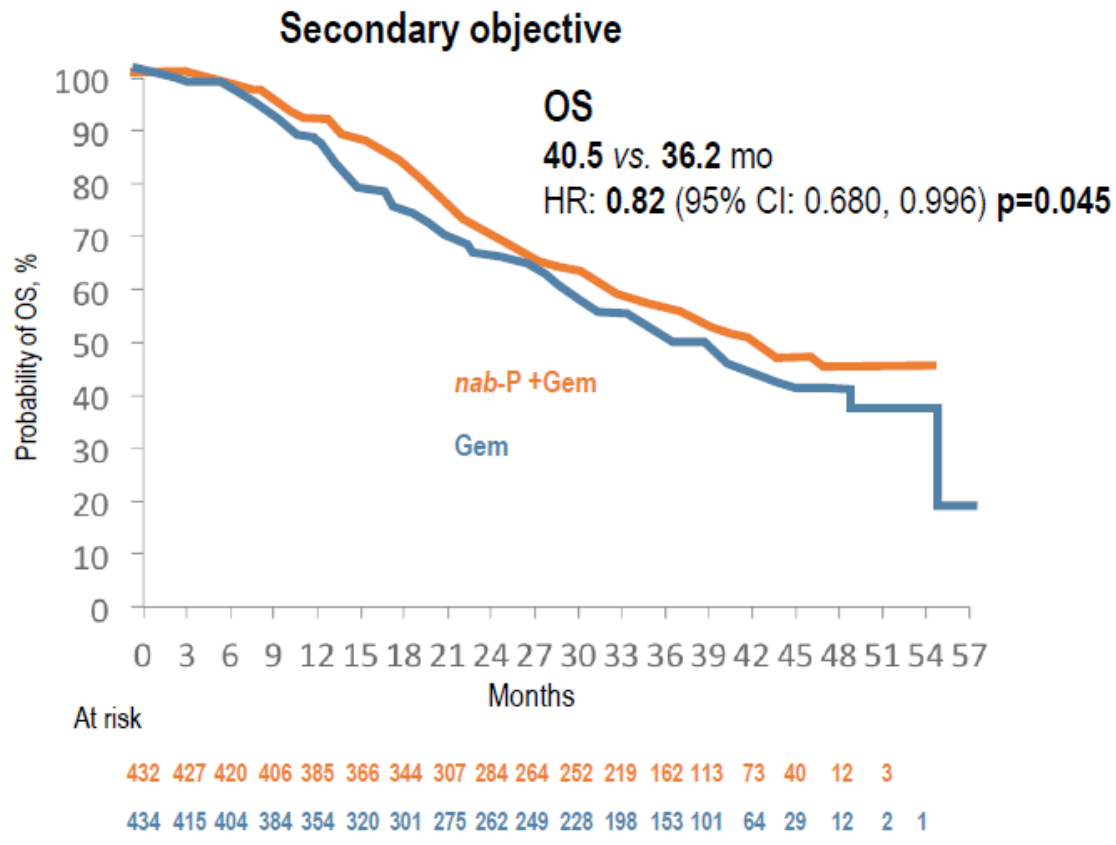
mOS: 54,4 *vs.* 35,0 months

No. at Risk											
Modified FOLFIRINOX	247	223	210	165	119	91	68	46	32	16	4
Gemcitabine	246	233	215	171	120	81	55	33	18	9	4

Gemcitabine+nab Paclitaxel in adjuvant setting APACT study



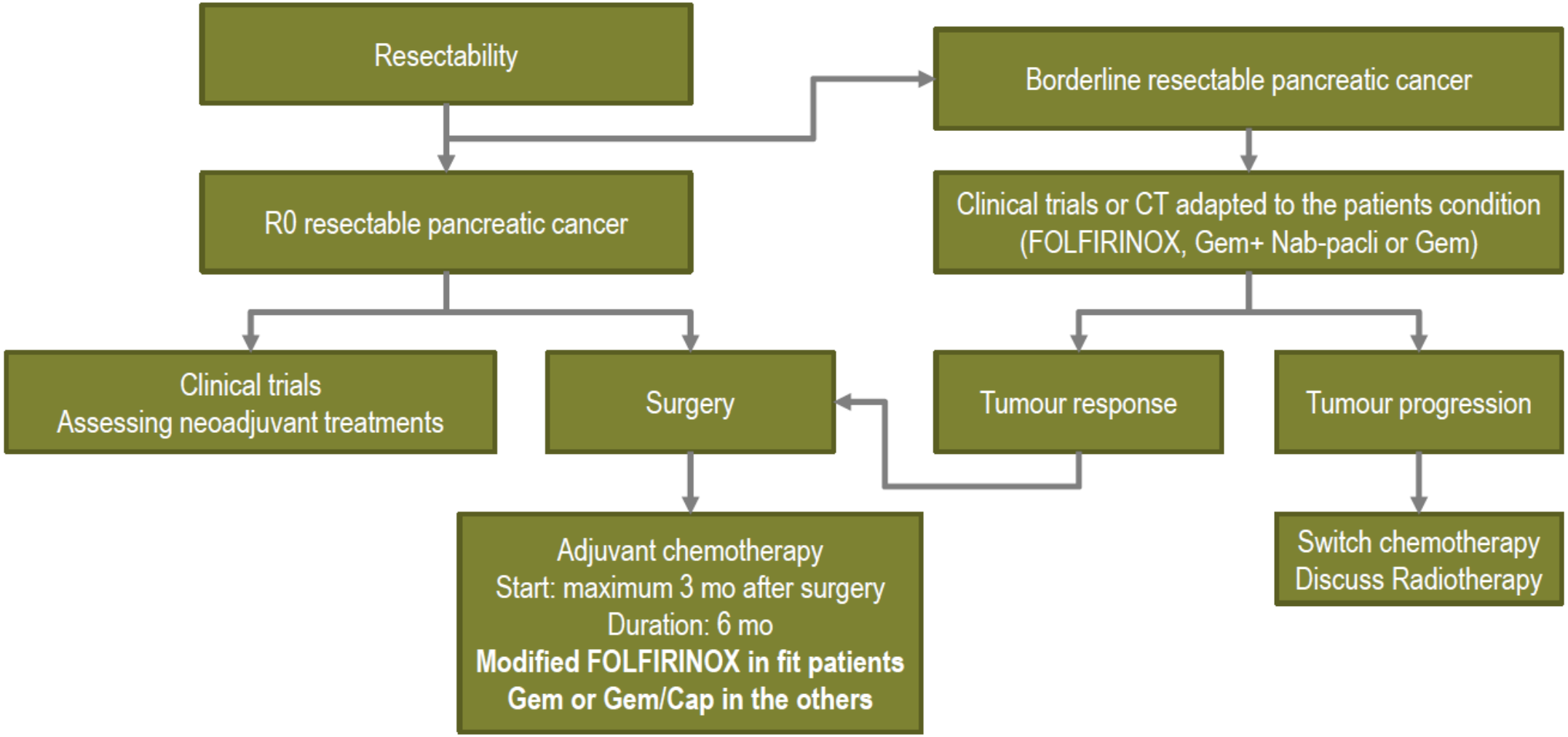

Primary objective
Phase III RCT
N=866 pts
DFS
19.4 vs. 18.8 mo
HR: 0.88 (95% CI: 0.729, 1.063) p=0.1824
nab-P +Gem
Gem
DFS %
Months
At risk
432 391 338 279 236 204 167 138 121 112 99 88 54 43 20 14 2 2
434 368 309 235 183 157 147 127 116 105 98 88 59 42 15 10 1


