Chemotherapy in Pancreatic Cancer

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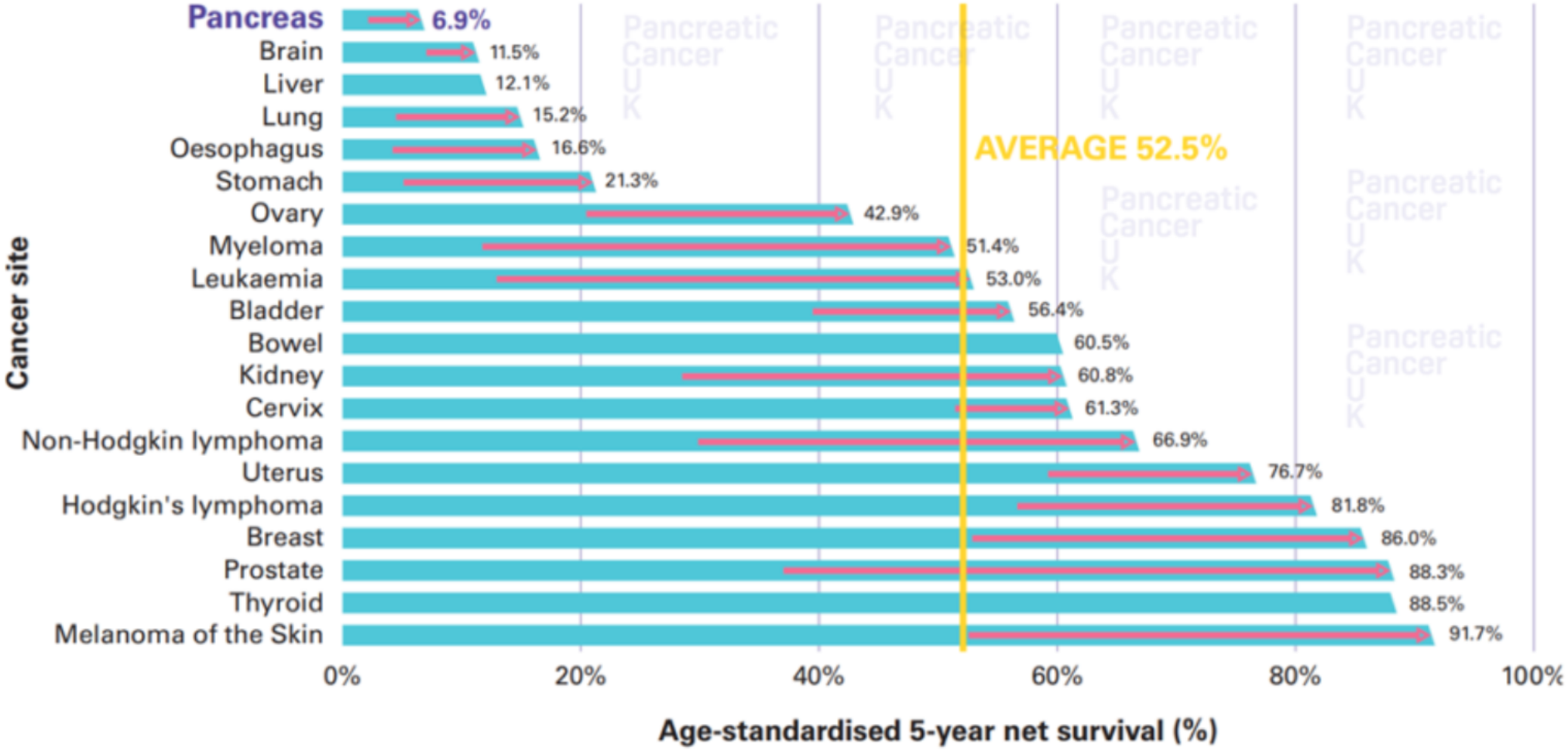
Where are we now



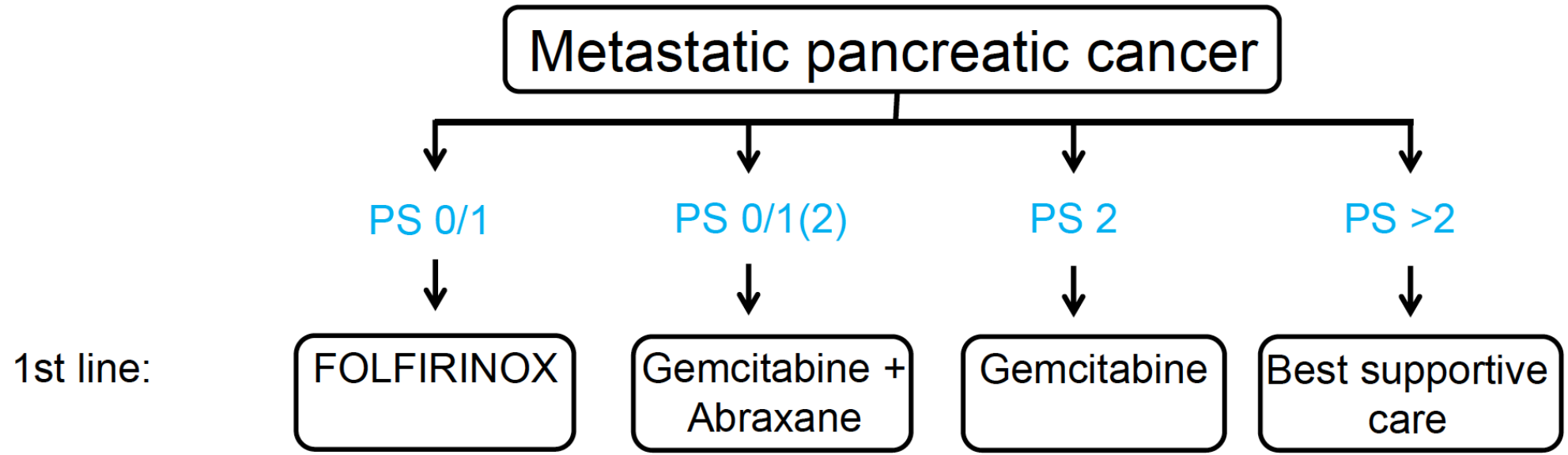
Courtesy of Pancreatic Cancer UK

3 indications to give chemotherapy

- Palliative
- Adjuvant
- Neoadjuvant

Palliative chemotherapy

- Given to patients with non-curative disease
- Chiefly metastatic patients (stage 4)- spread beyond pancreas


