FUNDACION MARIE CURIE
Córdoba - Argentina

Congreso sobre Avances Integrados en Oncología, Radiocirugía y Física Médica:
Innovación y Precisión en el tratamiento del cáncer

CANCER DE PANCREAS

Manejo sistémico

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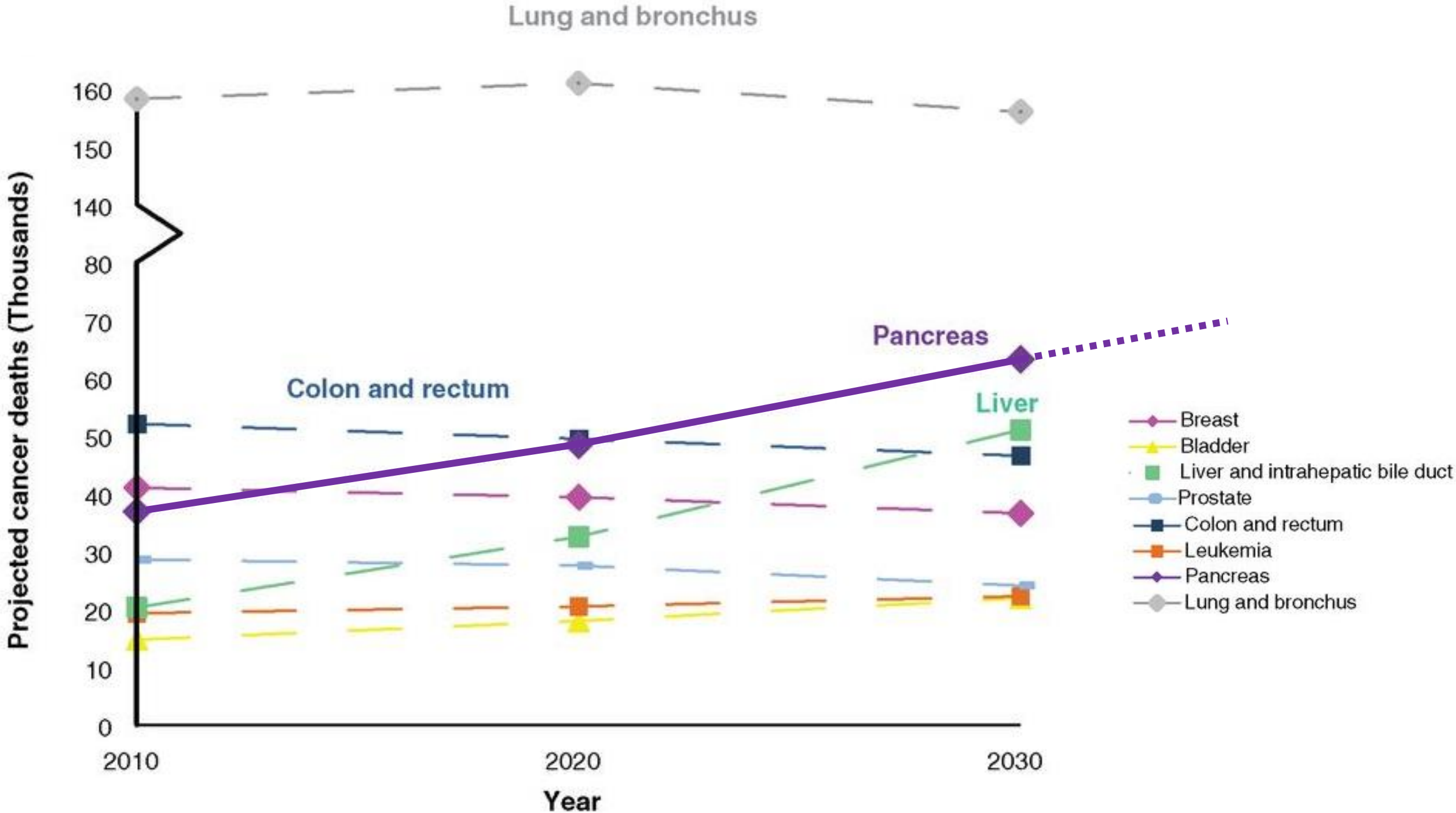
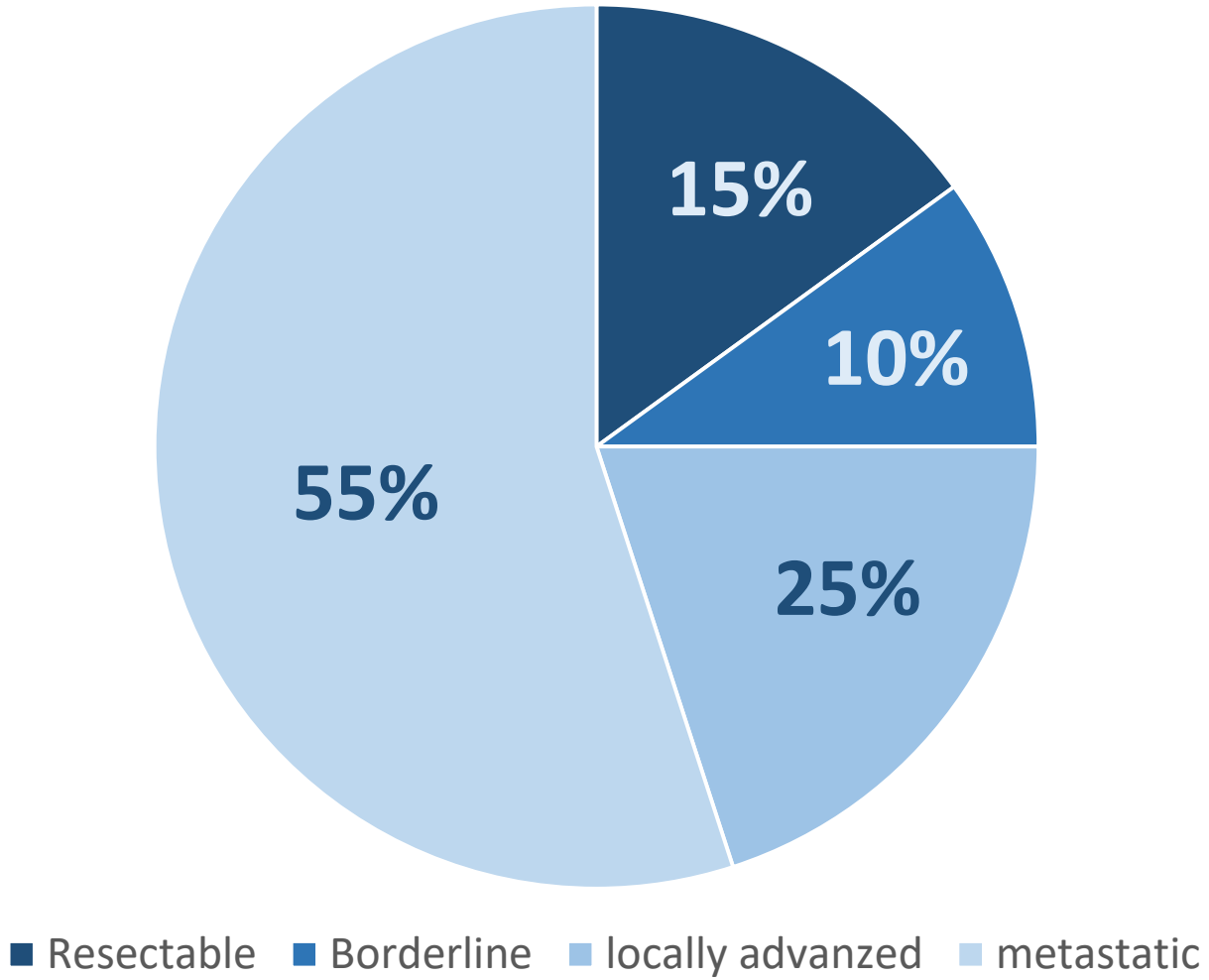
Immuno-oncology & Biotechnologies in Cancer - National Institut of Health and Medical Research in France (INSERM), Unit 1098. Clinical Investigational Center, CIC-1431. University Hospital of Besançon, France.

DISCLOSURES

Academic research funding: Amgen, Bioproject Pharma, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Genentech, Ipsen, Novartis, Pfizer, Roche, Sanofi, Servier, Teva. Advisory: Bayer, BeiGene, Boehringer Ingelheim, Ipsen, Merck Sereno, Merck Sharp and Dohme, Pierre Fabre, Sanofi, Servier, Takeda. Honoraria/Consultancy: Amgen, Astra Zeneca, Bayer, BeiGene, Boehringer Ingelheim, Bioprofarma Bagó, Bristol Myers Squibb, Incyte, Ipsen, Merck Sereno, Merck Sharp and Dohme, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Sanofi, Servier, Takeda, Teva. Travel acommodations: Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Ipsen, Merck Sereno, Merck Sharp and Dohme, Novartis, Pierre Fabre, Pfizer, Roche, Sanofi, Servier, Takeda, Teva.


Lung and bronchus
Pancreas
Colon and rectum
Liver
Projected cancer deaths (Thousands)
160
150
140
80
70
60
50
40
30
20
10
0
2010
2020
2030
Year
Breast
Bladder
Liver and intrahepatic bile duct
Prostate
Colon and rectum
Leukemia
Pancreas
Lung and bronchus