Secondary objective
OS
40.5 vs. 36.2 mo
HR: 0.82 (95% CI: 0.680, 0.996) p=0.045
nab-P +Gem
Gem
Probability of OS, %
Months
At risk
432 427 420 406 385 366 344 307 284 264 252 219 162 113 73 40 12 3
434 415 404 384 354 320 301 275 262 249 228 198 153 101 64 29 12 2 1

Summary

Non Metastatic Disease

Resectable Pancreatic Cancer and adjuvant treatment



Advance Metastatic Pancreatic Cancer

Metastatic Pancreatic Cancer

OS

Before 1997: 3-4 mo

1997 Gemcitabine: 5-6 mo

2005 Gemcitabine; option «doublet »

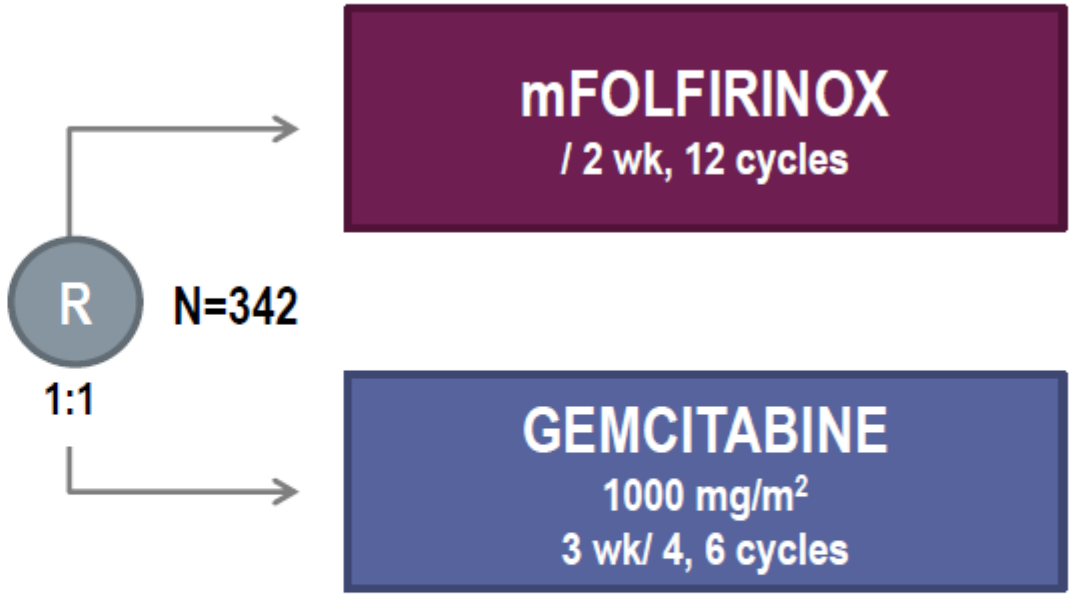
2010 FOLFIRINOX : 11-12 mo

2013 Gemcitabine + Abraxane : 9-10 mo

Frist Line Treatment for Metastatic Pancreatic Cancer

- Oxaliplatin 85 mg/m^2
- LV 400 mg/m^2
- Irinotecan 180 mg/m^2,*
- 5 FU continue 2.4 g/m^2 46 h

- Metastatic
- Chemotherapy naïve
- PS 0 or 1
- 18-75-year-old
- Bilirubinemia <1.5 xN