Metastatic pancreatic cancer
PS 0/1
PS 0/1(2)
PS 2
PS >2
1st line:
FOLFIRINOX
Gemcitabine + Abraxane
Gemcitabine
Best supportive care

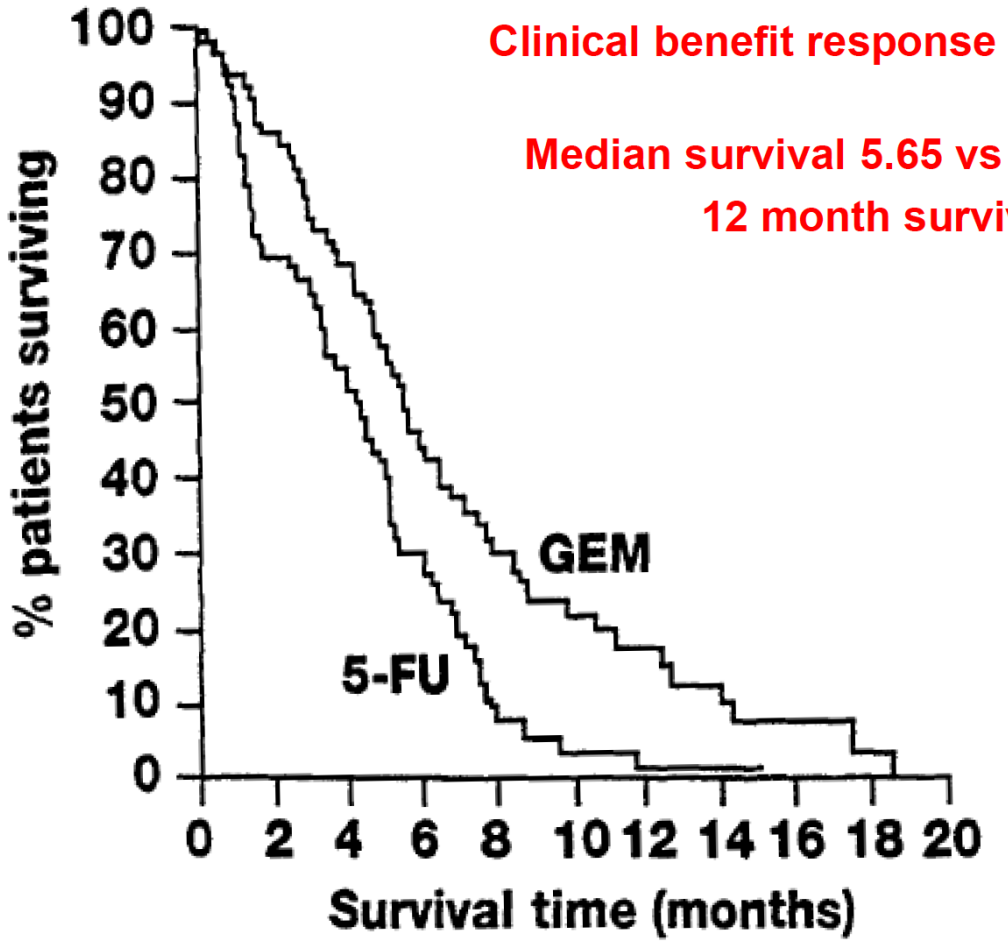
Burris *et al* 1997

- 126 patients with advanced symptomatic pancreatic cancer randomised to:
  - Gemcitabine
    - Induction 1000mg/m2 7 weeks on, one week off
    - Maintenance 1000mg/m2 D1,8,15 every 28 days
  - 5FU 600mg/m2 iv bolus weekly

Gemcitabine – nucleoside analogue; inhibits DNA synthesis

5-FU/Capecitabine – thymidylate synthase inhibition (blocks DNA repair)

J Clin Oncol 1997 Jun;15(6):2403-13



Clinical benefit response 23.8% vs 4.8%; p=0.0022

Median survival 5.65 vs 4.41 months; p=0.0025

12 month survival 18% vs 2%

J Clin Oncol 1997 Jun;15(6):2403-13

FOLFIRINOX

- PRODIGE 4/ACCORD 11 Trial

- 342 patients with metastatic pancreatic cancer randomised to:
  - FOLFIRINOX

    Oxaliplatin 85mg/m2 D1,
    Irinotecan 180 mg/m2 D1,
    FA 400mg/m2 D1,
    5FU 400mg/m2 bolus then 2400mg/m2 over 46 hours
    Every 2 weeks
  - Gemcitabine

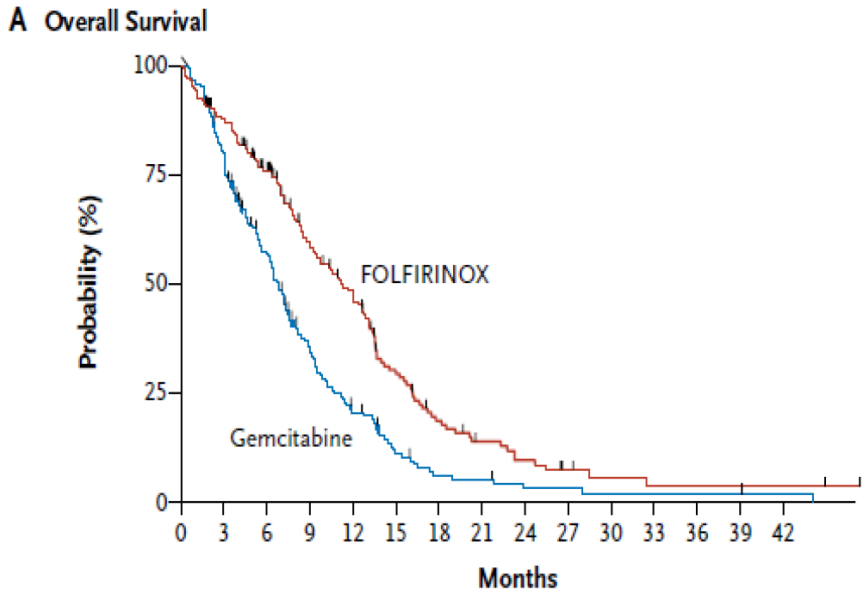
Gemcitabine – nucleoside analogue; inhibits DNA synthesis