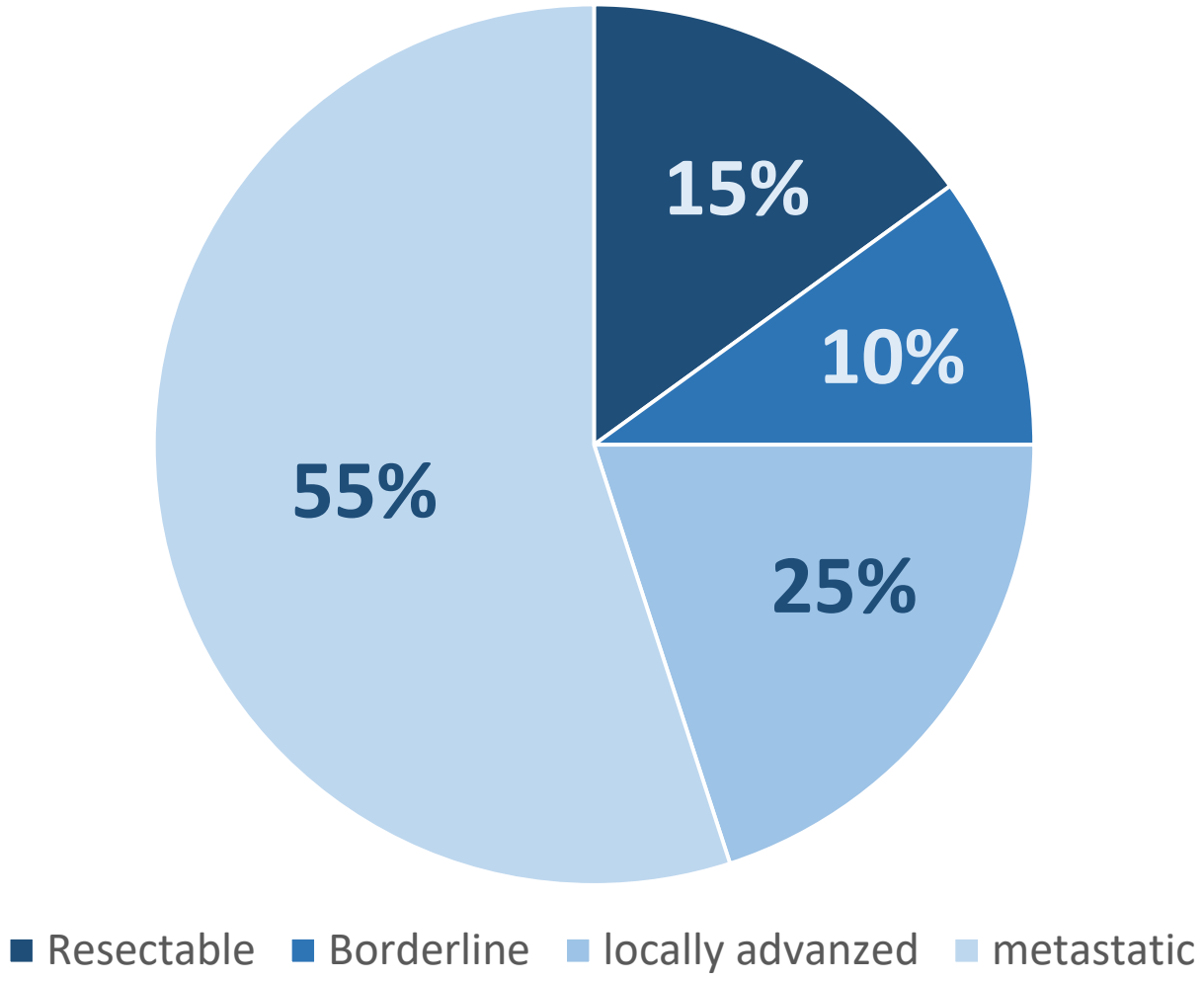
Stage at diagnosis and 5y OS rate



Stage	5y OS rate
IA	39%
IB	34%
IIA	28%
IIB	21%
III	11%
IV	10%

Adapted from SEER

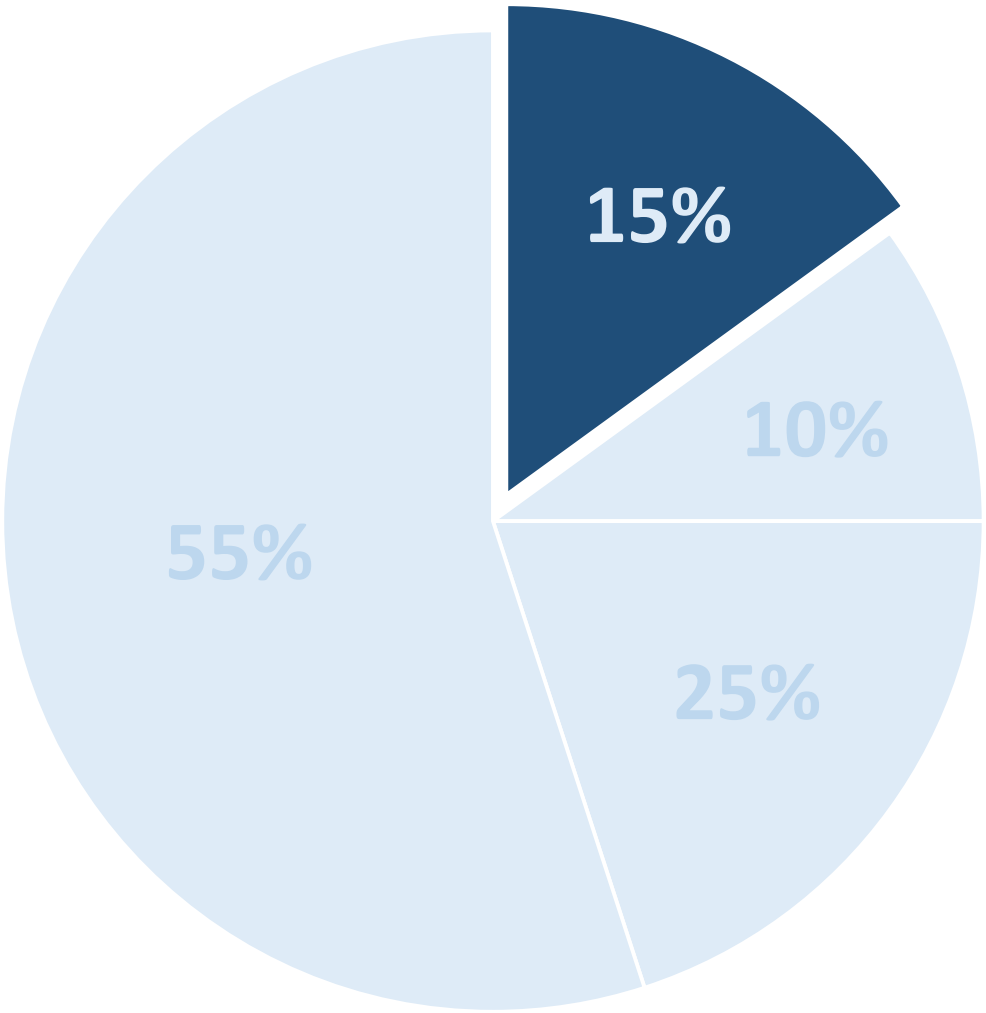
Stage at diagnosis and 5y OS rate

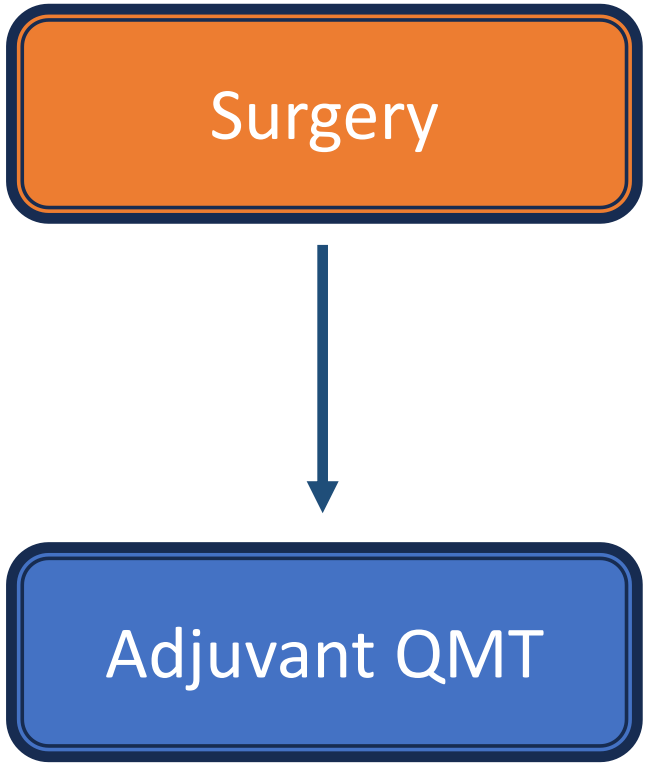


Stage	5y OS rate
IA	39%
IB	34%
IIA	28%
IIB	21%
III	11%
IV	10%

Adapted from SEER

Resectable pancreatic cancer



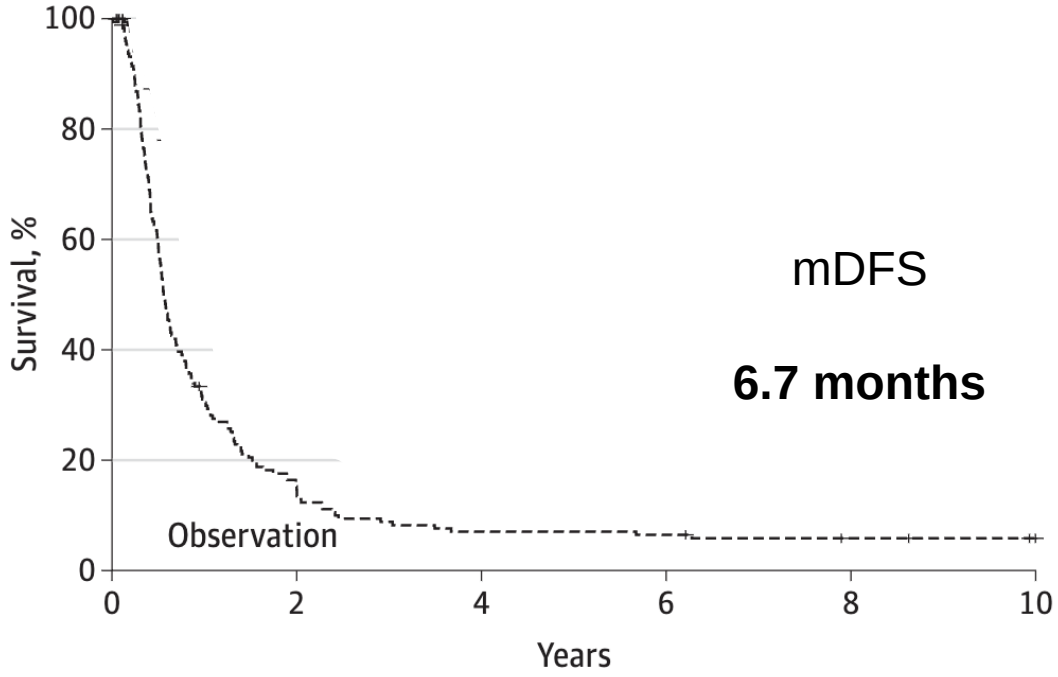


Adapted from ESMO guidelines

Resectable pancreatic cancer

Adjuvant chemotherapy | Gemcitabine vs Observation (CONKO-001), 2007

DFS

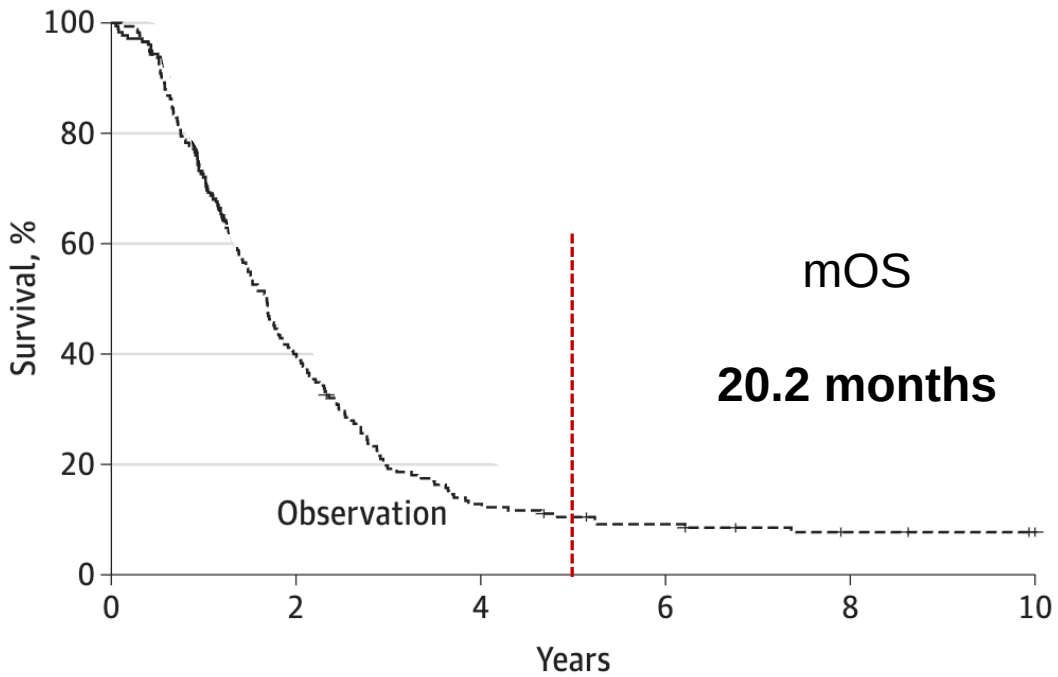


mDFS

6.7 months

No. at risk						
Gemcitabine	179	52	32	26	20	12
Observation	175	26	12	11	8	6

OS



mOS

20.2 months

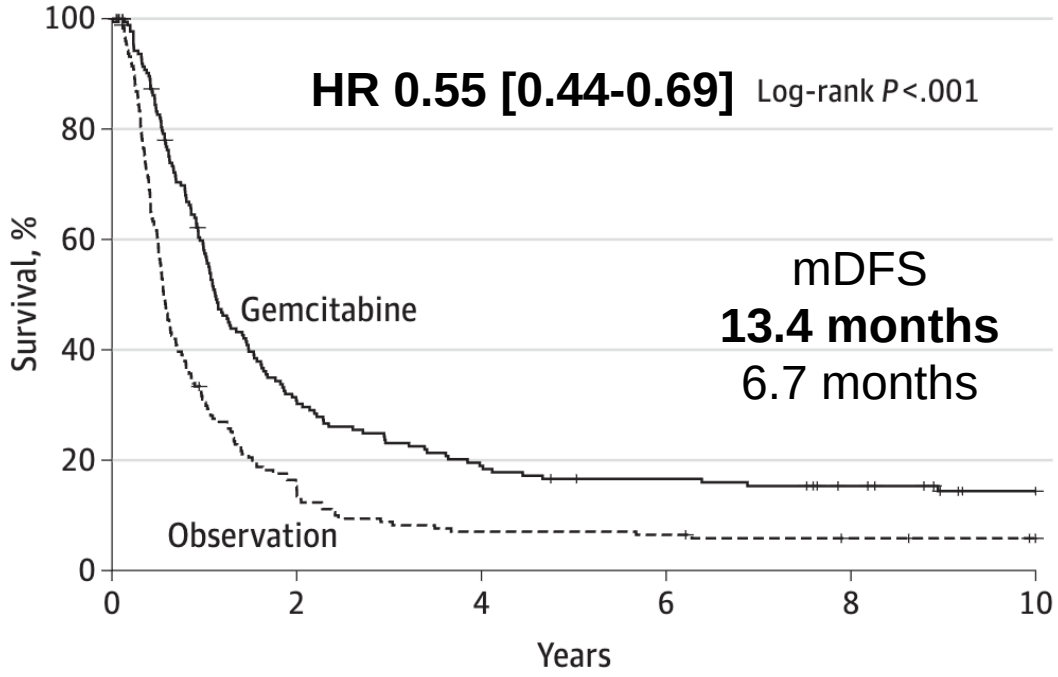
No. at risk						
Gemcitabine	179	87	47	31	24	14
Observation	175	70	22	14	9	7