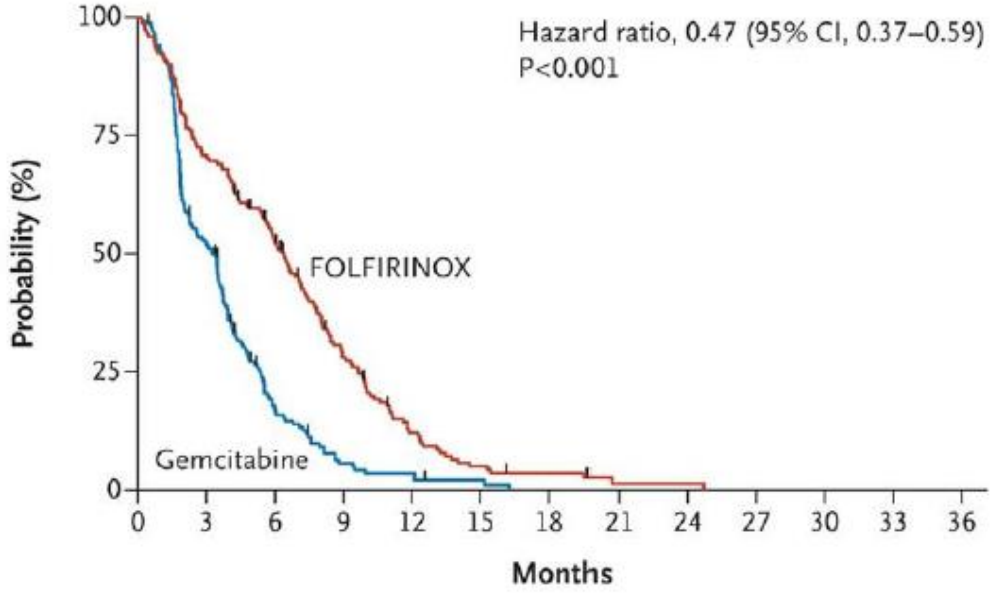
Primary objective: OS

Benefit

PFS

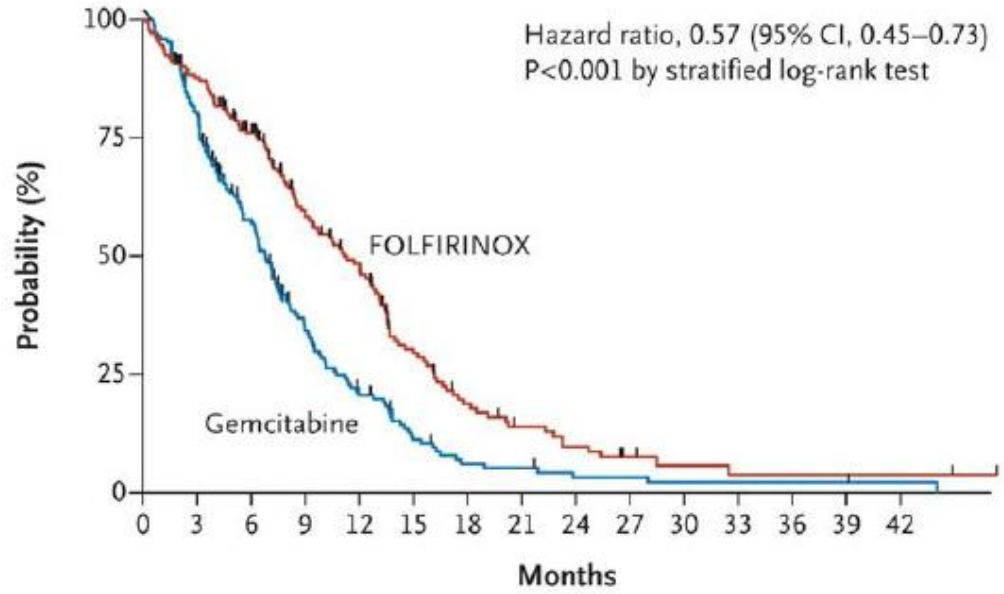
ORR = 31% *vs.* 9%; DCR = 70% *vs.* 51%

OS



No. at Risk													
Gemcitabine	171	88	26	8	5	2	0	0	0	0	0	0	0
FOLFIRINOX	171	121	85	42	17	7	4	1	1	0	0	0	0

6.4 mo *vs.* 3.3 mo

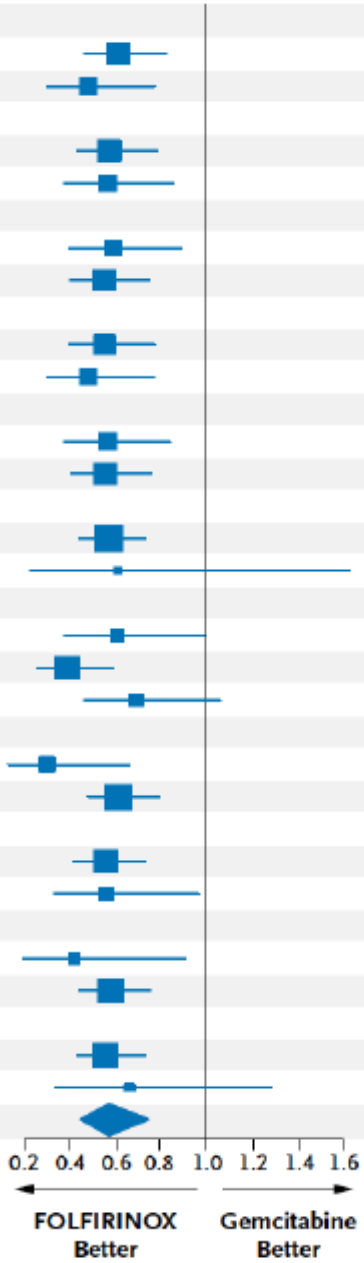


No. at Risk														
Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2	2

11.1 mo *vs.* 6.8 mo

FOLFIRINOX was favoured in subgroups

Subgroup	Gemcitabine	FOLFIRINOX	Hazard Ratio for Death (95% Confidence Interval)
	no. of events/no. of patients		
Age			
≤65 yr	104/121	93/123	0.61 (0.46–0.82)
>65 yr	43/50	33/48	0.48 (0.30–0.77)
Sex			
Male	92/105	81/106	0.57 (0.43–0.78)
Female	55/66	45/65	0.57 (0.38–0.85)
ECOG performance status			
0	52/64	42/63	0.59 (0.39–0.89)
1	95/107	84/108	0.55 (0.40–0.74)
Level of albumin			
Normal	73/84	61/82	0.55 (0.39–0.77)
Abnormal	37/41	43/54	0.48 (0.30–0.77)
Primary tumor location			
Head of pancreas	55/63	49/67	0.57 (0.38–0.84)
Other	92/108	77/104	0.56 (0.41–0.76)
Metastases			
Synchronous	140/161	115/155	0.57 (0.44–0.73)
Metachronous	7/10	10/15	0.61 (0.23–1.62)
No. of metastatic sites			
1	41/47	30/44	0.61 (0.38–0.99)
2	55/59	53/68	0.39 (0.26–0.59)
≥3	51/65	41/57	0.69 (0.46–1.05)
Hepatic metastases			
No	17/21	11/20	0.30 (0.13–0.66)
Yes	130/150	113/149	0.61 (0.48–0.79)
Pulmonary metastases			
No	109/122	101/136	0.56 (0.42–0.73)
Yes	38/49	23/33	0.56 (0.33–0.96)
Level of carbohydrate antigen 19-9			
Normal	17/24	14/23	0.42 (0.20–0.90)
Abnormal	126/142	108/142	0.58 (0.44–0.75)
Biliary stent			
No	130/149	107/144	0.56 (0.43–0.73)
Yes	17/22	18/27	0.66 (0.34–1.28)
Total	147/171	126/171	



It comes at cost of side effects

Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

* Events listed are those that occurred in more than 5% of patients in either group. NS denotes not significant.

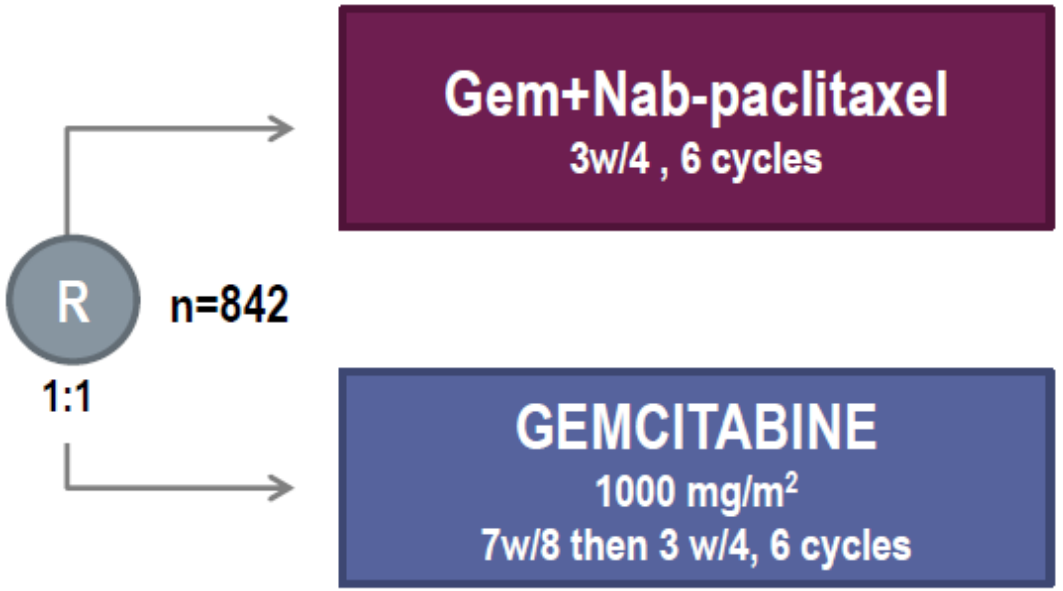
First Line Treatment:

- Gemcitabine 1000 mg/m^2
- Nab-paclitaxel 125 mg/m^2

- Metastatic
- Chemotherapy naive
- KPS ≥70
- Measurable tumour
- Bilirubinemia normal