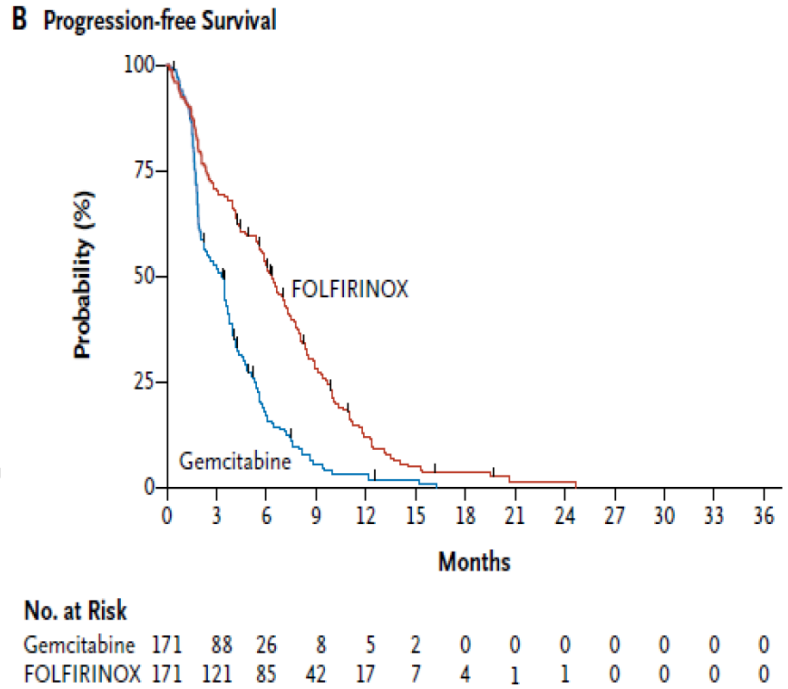
5-FU/Capecitabine – thymidylate synthase inhibition (blocks DNA repair)

Oxaliplatin – platinum crosslinking of DNA strands

Irinotecan – inhibits topoisomerase I → DNA damage

N Engl J Med 2011 May 12;364(19):1817-25





Median survival 11.1 vs 6.8 months
HR 0.57 (0.45-0.73); p<0.001

Median PFS 6.4 vs 3.3 months
HR 0.47 (0.37-0.59); p<0.001

N Engl J Med 2011 May 12;364(19):1817-25

Table 2. Objective Responses in the Intention-to-Treat Population.*

Variable	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
Response — no. (%)			
Complete response	1 (0.6)	0	
Partial response	53 (31.0)	16 (9.4)	
Stable disease	66 (38.6)	71 (41.5)	
Progressive disease	26 (15.2)	59 (34.5)	
Could not be evaluated	25 (14.6)	25 (14.6)	
Rate of objective response†			<0.001
No. (%)	54 (31.6)	16 (9.4)	
95% CI	24.7–39.1	5.4–14.7	
Rate of disease control‡			<0.001
No. (%)	120 (70.2)	87 (50.9)	
95% CI	62.7–76.9	43.1–58.6	
Response duration — mo			0.57
Median	5.9	3.9	
95% CI	4.9–7.1	3.1–7.1	

N Engl J Med 2011 May 12;364(19):1817-25

Toxicity (G3/G4)

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

N Engl J Med 2011 May 12;364(19):1817-25

Gemcitabine + Abraxane

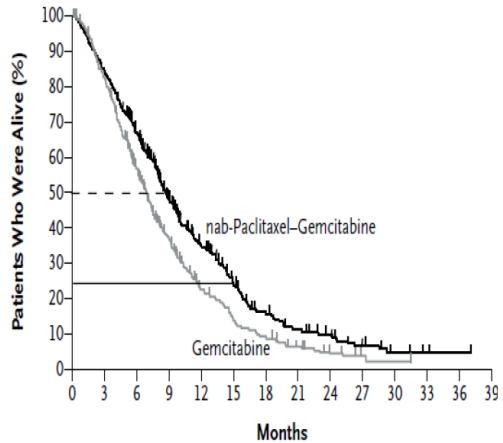
Randomized phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT).

Gemcitabine – nucleoside analogue; inhibits DNA synthesis

Nab-Paclitaxel – stabilizes microtubules, halting mitosis

N Engl J Med 2013; 369(18):1691-703

A Overall Survival

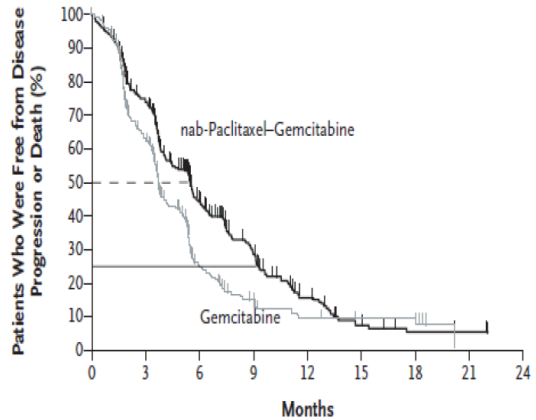


No. at Risk

nab-Paclitaxel–Gemcitabine	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gemcitabine	430	340	220	124	69	40	26	15	7	3	1	0	0	0

Median survival 8.5 vs 6.7 months
HR 0.72 (0.62-0.83); p<0.001

B Progression-free Survival, According to Independent Review



No. at Risk

nab-Paclitaxel–Gemcitabine	431	281	122	62	24	8	4	2	0
Gemcitabine	430	209	51	23	10	6	4	0	0