CONKO-001, JAMA. 2013;310(14):1473-1481

Resectable pancreatic cancer

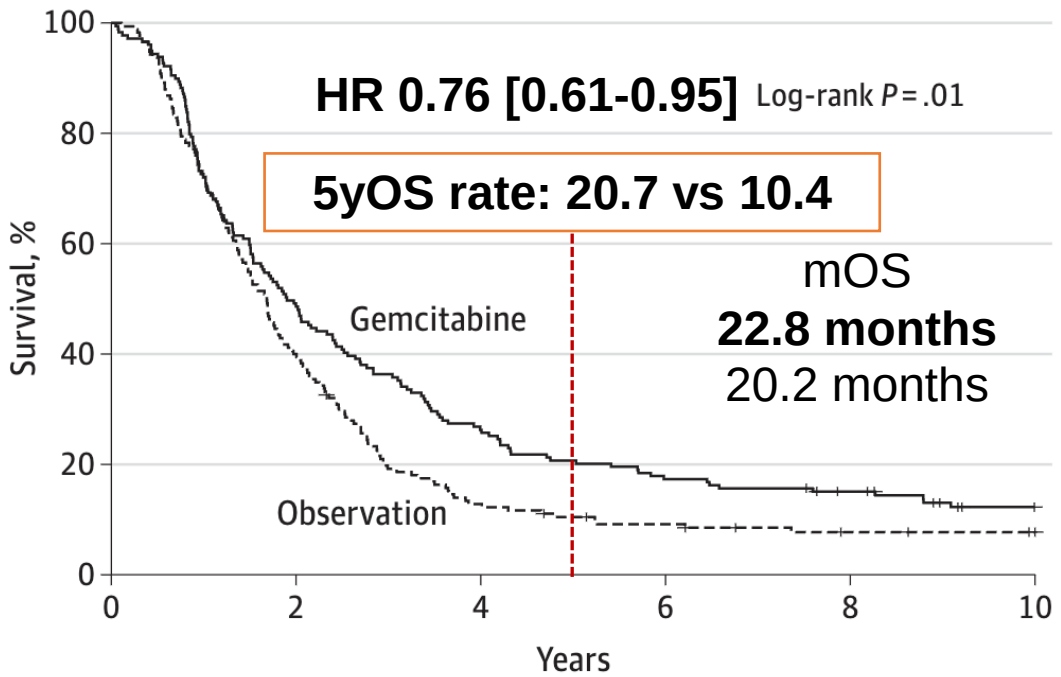
Adjuvant chemotherapy | Gemcitabine vs Observation (CONKO-001), 2007

DFS



No. at risk						
Gemcitabine	179	52	32	26	20	12
Observation	175	26	12	11	8	6

OS



No. at risk						
Gemcitabine	179	87	47	31	24	14
Observation	175	70	22	14	9	7

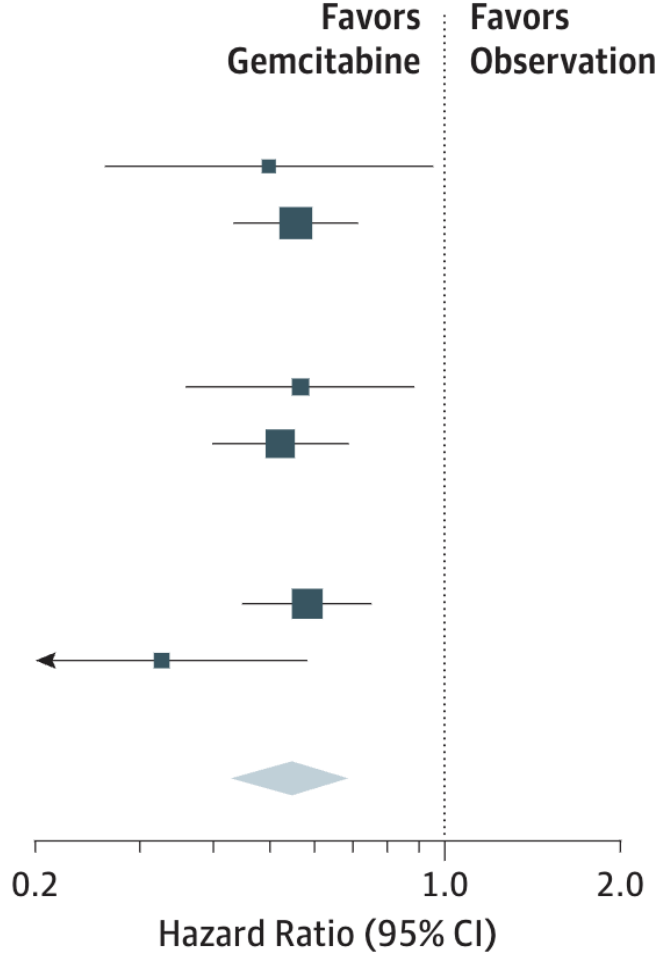
CONKO-001, JAMA. 2013;310(14):1473-1481

Resectable pancreatic cancer

Adjuvant chemotherapy | Gemcitabine vs Observation (CONKO-001), 2007

Disease-free survival

Subcategory	Gemcitabine Events, No.	Gemcitabine Total Patients, No.	Observation Events, No.	Observation Total Patients, No.	Hazard Ratio (95% CI)
Primary tumor stage					
T1-2	18	25	20	24	0.50 (0.26-0.95)
T3-4	127	154	143	151	0.56 (0.44-0.71)
Test for heterogeneity: $\chi^2_1 = 0.10$; $P = .76$; $I^2 = 0\%$					
Nodal status					
N0	37	52	42	48	0.57 (0.36-0.89)
N1	108	127	121	127	0.53 (0.40-0.68)
Test for heterogeneity: $\chi^2_1 = .09$; $P = .77$; $I^2 = 0\%$					
Resection status					
R0	117	145	137	148	0.59 (0.46-0.76)
R1	28	34	26	27	0.33 (0.19-0.58)
Test for heterogeneity: $\chi^2_1 = 3.46$; $P = .06$; $I^2 = 71\%$					
Total (95% CI)	145	179	163	175	0.55 (0.44-0.69)
Test for overall effect: $z = 5.17$; $P < .001$					

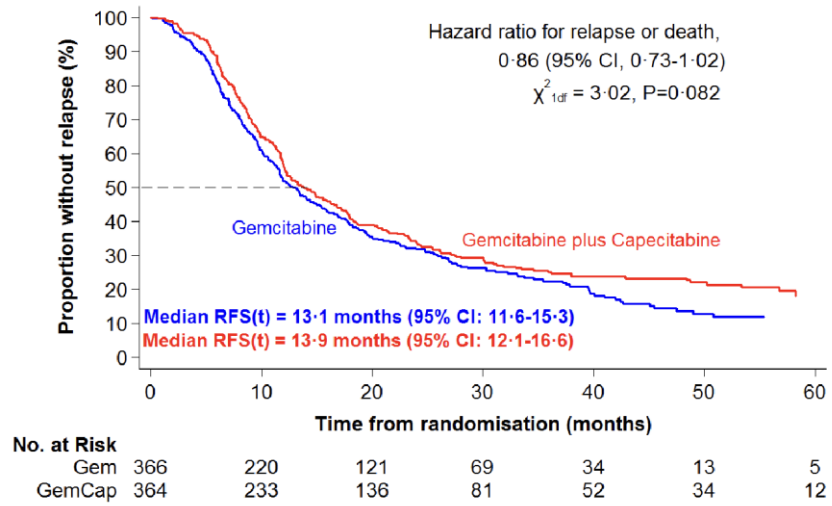


CONKO-001

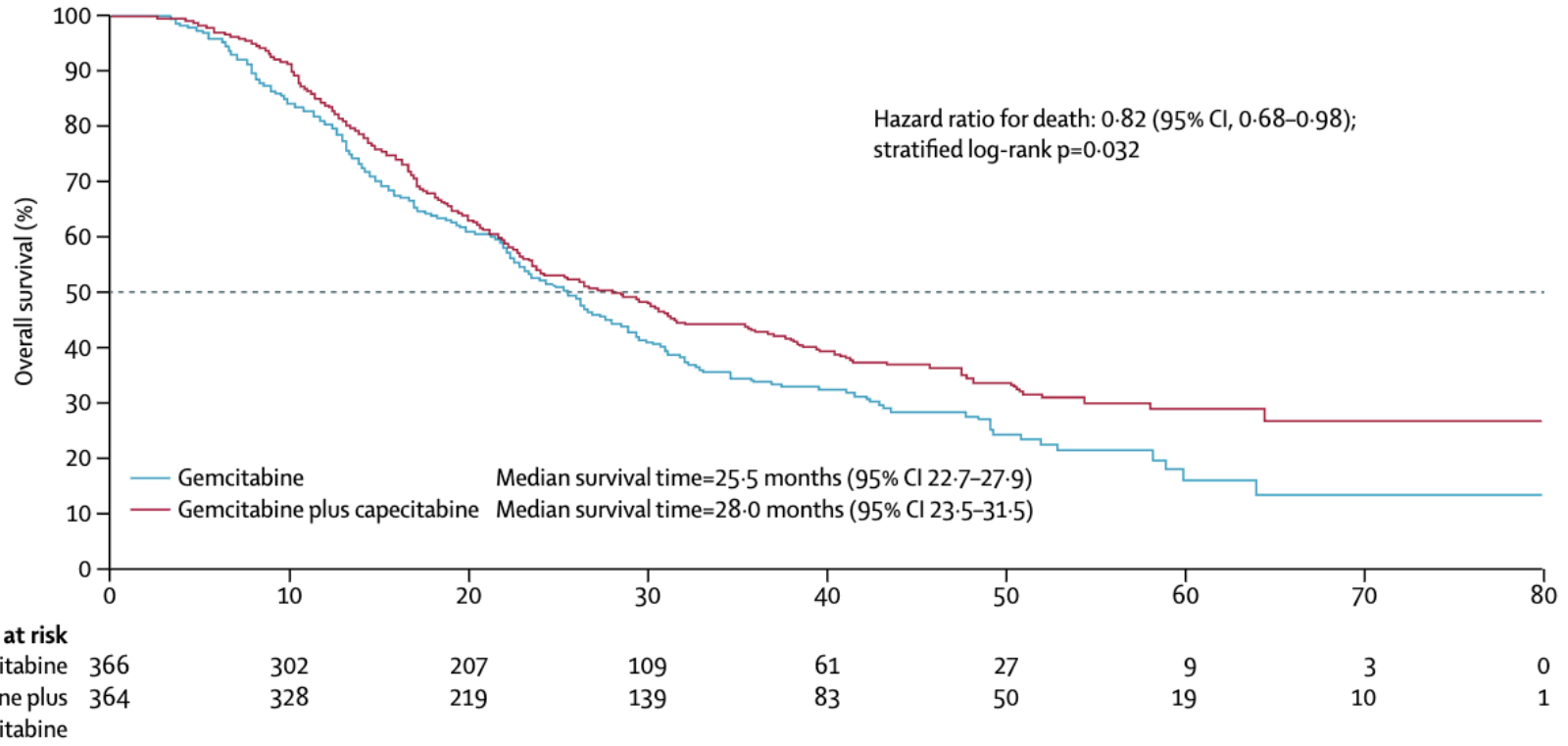
Resectable pancreatic cancer

Adjuvant chemotherapy | Gemcitabine + Capecitabine vs Gemcitabine (ESPAC-4), 2017