Stratification:

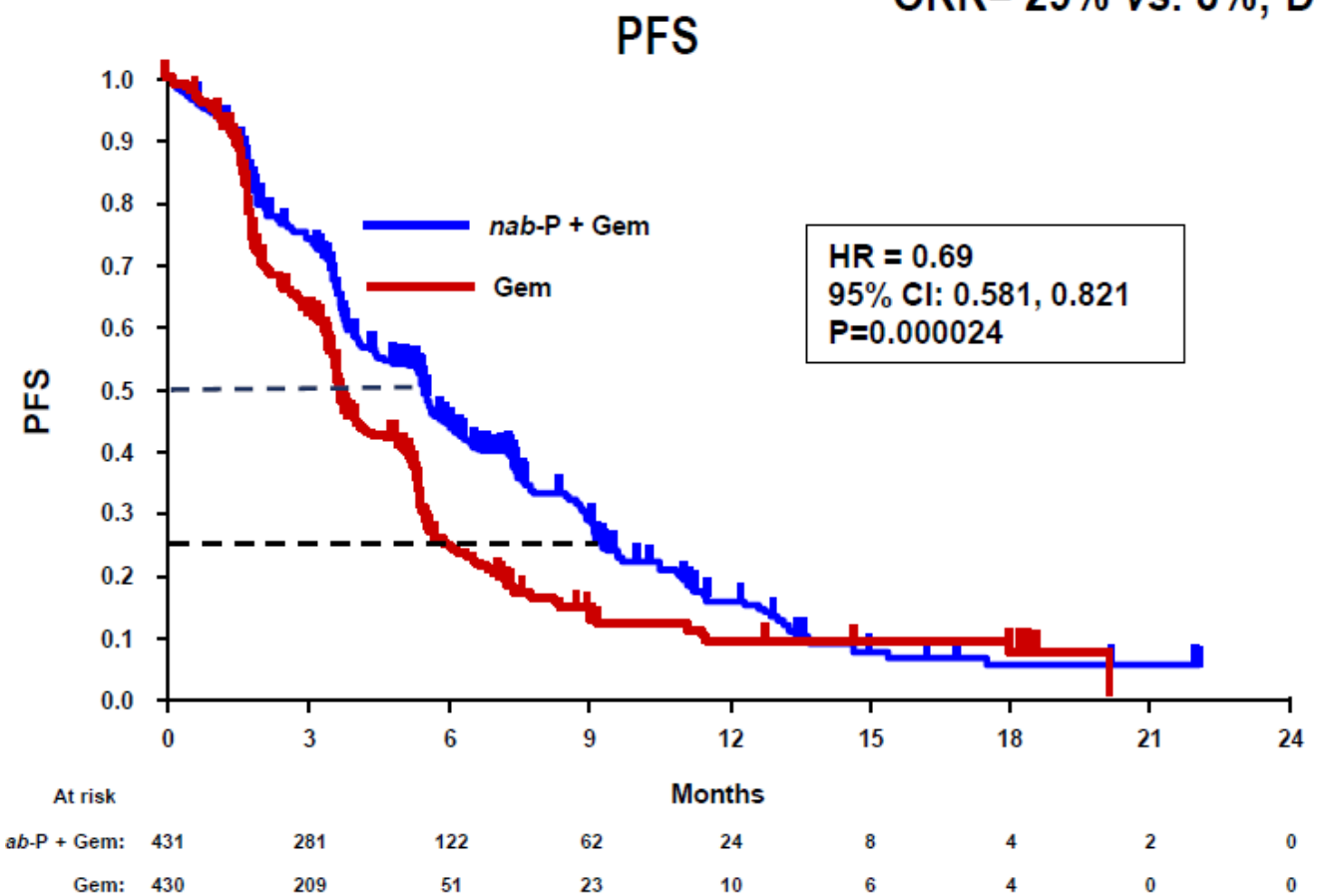
- PS
- Liver metastases
- Country



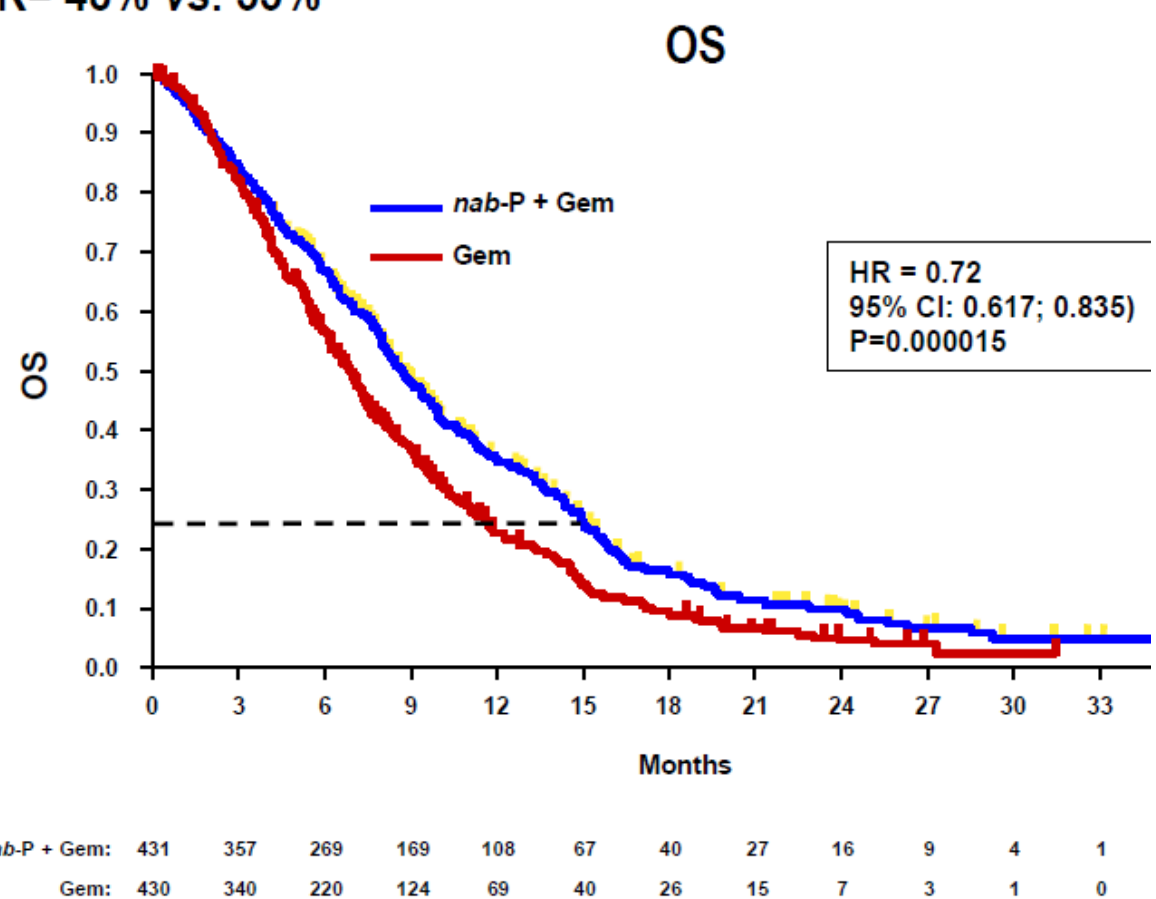
Primary objective: OS

Gem+ nab Paclitaxel

ORR= 29% *vs.* 8%; DCR= 48% *vs.* 33%



5.5 mo *vs.* 3.7 mo



8.5 mo *vs.* 6.7 mo

Gem +nabPaclitaxel

Table 3. Common Adverse Events of Grade 3 or Higher and Growth-Factor Use.*

Event	nab-Paclitaxel plus Gemcitabine (N=421)	Gemcitabine Alone (N=402)
Adverse event leading to death — no. (%)	18 (4)	18 (4)
Grade ≥3 hematologic adverse event — no./total no. (%)†		
Neutropenia	153/405 (38)	103/388 (27)
Leukopenia	124/405 (31)	63/388 (16)
Thrombocytopenia	52/405 (13)	36/388 (9)
Anemia	53/405 (13)	48/388 (12)
Receipt of growth factors — no./total no. (%)	110/431 (26)	63/431 (15)
Febrile neutropenia — no. (%)‡	14 (3)	6 (1)
Grade ≥3 nonhematologic adverse event occurring in >5% of patients — no. (%)‡		
Fatigue	70 (17)	27 (7)
Peripheral neuropathy§	70 (17)	3 (1)
Diarrhea	24 (6)	3 (1)
Grade ≥3 peripheral neuropathy		
Median time to onset — days	140	113
Median time to improvement by one grade — days	21	29
Median time to improvement to grade ≤1 — days	29	NR