Median PFS 5.5 vs 3.7 months
HR 0.69 (0.58-0.82); p<0.001

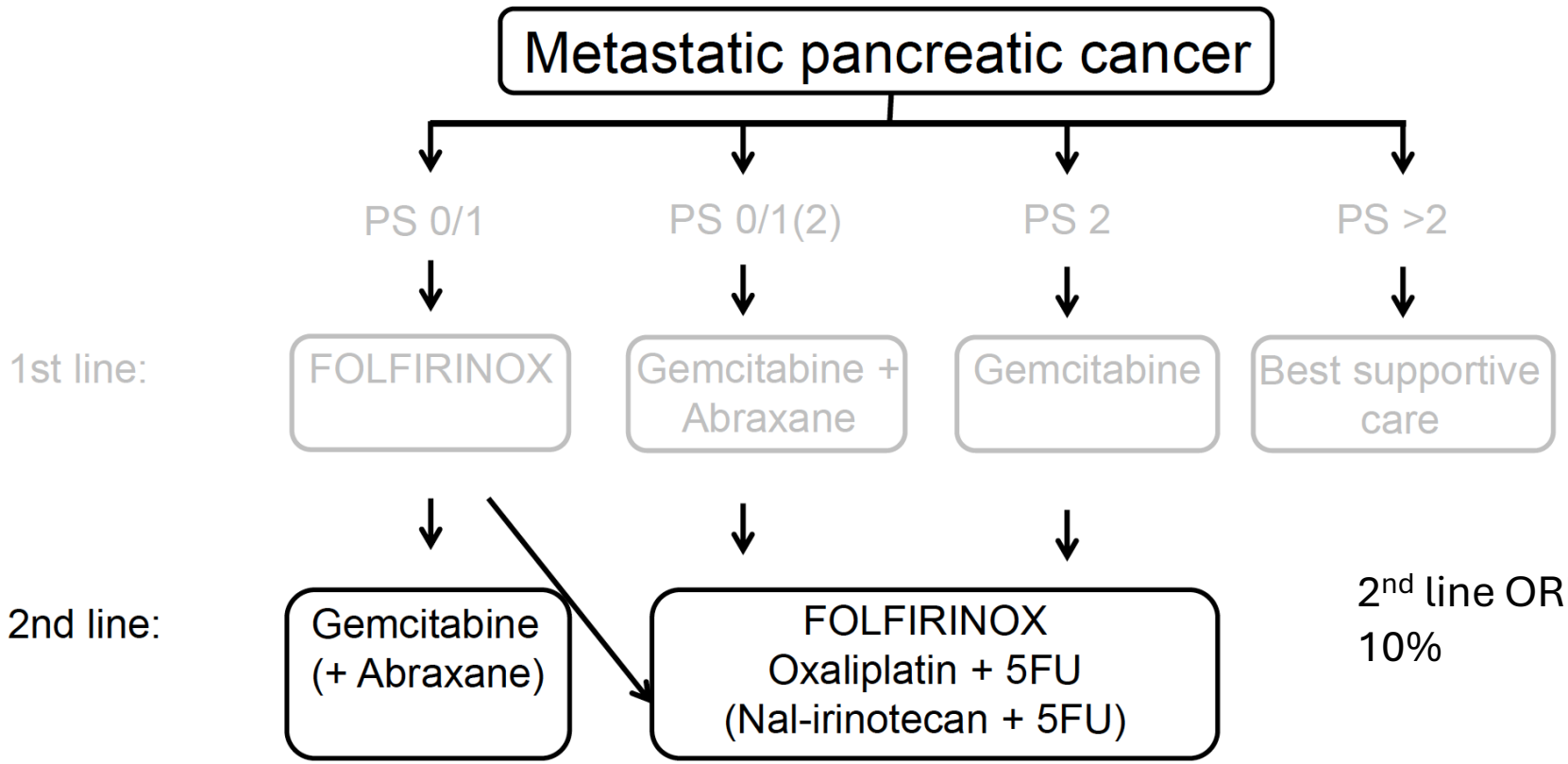
N Engl J Med 2013; 369(18):1691-703

Efficacy Variable	nab-Paclitaxel plus Gemcitabine (N=431)	Gemcitabine Alone (N=430)	Hazard Ratio or Response-Rate Ratio (95% CI)*	P Value
Response				
Rate of objective response				
Independent review				
No. of patients with a response	99	31	3.19 (2.18–4.66)	<0.001
% (95% CI)	23 (19–27)	7 (5–10)		
Investigator review				
No. of patients with a response	126	33	3.81 (2.66–5.46)	<0.001
% (95% CI)	29 (25–34)	8 (5–11)		
Rate of disease control†				
No. of patients	206	141	1.46 (1.23–1.72)	<0.001
% (95% CI)	48 (43–53)	33 (28–37)		
Best response according to independent review — no. (%)				
Complete response	1 (<1)	0		
Partial response	98 (23)	31 (7)		
Stable disease	118 (27)	122 (28)		
Progressive disease	86 (20)	110 (26)		
Could not be evaluated‡	128 (30)	167 (39)		

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

N Engl J Med 2013; 369(18):1691-703

Only one positive 2nd line trial,
Liposomal irinotecan after gemcitabine



2nd line ORR across pdac is 10%

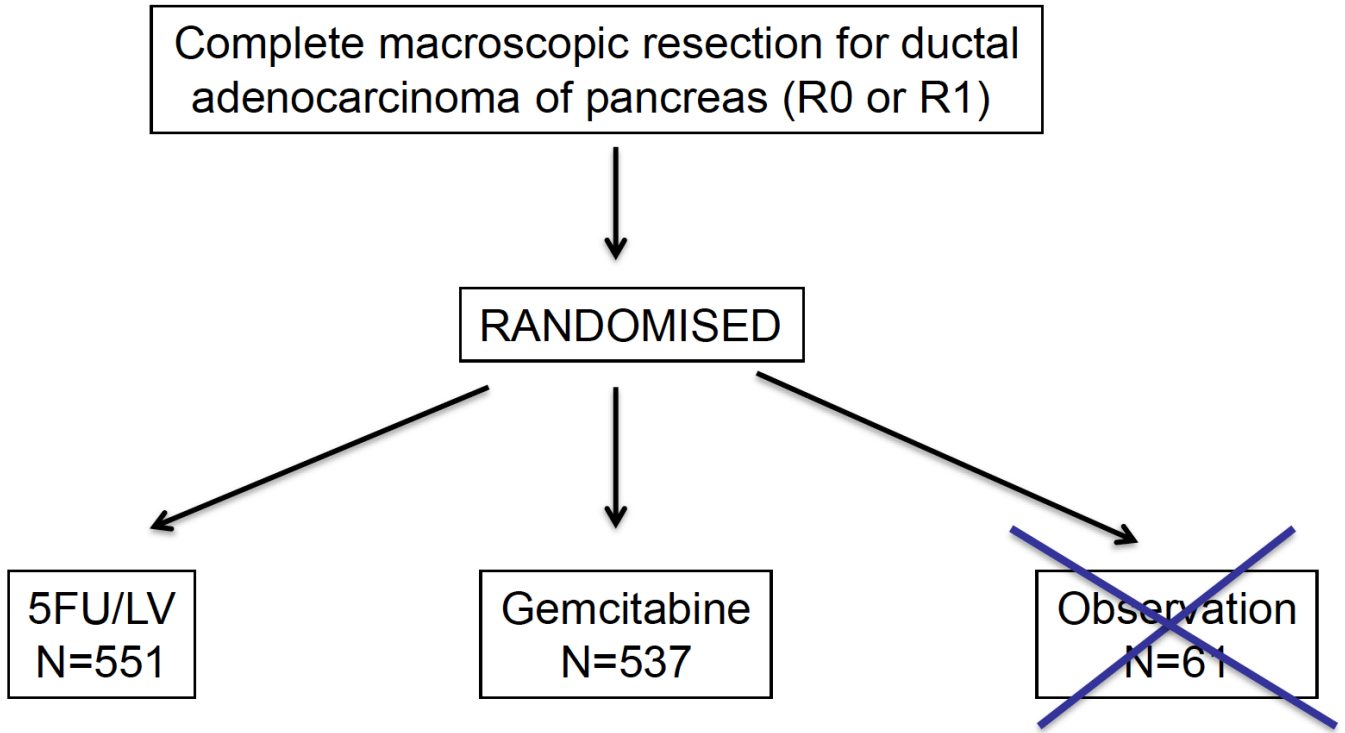
In UK, can't give gem-Abraxane 2nd line in public sector,so can only give gemcitabine, capecitabine