RFS



OS

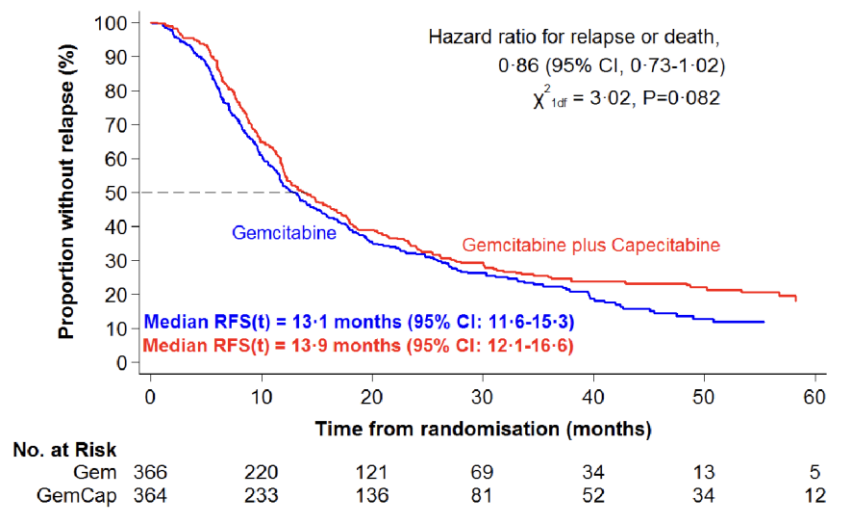


ESPAC-4, Lancet 2017; 389: 1011–24

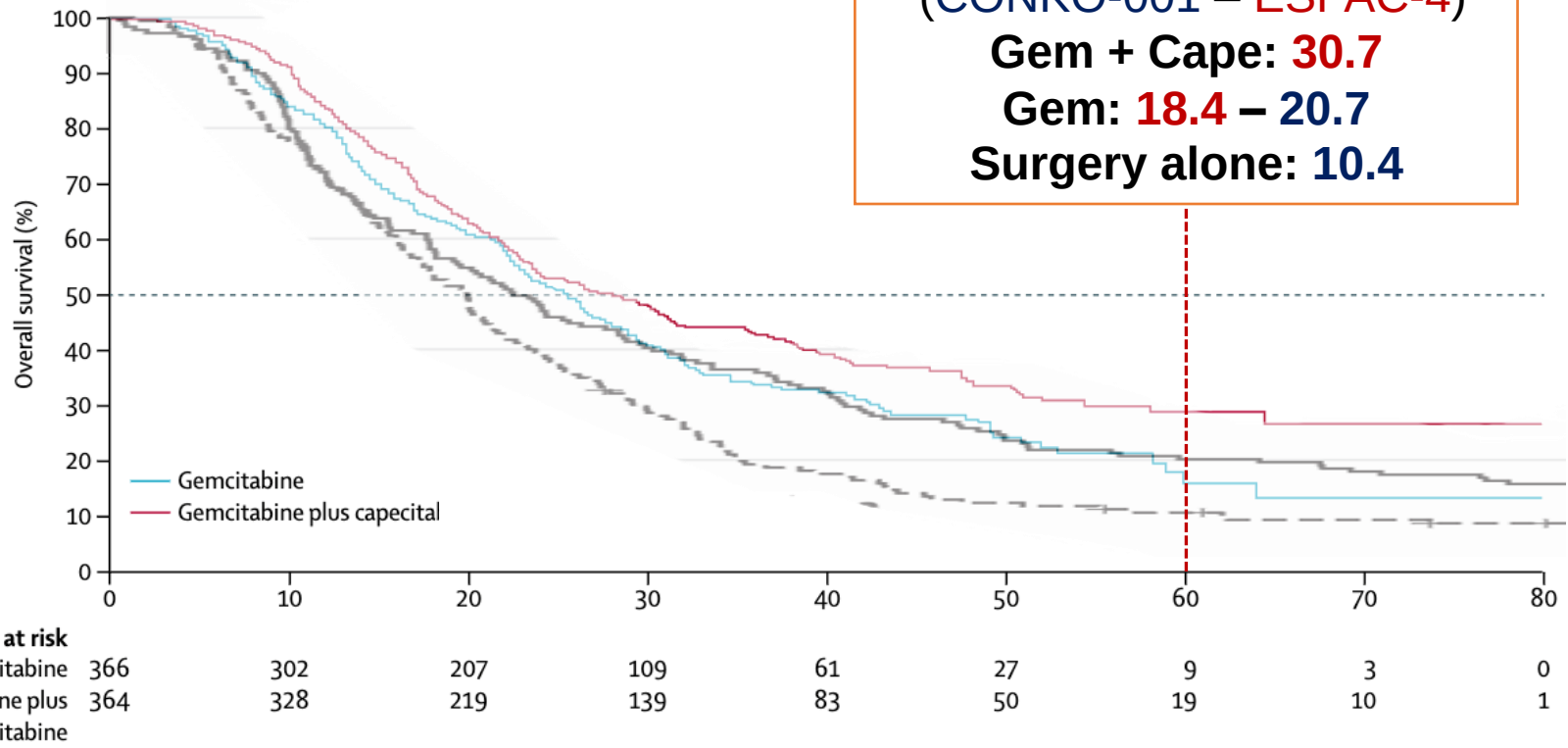
Resectable pancreatic cancer

Adjuvant chemotherapy | Gemcitabine + Capecitabine vs Gemcitabine (ESPAC-4), 2017

RFS



5yOS rate
(CONKO-001 – ESPAC-4)
Gem + Cape: 30.7
Gem: 18.4 – 20.7
Surgery alone: 10.4

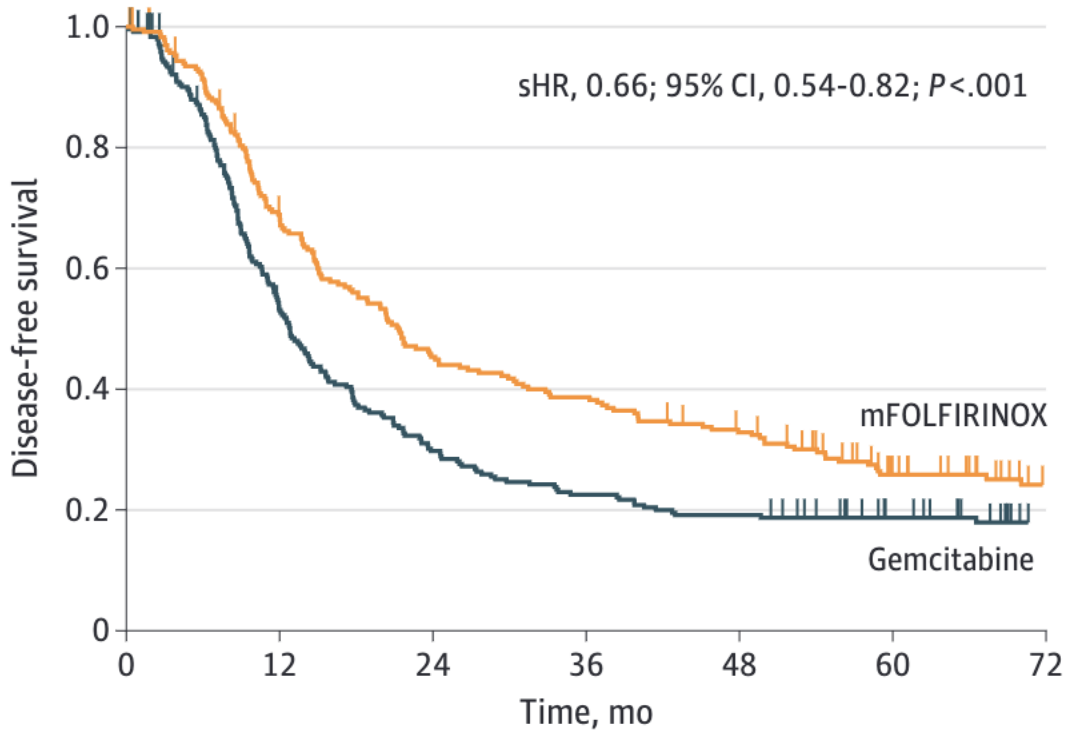


ESPAC-4, Lancet 2017; 389: 1011–24

Resectable pancreatic cancer

Adjuvant chemotherapy | mFOLFIRINOX vs Gemcitabine (PRODIGE-24), 2018

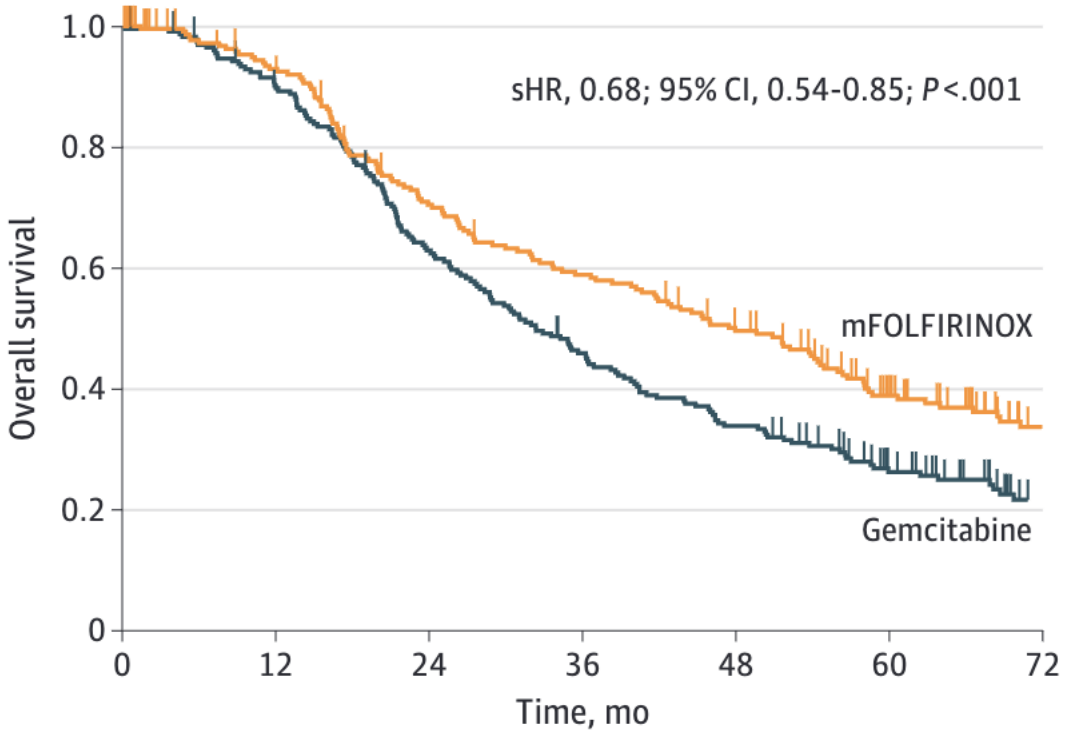
DFS



No. at risk

mFOLFIRINOX	247	156	103	88	72	43	26
Gemcitabine	246	126	71	54	46	31	16

OS



No. at risk

mFOLFIRINOX	247	211	162	137	114	75	45
Gemcitabine	246	215	154	115	89	56	30

PRODIGE24, N Engl J Med 2018;379:2395-406. JAMA Oncol. 2022;8(11):1571-1578

Resectable pancreatic cancer

Adjuvant chemotherapy | mFOLFIRINOX vs Gemcitabine (PRODIGE-24), 2018

5yOS rate

(CONKO-001,ESPAC-4, PRODIGE-24)