Use of nab-paclitaxel resumed — no./total no. (%)	31/70 (44)	NA

* NA denotes not applicable, and NR not reached.
† Assessment of the event was made on the basis of laboratory values.
‡ Assessment of the event was made on the basis of investigator assessment of treatment-related adverse events.
§ Peripheral neuropathy was reported on the basis of groupings of preferred terms defined by standardized queries in the *Medical Dictionary for Regulatory Activities*.

Which regimen to choose as first line treatment?

Efficacy[1]

	FOLFIRINOX	Gem+ Nab-pacli
Performance status	PS2 <1%	KPS 70-80: 40%
ORR	31.6%	29%
PFS	6.4 mo	5.5 mo
with gem	3.3 mo	3.7 mo
2nd Line	47%	38%
OS	11.1 mo	8.5 mo
with gem	6.8 mo	6.7 mo

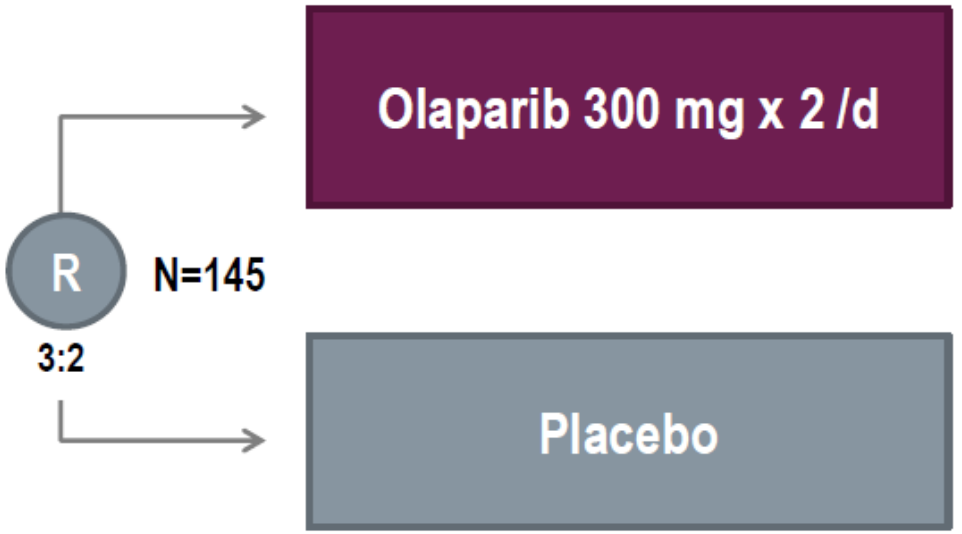
Safety[2]

	FOLFIRINOX	Gem+ Nab-pacli
Neutropenia	45.7%	38%
+ febrile	5.4%	3%
Thrombopenia	9.1%	13%
Anaemia	7.8%	13%
Neuropathy*	9%	17%
Diarrhea	12.7%	6%
Alopecia	11.4%	50%

Germ Line BRCA-2 mutated pancreatic cancer

POLO Study

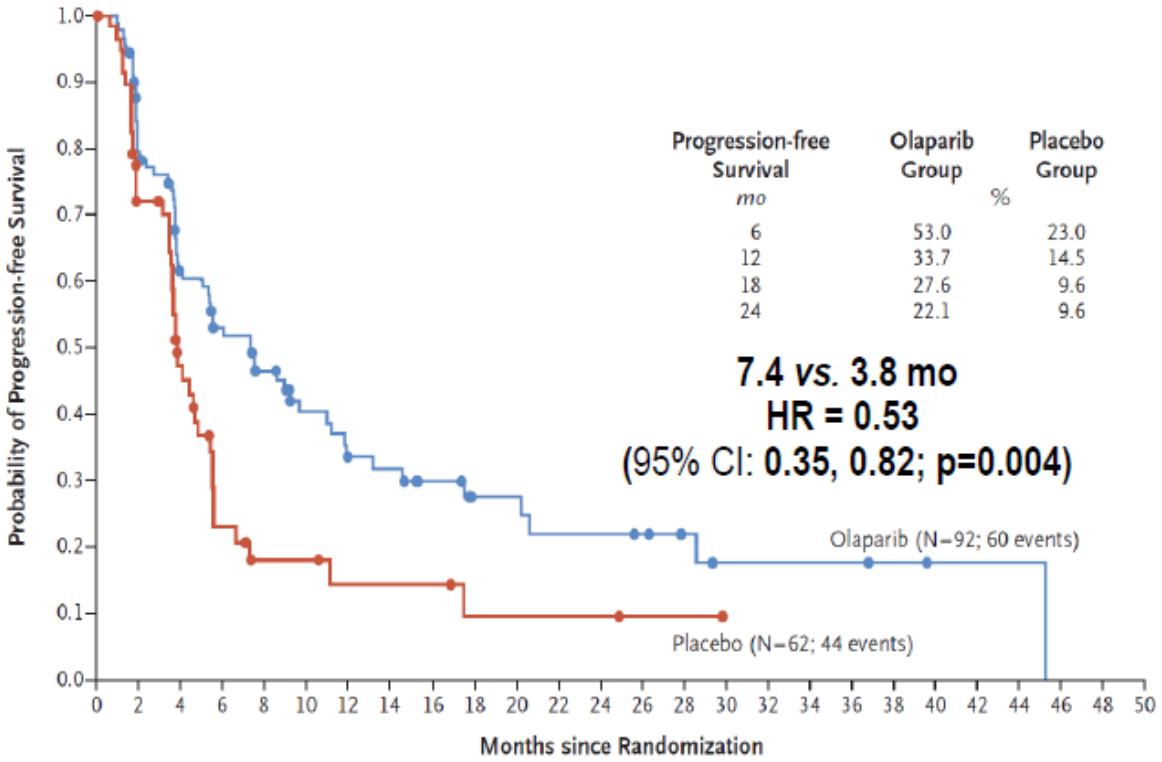
- Pancreatic adenocarcinoma
- Germline Mutated *BRCA 1/2*
- Treated with a first line platinum
- Without disease progression within 16 weeks