Adjuvant chemotherapy

- To prevent recurrence.

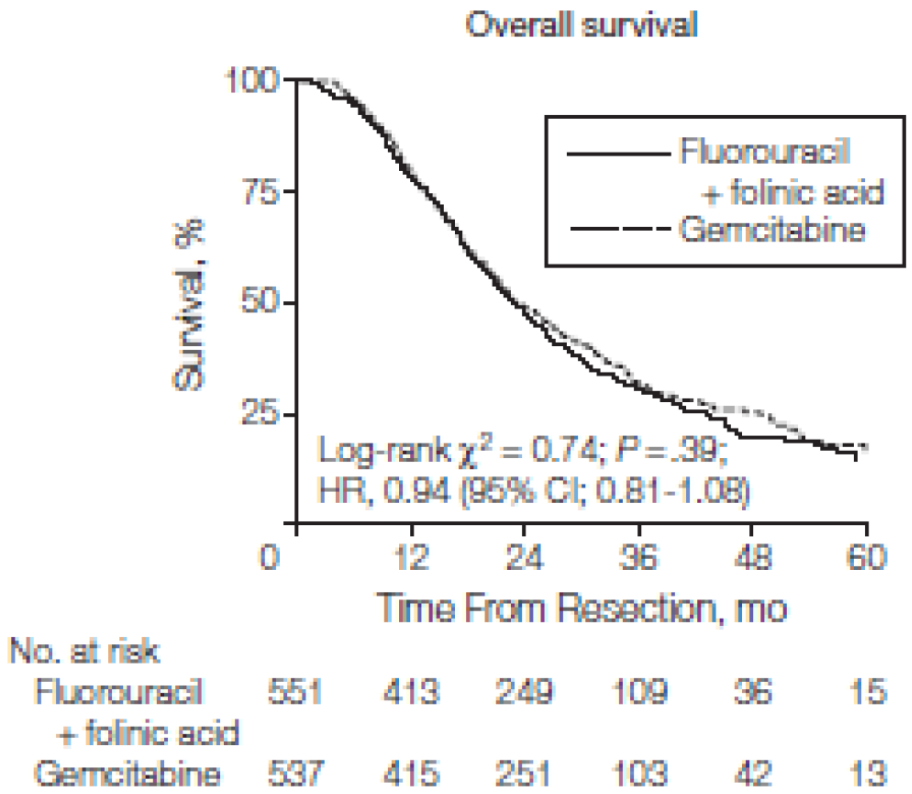
- Still resecting pancreatic cancer is a poor situation. Main output is overall survival.

ESPAC 3 (v2)

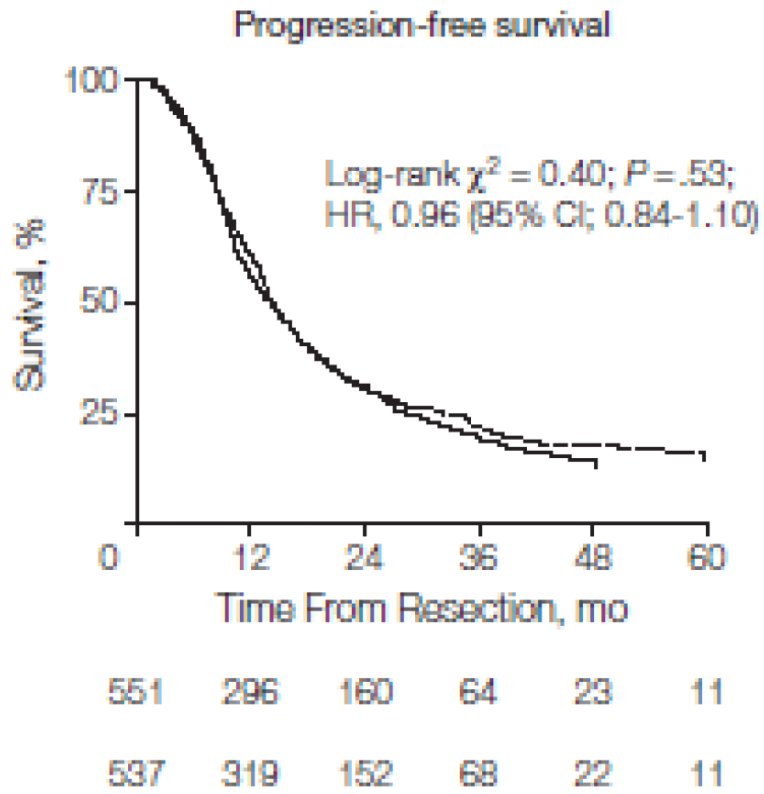


JAMA 2010 Sep 8;304(10):1073-81.