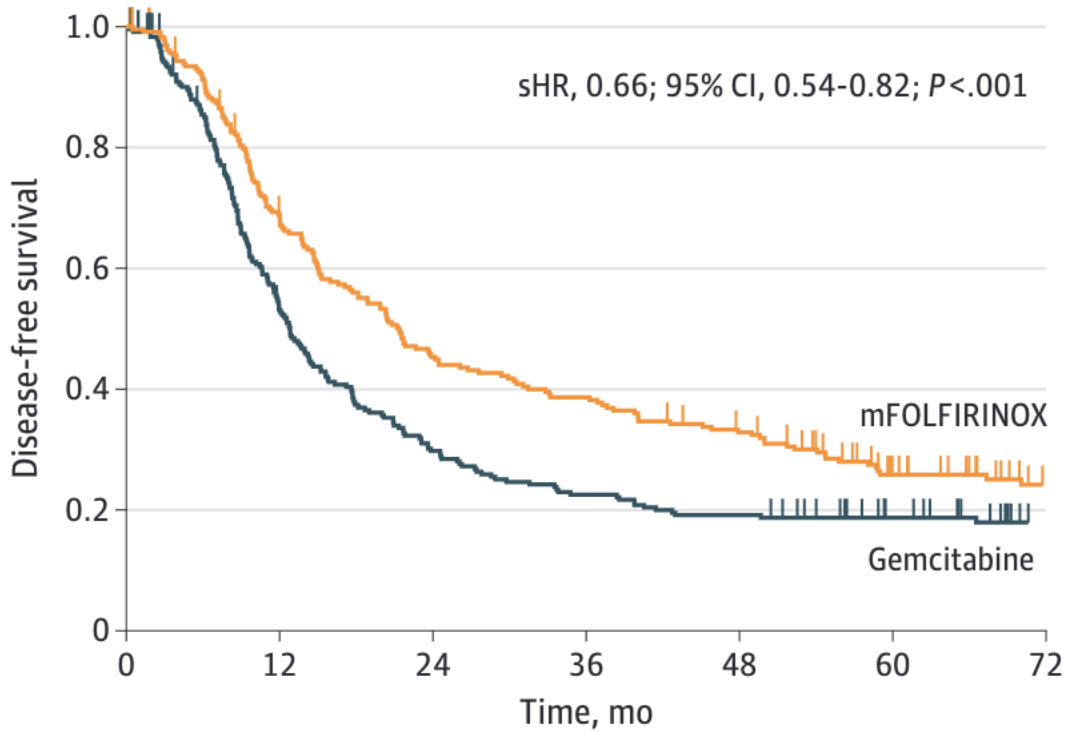
mFOLFIRINOX: 43.2%

Gem + Cape: 30.7

Gem: 18.4 - 20.7 - 31.4

Surgery alone: 10.4

DFS



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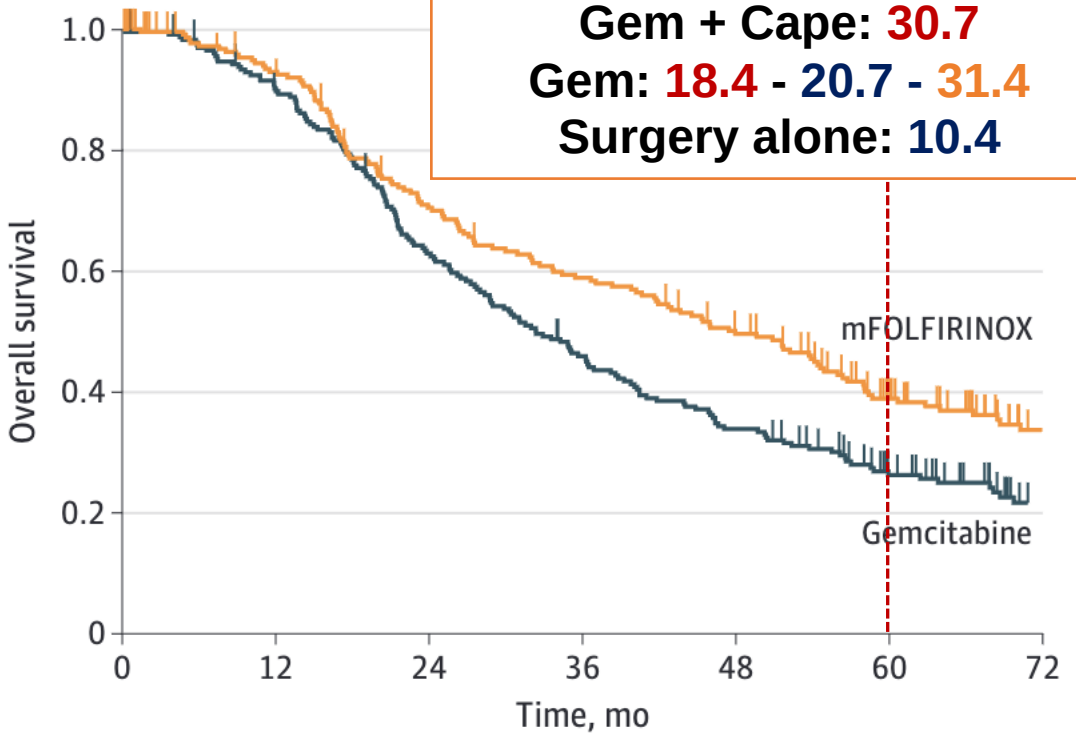

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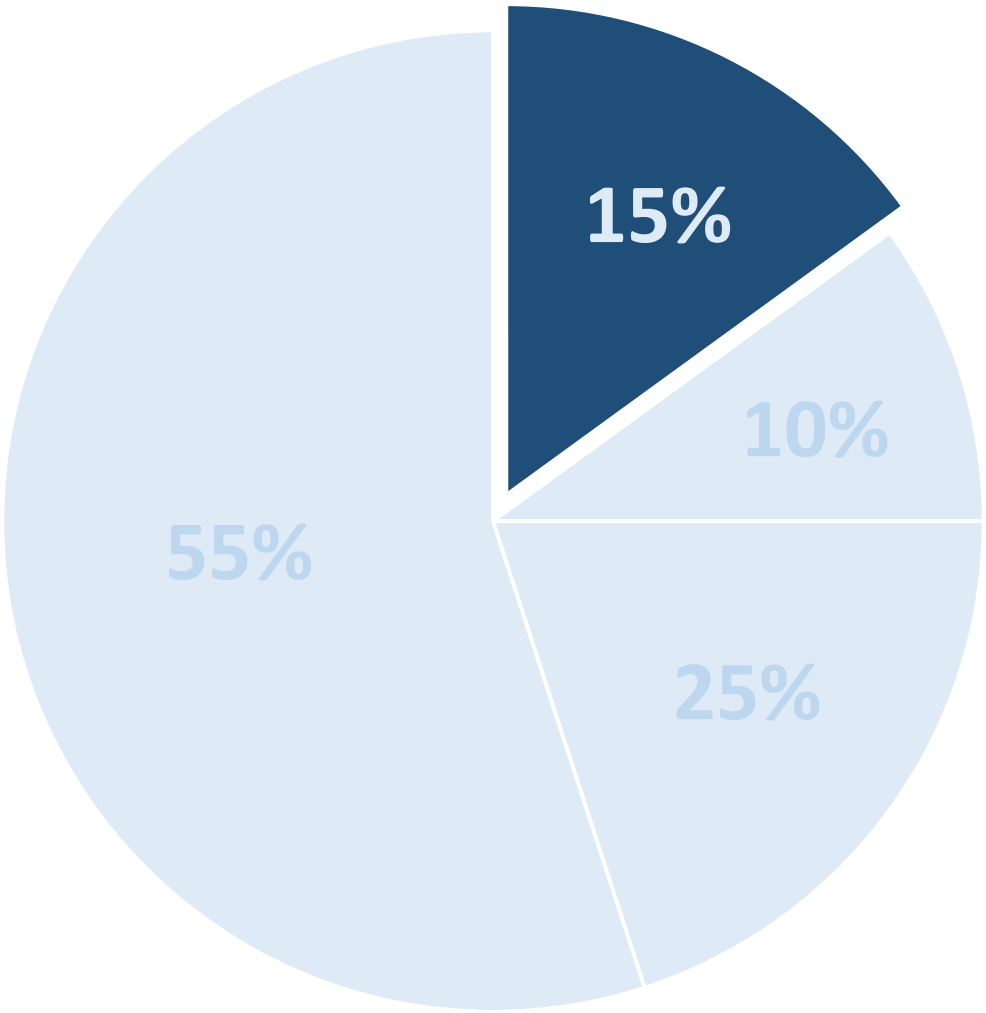
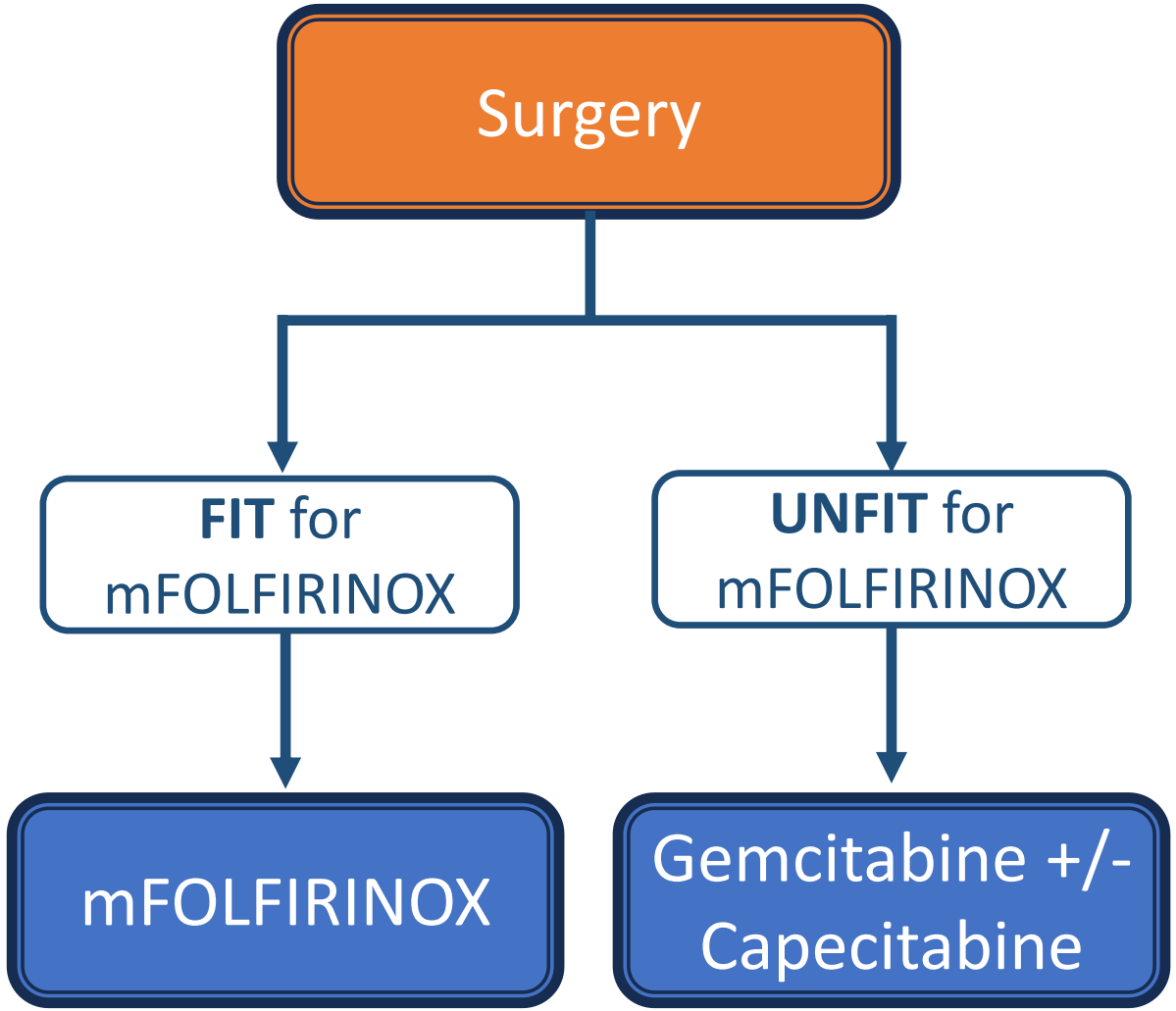
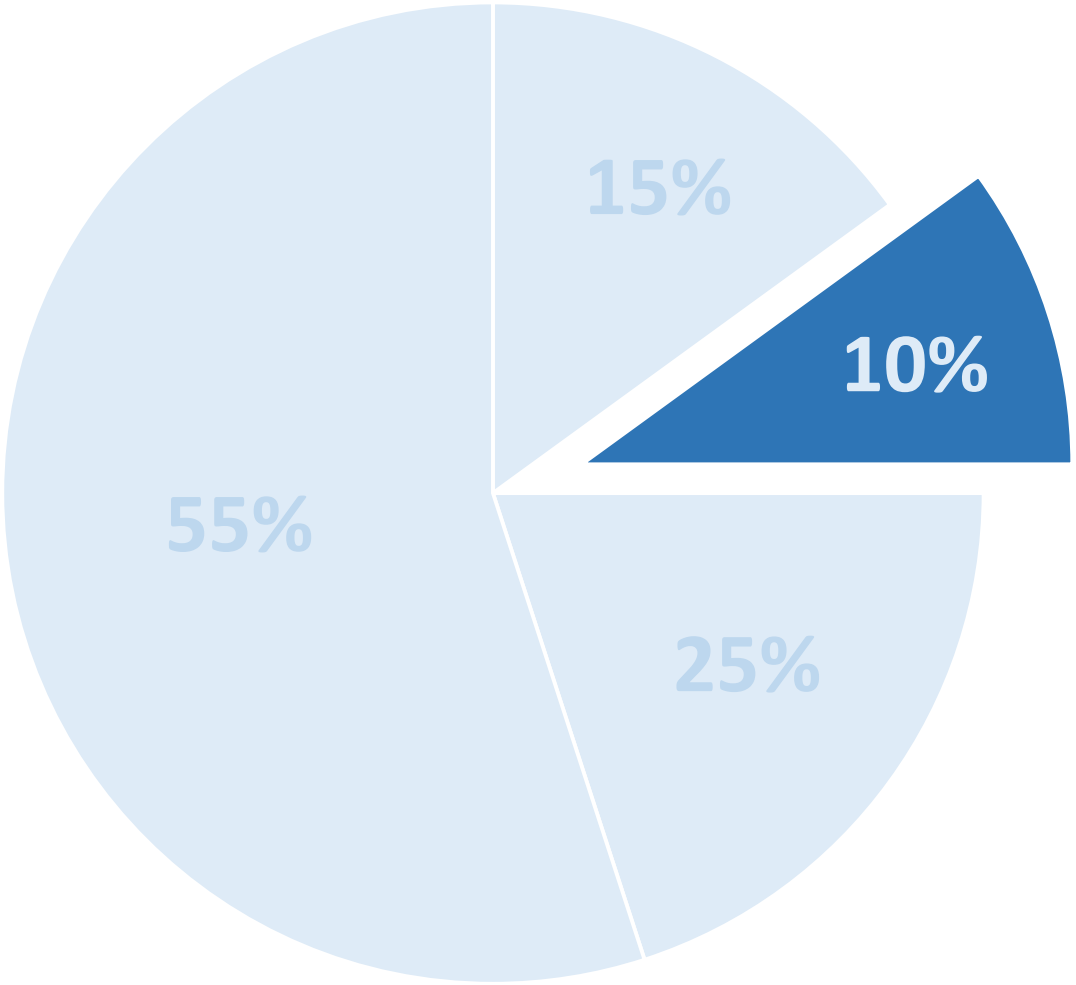
Resectable pancreatic cancer