Primary objective:
Progression free survival

Effectiveness

PFS



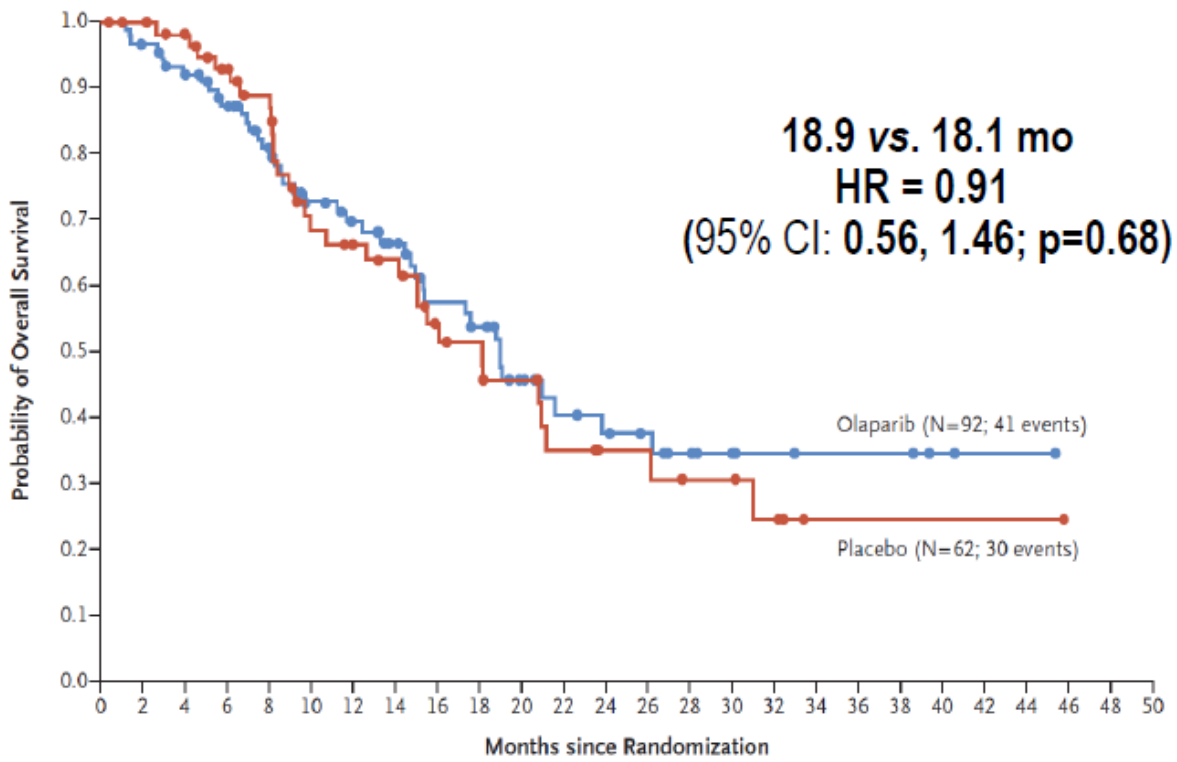
Progression-free Survival	Olaparib Group	Placebo Group
mo	%	
6	53.0	23.0
12	33.7	14.5
18	27.6	9.6
24	22.1	9.6

7.4 *vs.* 3.8 mo
HR = 0.53
(95% CI: **0.35, 0.82; p=0.004**)

No. at Risk

Olaparib	92	69	50	41	34	24	18	17	14	10	10	8	8	7	5	3	3	3	3	2	1	1	1	0
Placebo	62	39	23	10	6	6	4	4	4	2	2	2	2	1	1	0								