Survival results by randomised treatment

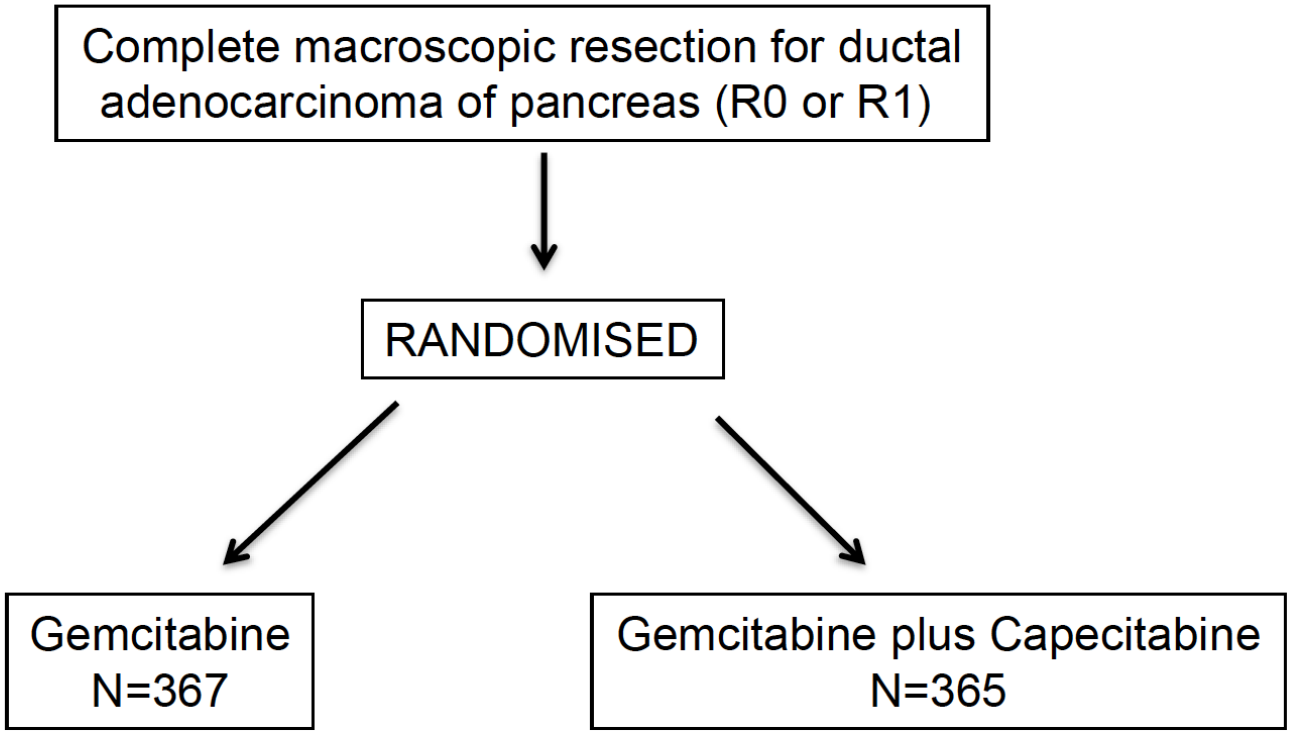


Median survival 23 vs 23.6 months

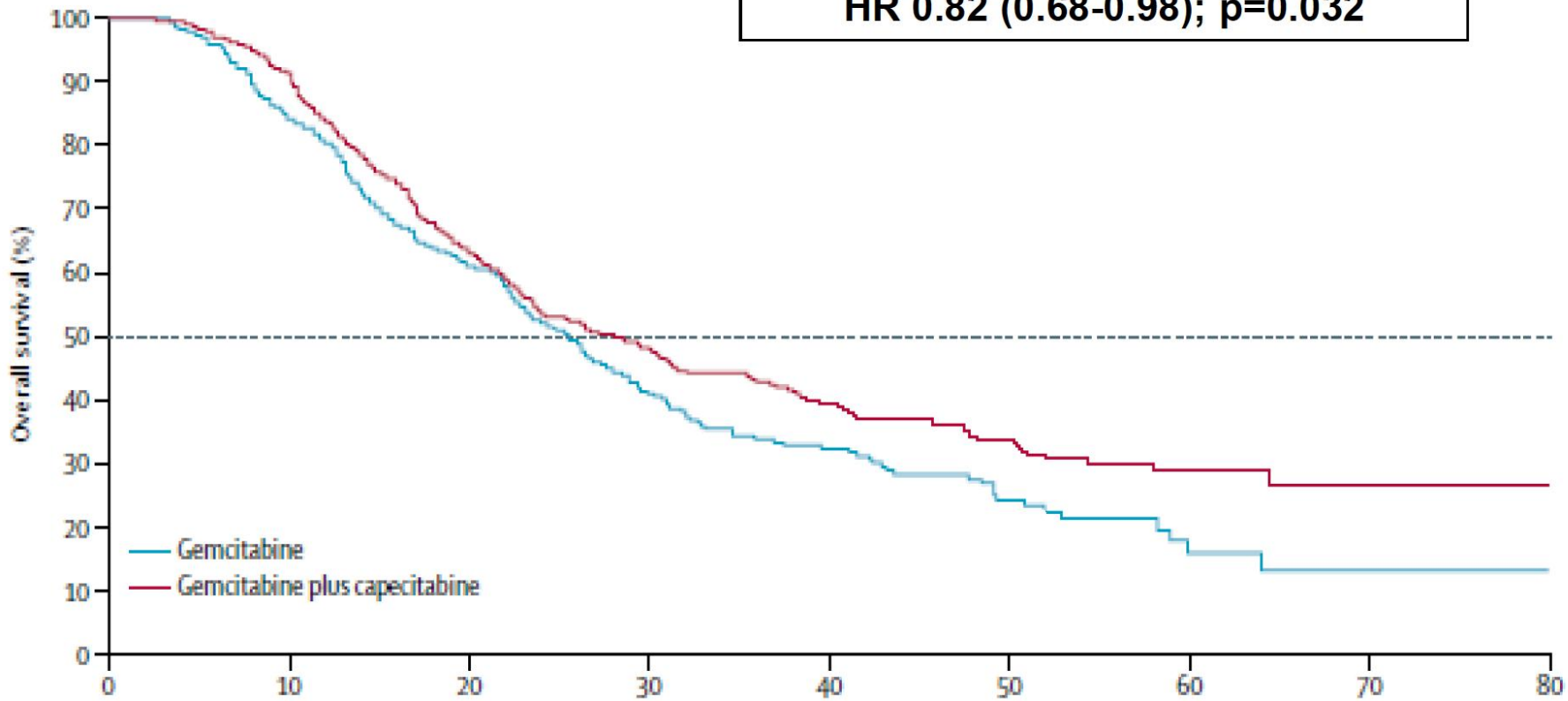


Median PFS 14.1 vs 14.3 months

ESPAC-4


Complete macroscopic resection for ductal adenocarcinoma of pancreas (R0 or R1)
RANDOMISED
Gemcitabine
N=367
Gemcitabine plus Capecitabine
N=365