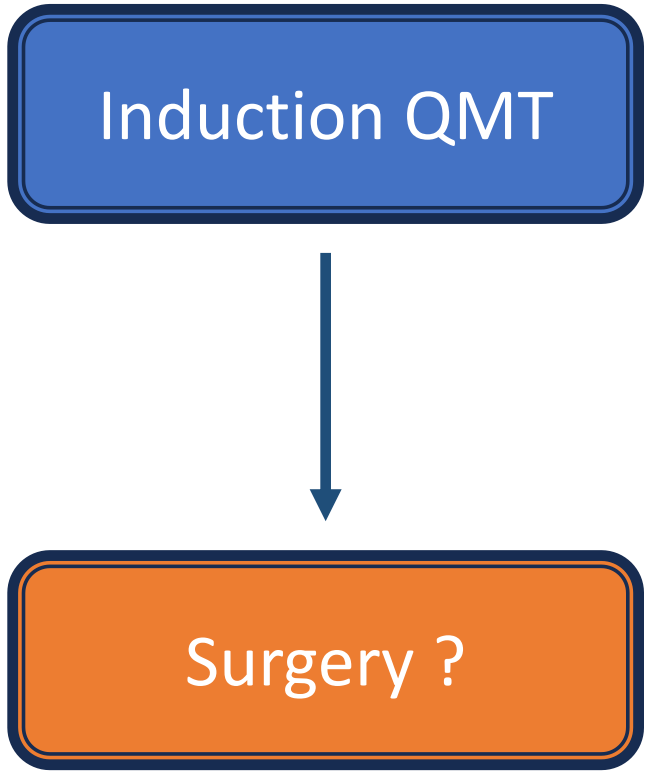




Adapted from ESMO guidelines

Borderline resectable pancreatic cancer





Adapted from ESMO guidelines

Borderline resectable pancreatic cancer

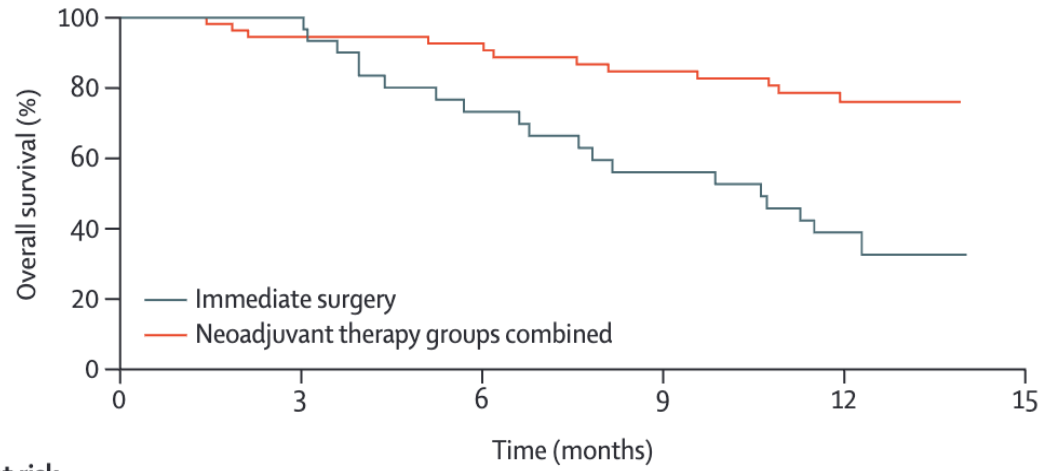
Induction chemotherapy		Chemotherapy and/or Chemoradiotherapy > Surgery and adj CT		
Jang et al. (2018)[61] NA CRT->Cx vs Cx->Adj CRT	Republic of Korea; BRPC[b,c]	Neoadjuvant GEM (6 weeks)+EBRT (45 Gy in 25 fractions or 9 Gy in 5 fractions) followed by surgery and adjuvant GEM (4c)+EBRT (arm A) vs upfront surgery followed by adjuvant GEM (4c)+EBRT (arm B)	Arm A: *n*=17/27 (63%) R0: *n*=14/17 (82%) Arm B: *n*=18/23 (78%) R0: *n*=6/18 (33%) (*P*=0.010)	mOS: Arm A: 21 months Arm B: 12 months 2-year OS: HR 1.97 (95% CI 1.07–3.62)
Versteijne et al. (2020)[62] and Versteijne et al. (2022)[63] (PREOPANC) NA CRT->Cx vs Cx->Adj CT	The Netherlands; PRPC and BRPC[b,d,e]	Neoadjuvant GEM (3c)+EBRT (36 Gy in 15 fractions) followed by surgery and adjuvant GEM (4c) (arm A) vs upfront surgery followed by adjuvant GEM (6c) (arm B)	Arm A: *n*=28/54 (52%) R0: *n*=22/28 (79%) Arm B: *n*=38/59 (64%) (*P*=0.190) R0: *n*=5/38 (13%) (*P*< 0.001)	mOS: Arm A: 18 months Arm B: 13 months HR 0.67 (95% CI 0.45–0.99) 5-year OS: Arm A: *n*=6/54 (4%) Arm B: *n*=1/59 (2%)
Ghaneh et al. (2023)[64] (ESPAC5) NA CT/CRT->Cx vs Cx->Adj CT	UK; BRPC[b,e]	Upfront surgery with adjuvant chemotherapy (arm A) vs neoadjuvant GEM-CAP (2c) (arm B) vs neoadjuvant FFX (4c) (arm C) vs neoadjuvant CAP+EBRT (50.4 Gy in 28 fractions for 5.5 weeks) (arm D); arms B, C and D followed by surgery and adjuvant chemotherapy	Arm A: *n*=21/31 (68%) R0: *n*=3/21 (14%) Arm B: *n*=11/19 (58%) R0: *n*=2/11 (18%) Arm C: *n*=11/20 (55%) R0: *n*=2/11 (18%) Arm D: *n*=8/16 (50%) R0: *n*=3/8 (37%)	1-year OS: Arm A: 39% (95% CI 24–61) Arm B: 78% (95% CI 60–100) Arm C: 84% (95% CI 70–100) Arm D: 60% (95% CI 37–97) (*P*=0.0028)

JY Jang. Ann. Surg 2018; E Versteijne J. Clin. Oncol 2020; P Ghaneh Lancet Gastroenterol. Hepatol 2023

Borderline resectable pancreatic cancer

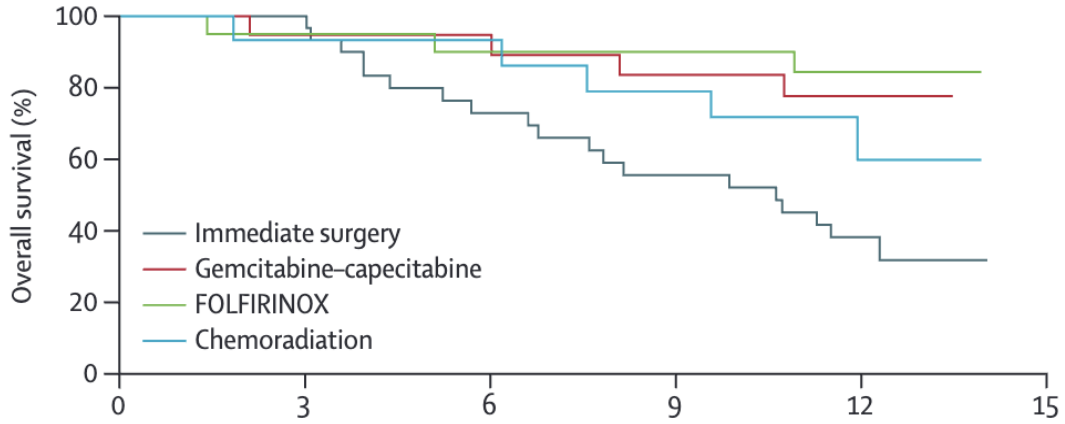
Induction chemotherapy | Chemotherapy vs Chemoradiotherapy vs Surgery (ESPAC-5)

NAT vs Surgery



Numbers at risk (number censored)						
Neoadjuvant therapy groups combined	55 (1)	51 (3)	47 (1)	42 (15)	23 (23)	0
Immediate surgery	31 (1)	30 (1)	21 (0)	16 (4)	7 (6)	0

FOLFIRINOX vs Gem-Cape vs CRT vs Surgery



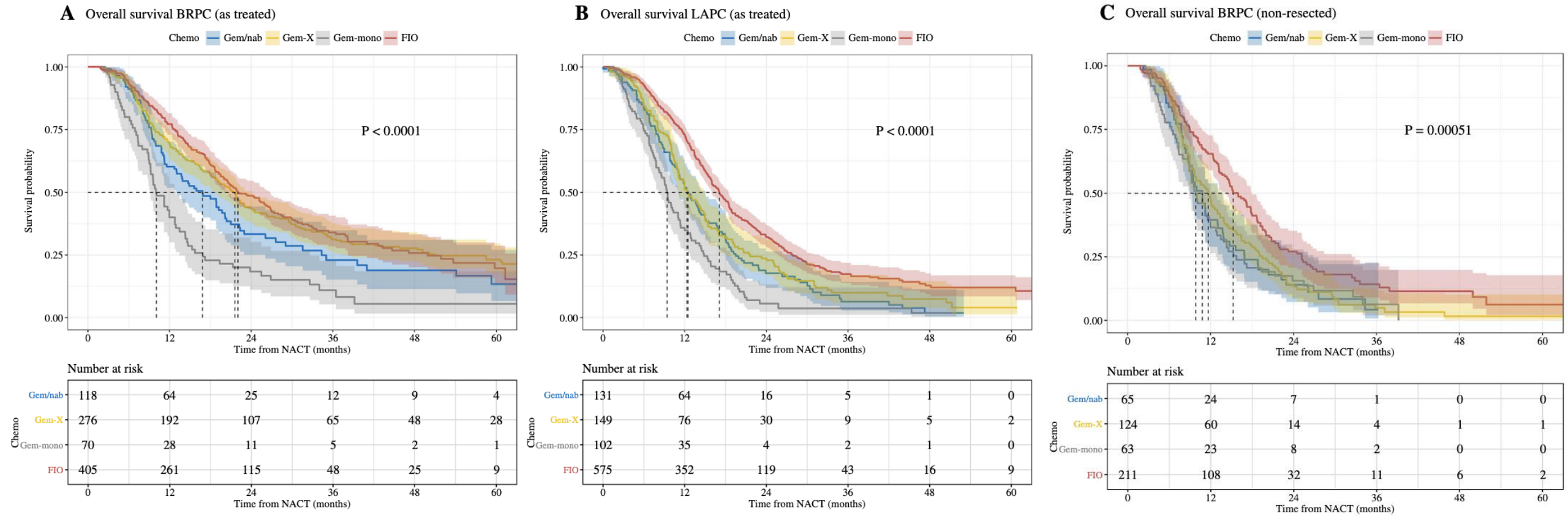
Numbers at risk (number censored)						
Surgery	31 (1)	30 (1)	21 (0)	16 (4)	7 (6)	0
Gemcitabine–capecitabine	19 (0)	18 (1)	17 (0)	15 (9)	5 (5)	0
FOLFIRINOX	20 (0)	19 (1)	17 (1)	16 (2)	13 (13)	0
Chemoradiation	16 (1)	14 (1)	13 (0)	11 (4)	5 (5)	0