OS

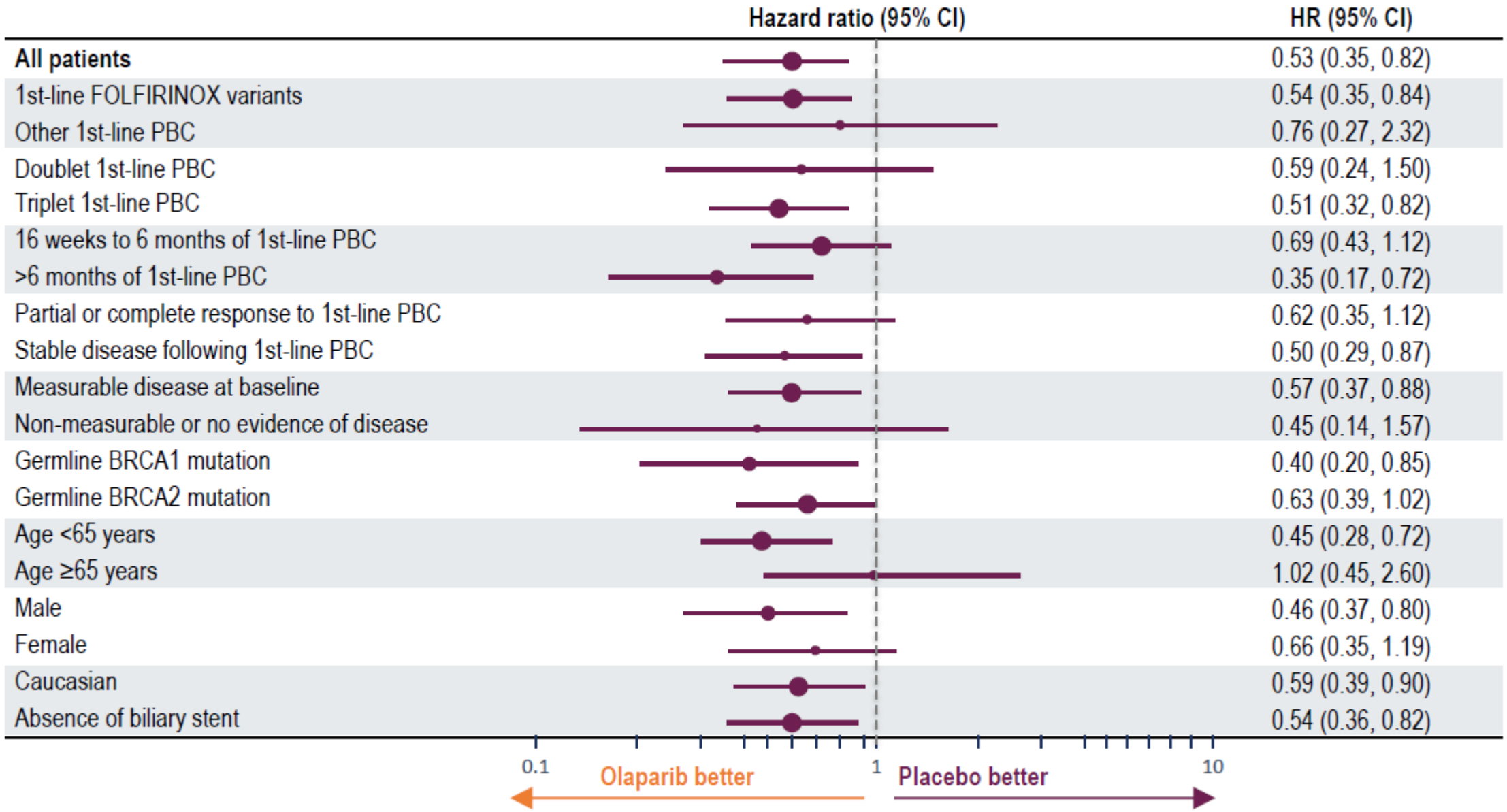


18.9 *vs.* 18.1 mo
HR = 0.91
(95% CI: **0.56, 1.46; p=0.68**)

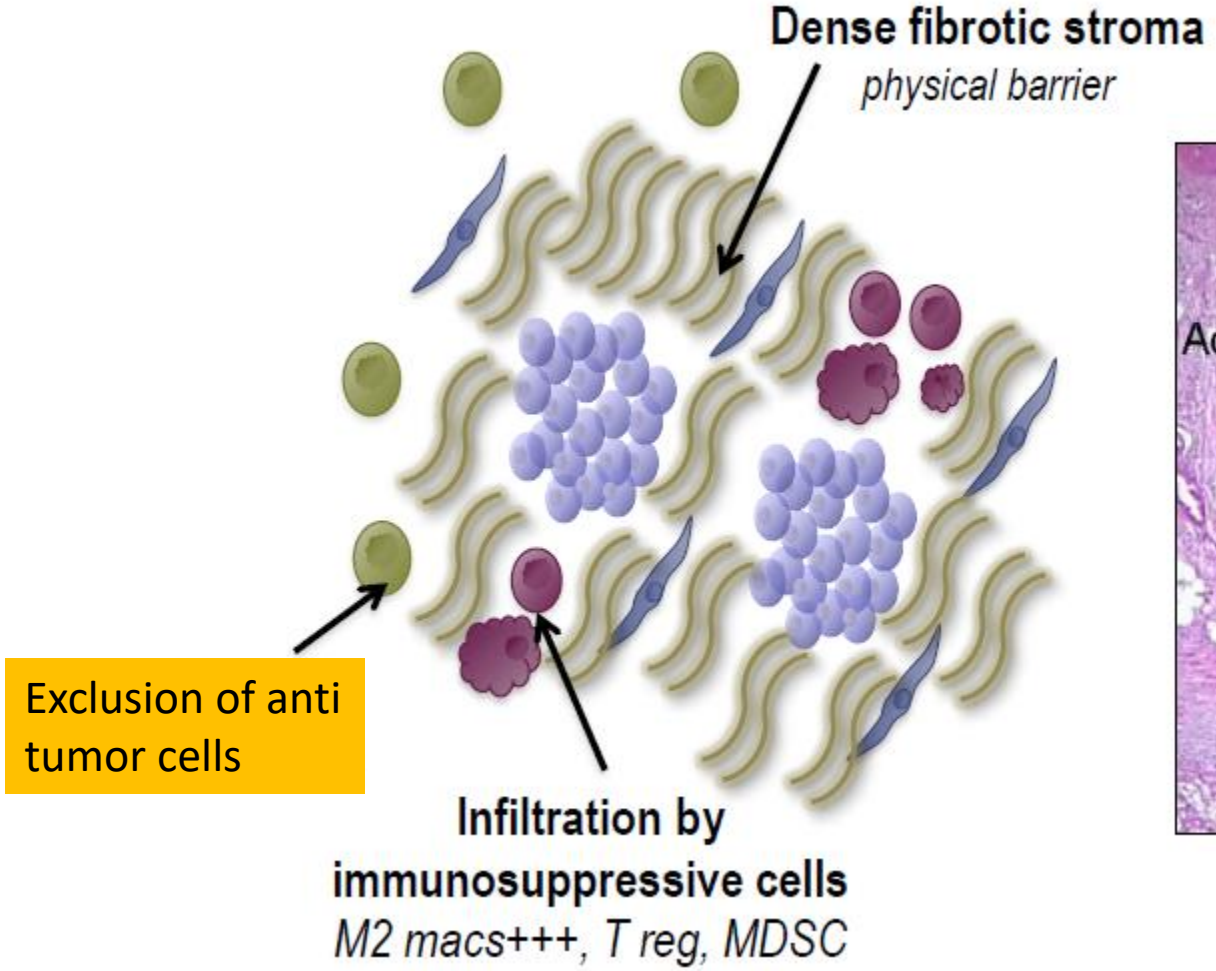
No. at Risk

Olaparib	92	87	80	71	61	51	46	39	31	28	20	16	14	12	9	6	5	4	4	4	2	1	1	0
Placebo	62	60	56	50	44	32	29	27	20	18	14	10	8	8	6	6	4	1	1	1	1	1	1	0

BRCA mutated Pancreatic cancer



Possible explanation of lack of effectiveness of immunotherapy in pancreatic cancer