Median survival 28.0 vs 25.5 months
HR 0.82 (0.68-0.98); p=0.032



Number at risk									
Gemcitabine	366	302	207	109	61	27	9	3	0
Gemcitabine plus capecitabine	364	328	219	139	83	50	19	10	1

PRODIGE 24/CCTG PA.6 trial: study design

NCT01526135

- R0 or R1 resected pancreatic cancer
- postoperative CT-scan mandatory
- CA19-9 level < 180 U/mL within 12 weeks after surgery

Stratification:
- center
- resection margin (R0 vs R1)
- CA19-9 level (≤ 90 vs 91-179 U/mL)
- pN0 (< 12 vs ≥ 12 examined nodes) vs pN1

RANDOMIZE

1:1

mFolfirinox

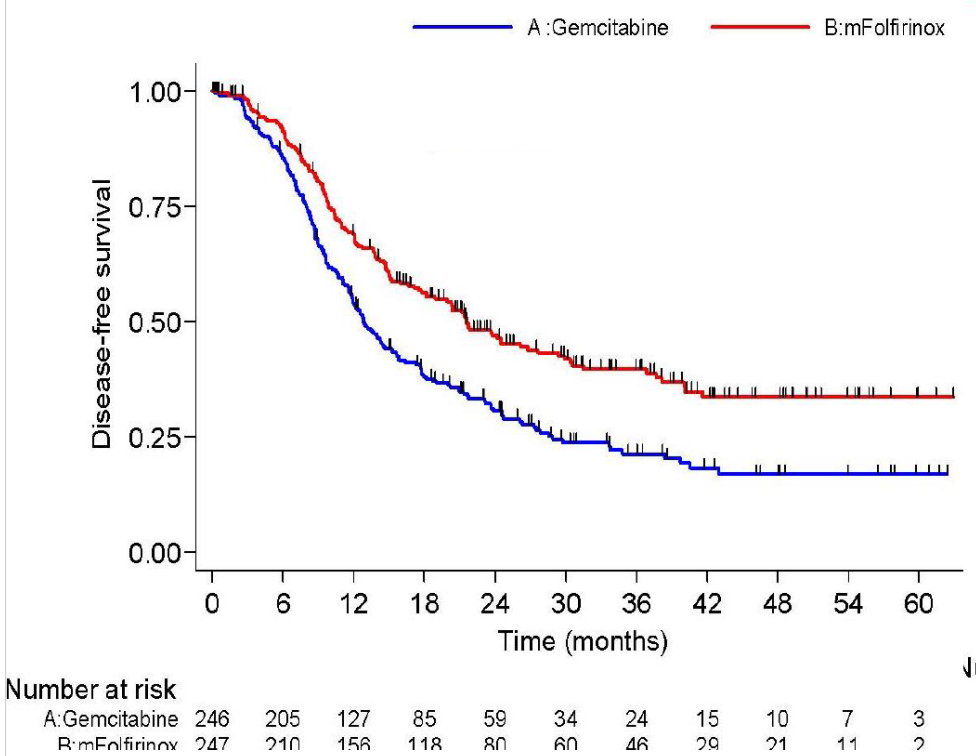
Oxaliplatin 85 mg/m², Leucovorin 400 mg/m²,
Irinotecan 180 mg/m²*, all at D1
Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours
Every 2 weeks; 12 cycles
**Reduced to 150 mg/m² after patient 162*

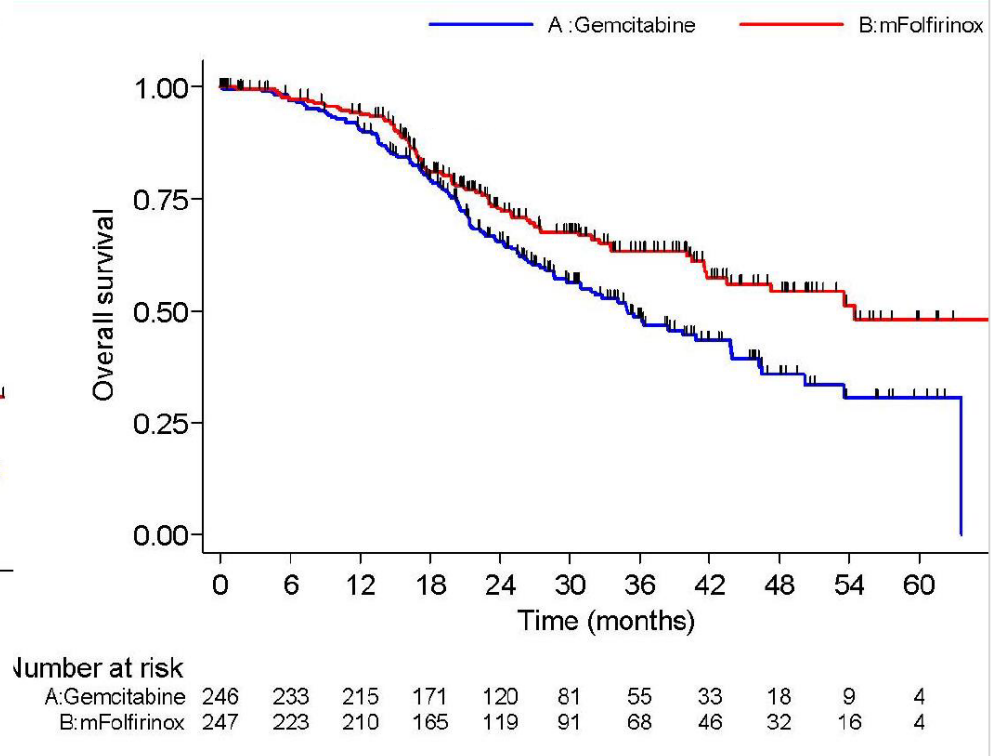
Gemcitabine

1000 mg/m², qw 3/4 *weeks;*
6 cycles

for both arms:
- 6 months of chemotherapy
- CT scans: every 3 months

	FOLFIRINOX	Gem	HR	P value		FOLFIRINOX	Gem	HR	P value
Median DFS	**21.6 mths**	**12.8 mths**	**0.58 (0.46-0.73)**	**P<0.0001**	**Median survival**	**54.4 mths**	**35 mths**	**0.64 (0.48-0.86)**	**P<0.003**
3 year DFS	**39.7%**	**21.4%**			**3 year OS**	**63.4%**	**48.6%**		