ESPAC-5, Lancet Gastroenterol. Hepatol 2023

Borderline resectable pancreatic cancer

Induction chemotherapy | FOLFIRINOX vs Gemcitabine-based CT

FOLFIRINOX or Gemcitabine-based Chemotherapy for Borderline Resectable and Locally Advanced Pancreatic Cancer: A Multi-institutional, Patient-Level, Meta-analysis and Systematic Review



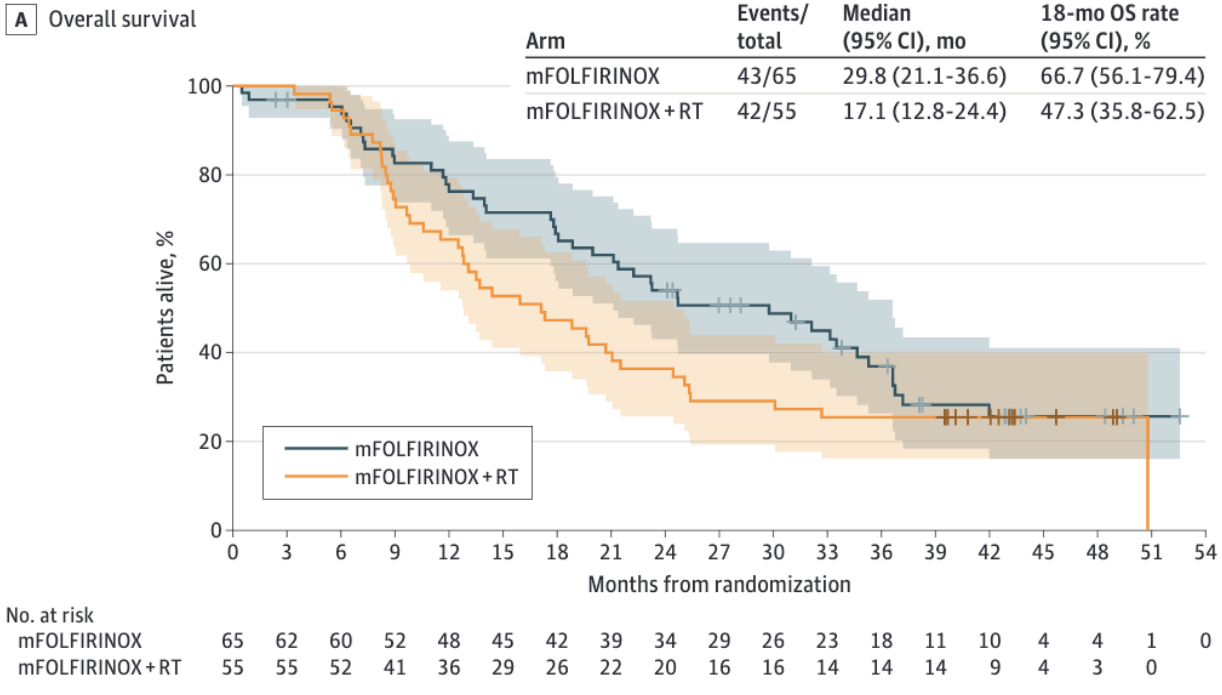
Ann Surg Oncol (2023) 30:4417–4428

Borderline resectable pancreatic cancer

Induction chemotherapy | FOLFIRINOX > FOLFIRINOX + RT

Efficacy of Preoperative mFOLFIRINOX vs mFOLFIRINOX Plus Hypofractionated Radiotherapy for Borderline Resectable Adenocarcinoma of the Pancreas
The A021501 Phase 2 Randomized Clinical Trial

OS



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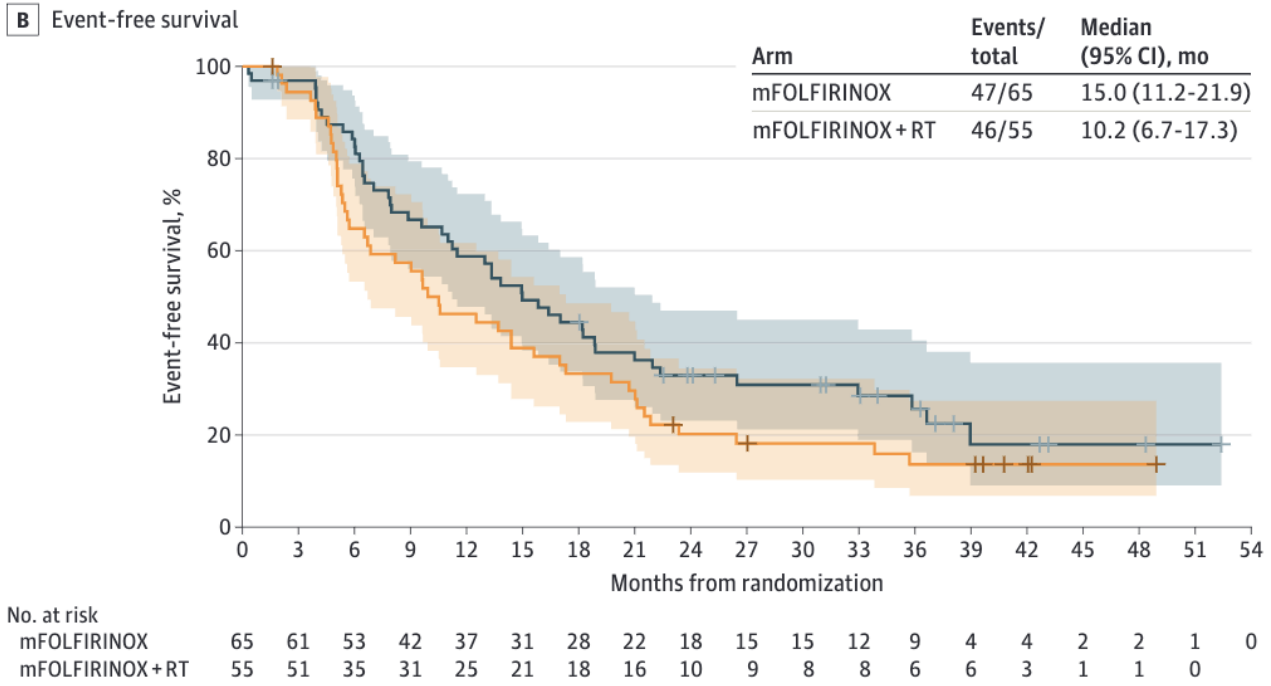
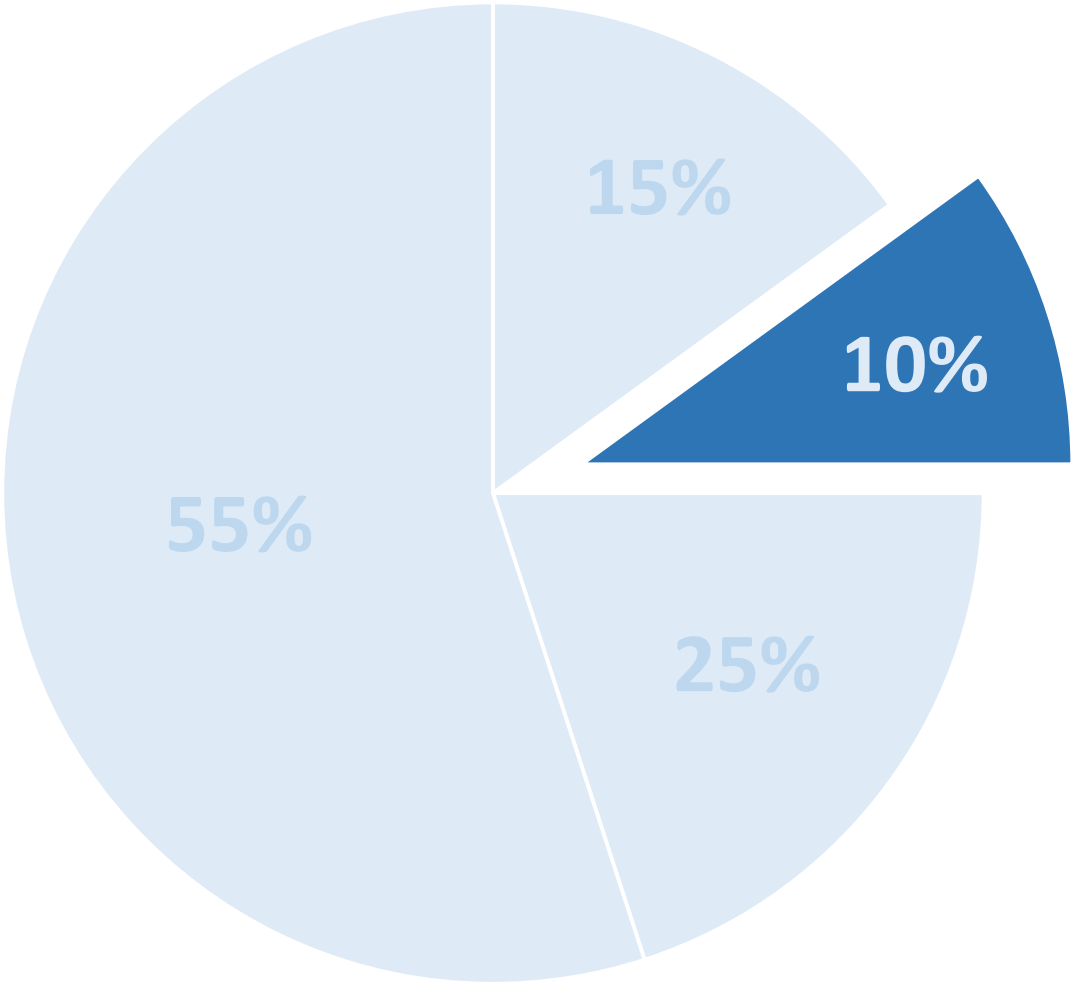
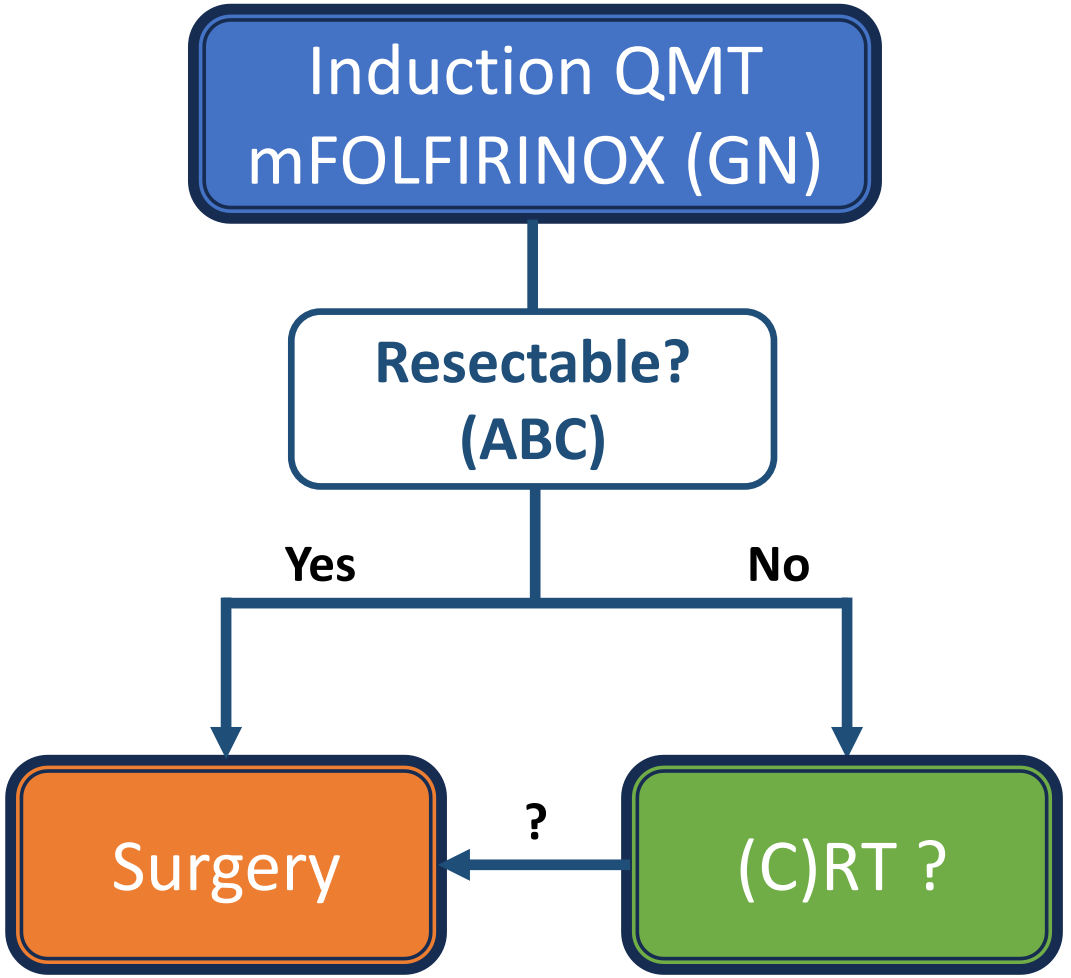