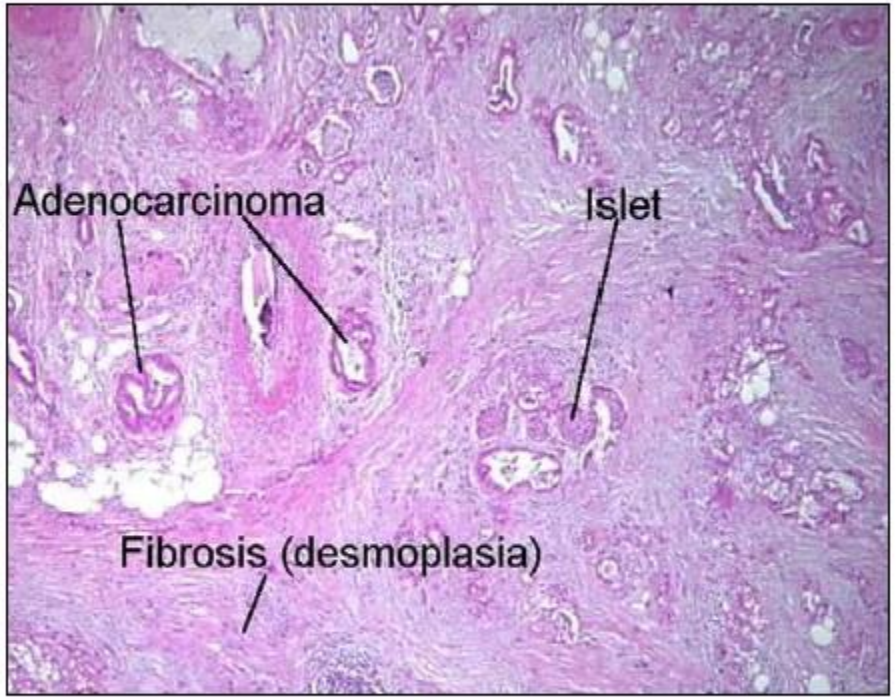
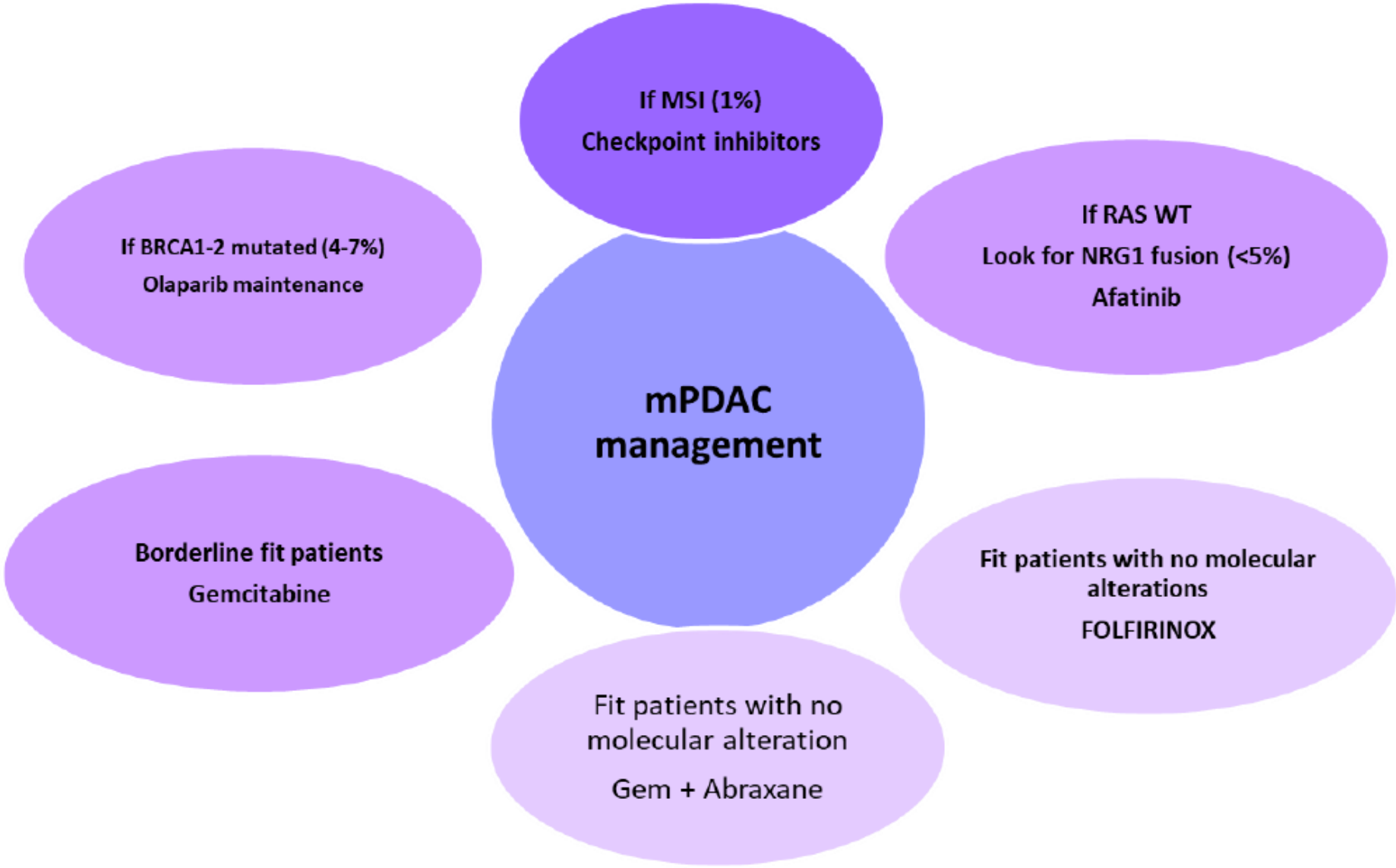


Image courtesy of Dr Cindy Neuzillet, Curie Institute Saint-Cloud

Summary

Metastatic Pancreatic Cancer

Treatment Spectrum



Polling Question

- After successful completion of adjuvant treatment follow up should include:
- 1-Every 3 to 6 months, history and physical, CA19-9, CT chest/abdomen and pelvis for five year.
- 2-There is no evidence that routine imaging or CA19-9 level improve survival. So tests should be directed only based on clinical circumstances.

Follow up and surveillance

Surveillance every 3–6 mo for 2 years, then every 6–12 mo as clinically indicated:

- **H&P for symptom assessment**
- **CA 19-9 level (category 2B)[cc]**
- **Chest CT and CT or MRI of abdomen and pelvis with contrast (unless contraindicated)**

- There is no evidence that routine imaging or laboratory investigations are useful in detecting recurrences or metastases at a stage where interventions are curative. Early detection of asymptomatic metastases does not enhance survival.
- Investigations should be performed based on the clinical presentation of a patient who is suspected of having recurrent or metastatic disease.

At this time, the panel does not recommend neoadjuvant therapy for clearly resectable patients without high-risk features, except in a clinical trial. There is limited evidence to recommend specific neoadjuvant regimens off study, and practices vary with regard to the use of chemotherapy and chemoradiation. For selected patients who appear technically resectable but have poor prognostic features (ie, markedly elevated CA 19-9; large primary tumors; large regional lymph nodes; excessive weight loss; extreme pain) consideration can be given to neoadjuvant therapy after biopsy confirmation, and therapy should be administered preferably at or coordinated through a high-volume center.

Surveillance of Patients with Resected Disease

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are very limited,[604-606] recommendations are based on the consensus that earlier identification of disease may facilitate patient eligibility for investigational studies or other forms of treatment. The panel recommends history and physical examination for symptom assessment every 3 to 6 months for 2 years, then every 6 to 12 months as clinically indicated. CA 19-9 determinations and follow-up CT scans (chest, abdomen, and pelvis) with contrast every 3 to 6 months for 2 years after surgical resection are category 2B recommendations, because data are not available to show that earlier treatment of recurrences, following

detection by increased tumor marker levels or CT scan, leads to better patient outcomes. In fact, an analysis of the SEER-Medicare database showed no significant survival benefit for patients who received regular surveillance CT scans.[607]

recommends that an alternative chemotherapy option be administered (eg, switching to a gemcitabine-based regimen if fluoropyrimidine-based therapy was previously used, or vice versa). When this period is 6 months or greater, repeating systemic therapy as previously administered or switching to any other systemic regimen is recommended.

Thank you

Questions and Comments