Adjuvant chemotherapy

- 6 months adjuvant chemotherapy with modified FOLFIRINOX if good PS

- Gemcitabine + capecitabine if patient not fit enough or can’t tolerate FOLFIRINOX

Locally advanced pancreatic cancer/Borderline resectable

- Locally advanced tumours are not operable due to artery involvement but not metastatic
- 1 in 3 patients
- Borderline- resectable but vein involvement
- Indication to give neoadjuvant chemotherapy
- Usually FOLFIRINOX, no level 1 evidence

NCCN resectability criteria

Resectable	Borderline	Irresectable
Arterial No contact	**Head/uncinate process:** - Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation or abutment and no extention to the SMA or variant artery* **Body/tail:** - Abutment (≤180°) to the celiac axis or encasement of the celiac axis without involvement of the aorta or gastroduodenal a.	**H/U process:** > 180° SMA or CA **Body/tail:** > 180° SMA or CA or ≤180° CA and aortic involvement
Venous ≤ 180° without contour irregularity	> 180° or with contour irregularity / thrombosis resection & reconstruction possible	> 180° or with contour irregularity or thrombosis resection & reconstruction **not** possible

Unanswered questions in neoadjuvant chemotherapy

- How long for?
- Is there a benefit?
- Optimal regime- currently folfirinox, can’t give gem-abraxane
- Recent studies are still unclear

Chemotherapy pathway in metastatic setting

- 1 in 2 patients currently get no chemotherapy
- In local audit, average time from CT scan diagnosing stage 4 pdac to first cycle of chemo is 70 days
- Barriers- referral pathway, biopsy, time to oncologist, time to chemo

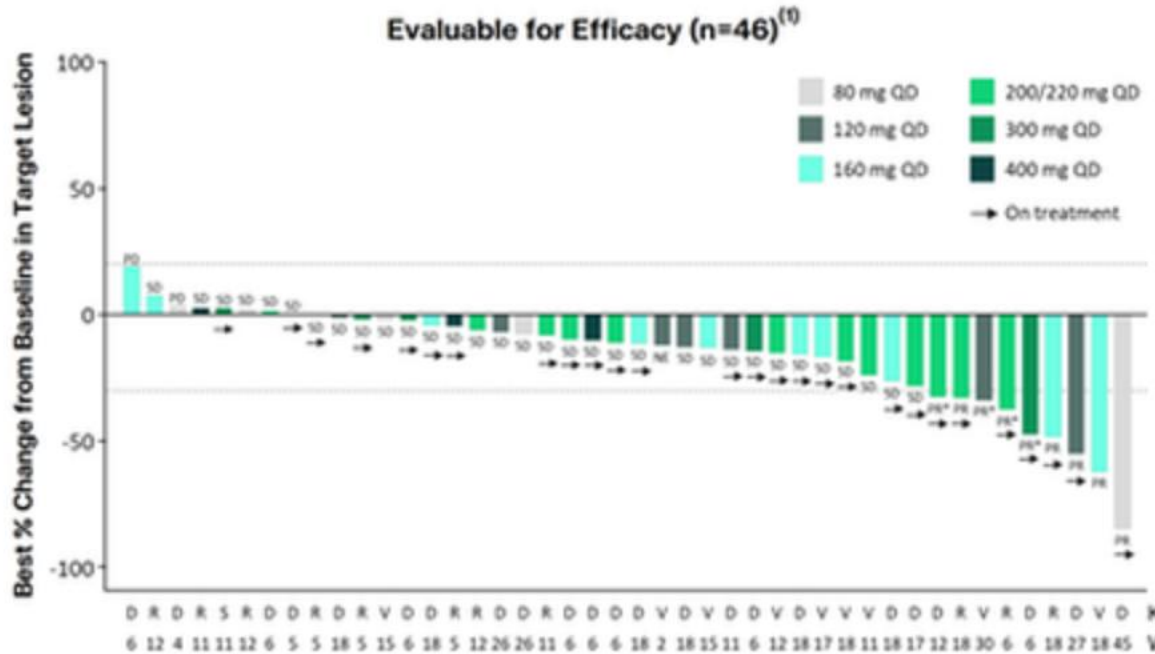
- Birmingham implementing new pathway
- From CT scan, aspiration 90% of patients get oncology appointment in 2 weeks. Concurrent biopsy and oncology to also without biopsy results. Early findings showing more people getting chemotherapy

Novel therapeutics

- In 2026

- Kras inhibitors- pan-ras (90%), G12D (40%)
- PRMT5 inhibitors (30%)
- Claudin 18.2 (20%
- CD73 (phase 3 accrued)
- mRNA vaccine in adjuvant setting, kras specific vaccines in adjuvant setting
- C-MET ADC
- GDF15 agonists for cachexia

KRAS G12X PDAC: Best Overall Response to RMC-6236



RMC-6236-001: Clinical Activity in KRAS G12X PDAC[2]	
Best overall response, n (%)	
Partial response	9 (20)
Stable disease	31 (67)
Progressive disease	3 (7)
Not evaluable[3]	3 (7)
ORR, n (%)	9 (20)
Confirmed, n	5
DCR (CR+PR+SD), n (%)	40 (87)
SOC Benchmarks[4]	
GnP, ORR (%)	(11)
DCR (%)	(56)

(1) Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.
(2) Tumor response per RECIST 1.1.
(3) Two patients died prior to first post-baseline scan; 1 patient had scan after 11 days of treatment and subsequently died due to PD.
(4) SOC=standard of care; no clearly established standard of care in 2L PDAC; GnP=Gemcitabine plus nab-paclitaxel; efficacy benchmarks for GnP taken from Br J Cancer (2022) 126:1394-1400.
*Unconfirmed PR per RECIST 1.1.

Revolution Medicines

Data Extracted 12 Oct 2023.

THANK YOU FOR LISTENING