JAMA Oncol. 2022;8(9):1263-1270

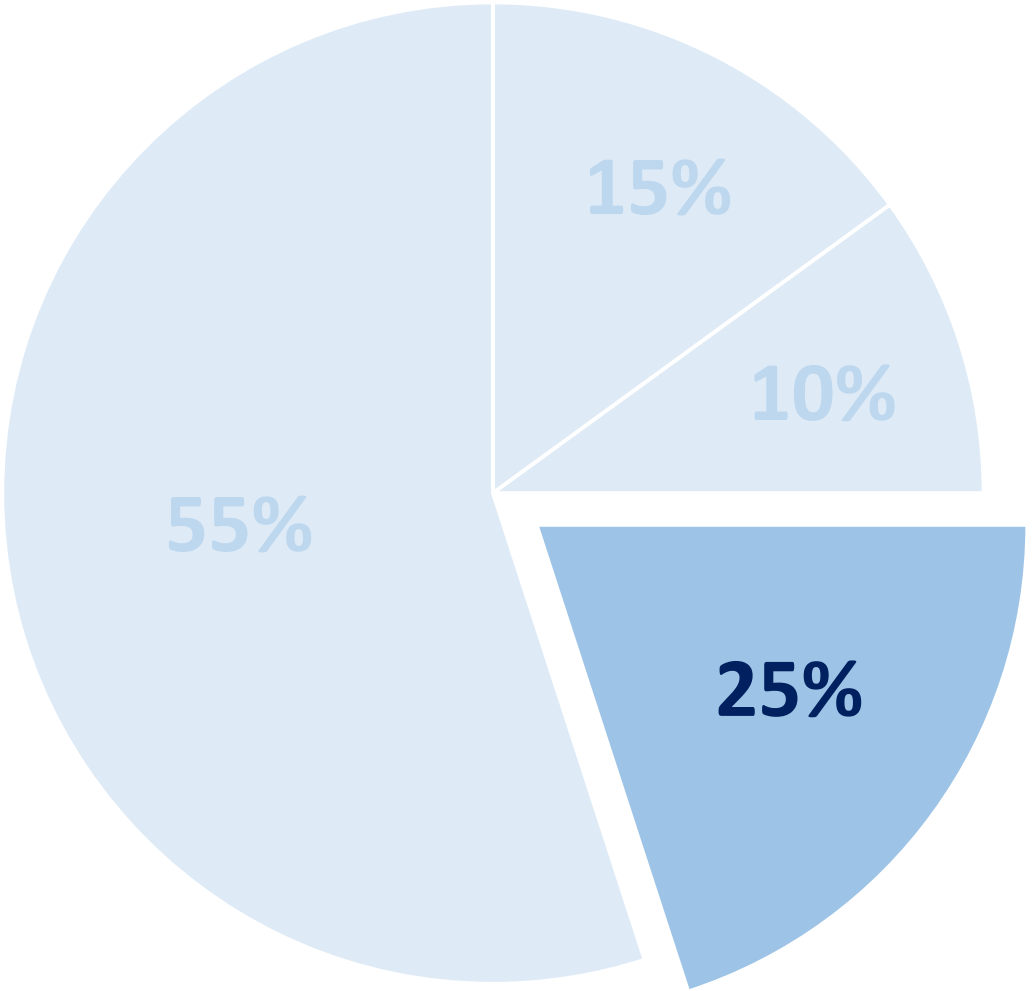
Borderline resectable pancreatic cancer

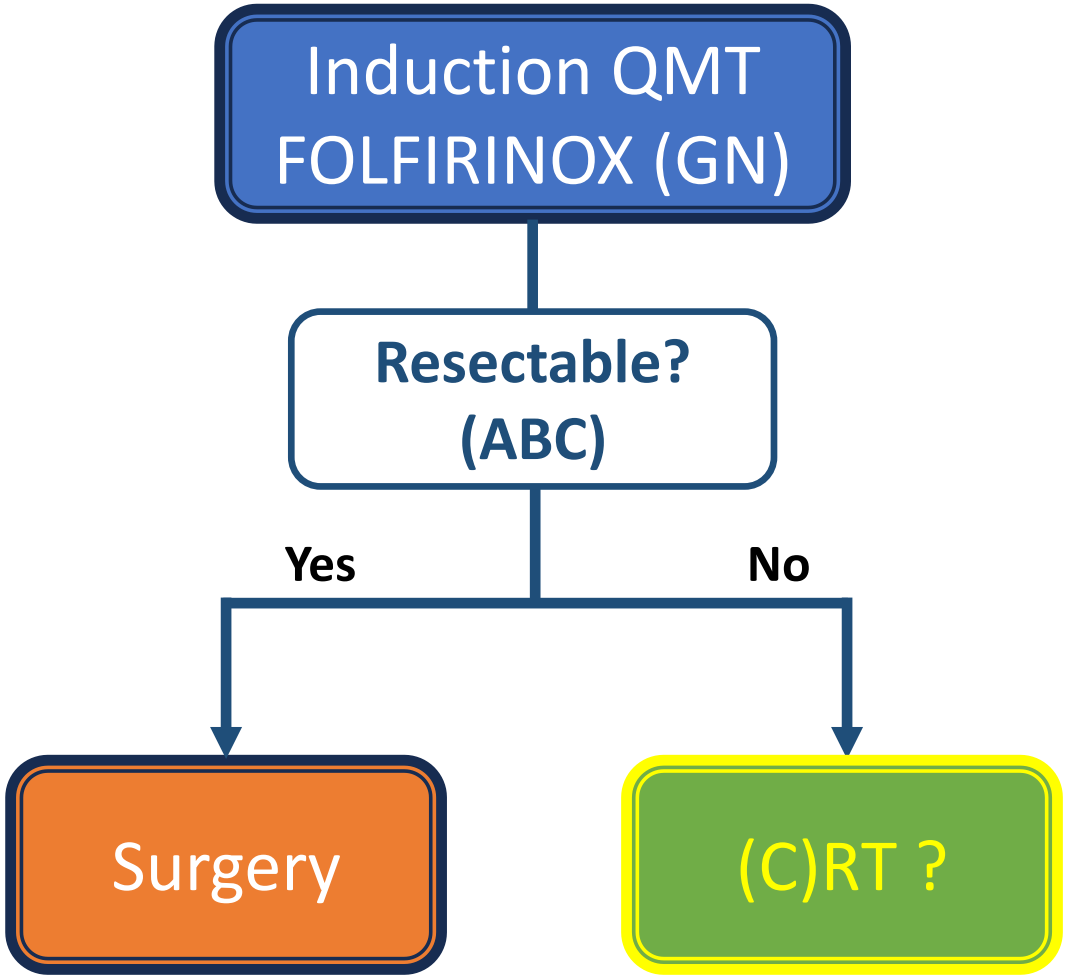




Adapted from ESMO guidelines

Locally advanced pancreatic cancer





Adapted from ESMO guidelines

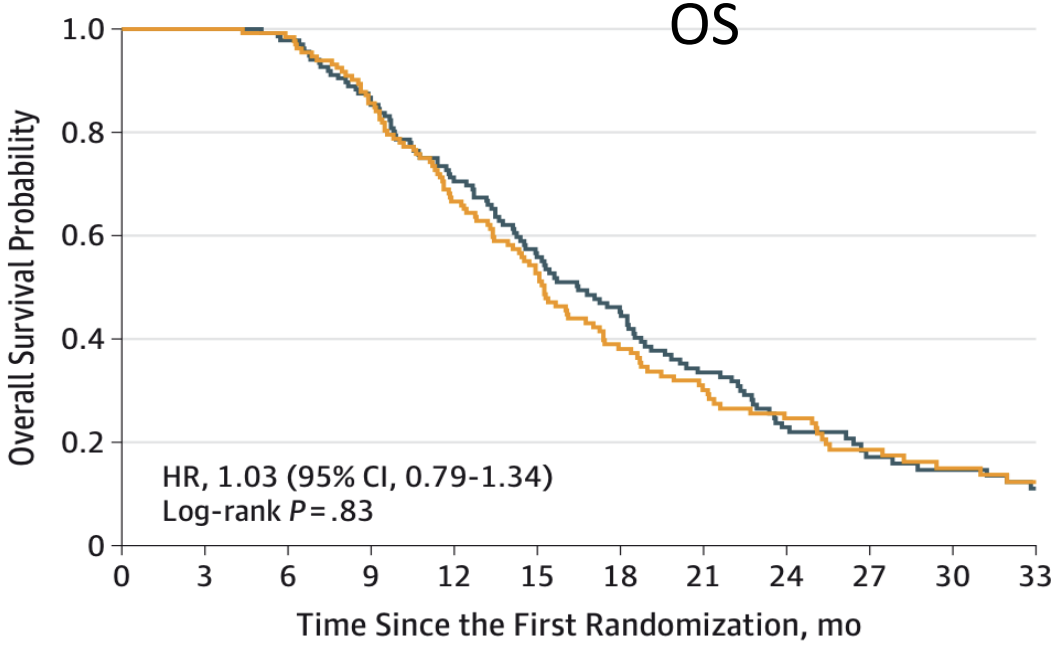
Locally advanced pancreatic cancer

Radiotherapy | consolidation radiotherapy

Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib

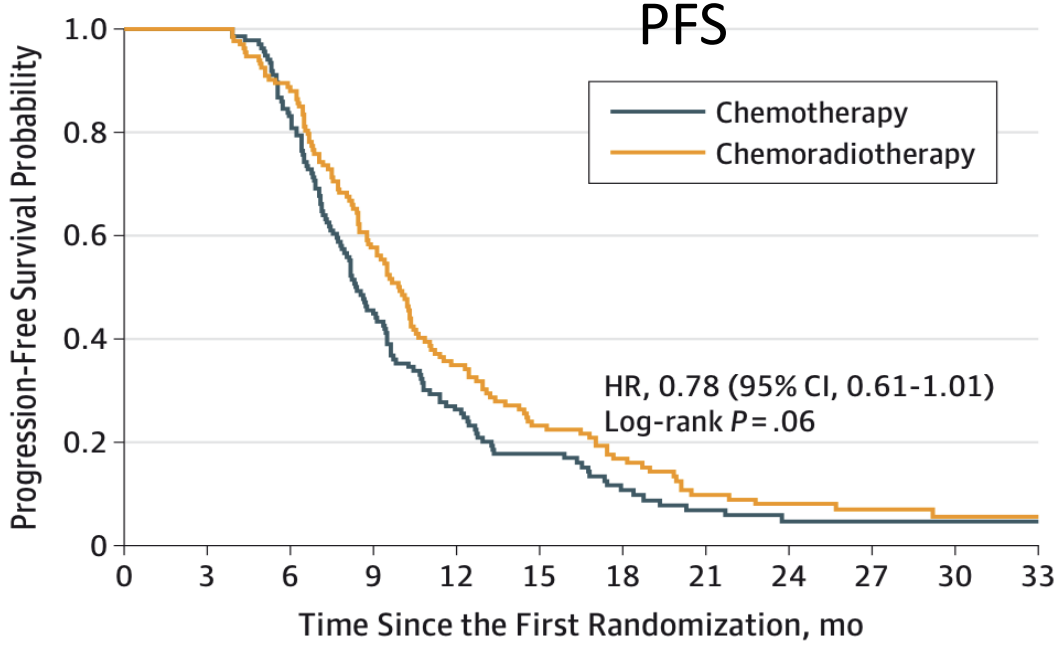
The LAP07 Randomized Clinical Trial

OS



Chemotherapy												
No. at risk	136	136	133	117	94	70	55	39	24	14	12	8
No. of events	0	0	4	20	40	60	73	87	99	104	106	109
Chemoradiotherapy												
No. at risk	133	133	131	113	87	66	45	34	26	18	12	9
No. of events	0	0	3	20	45	63	80	89	96	101	105	106

PFS



Chemotherapy												
No. at risk	136	136	113	61	35	21	12	7	3	1	1	1
No. of events	0	0	24	76	101	112	119	124	125	125	125	125
Chemoradiotherapy												
No. at risk	133	133	117	76	45	30	21	11	8	7	4	4
No. of events	0	0	18	57	87	102	110	118	120	120	121	121

JAMA. 2016;315(17):1844-1853

Locally advanced pancreatic cancer

Radiotherapy	consolidation radiotherapy

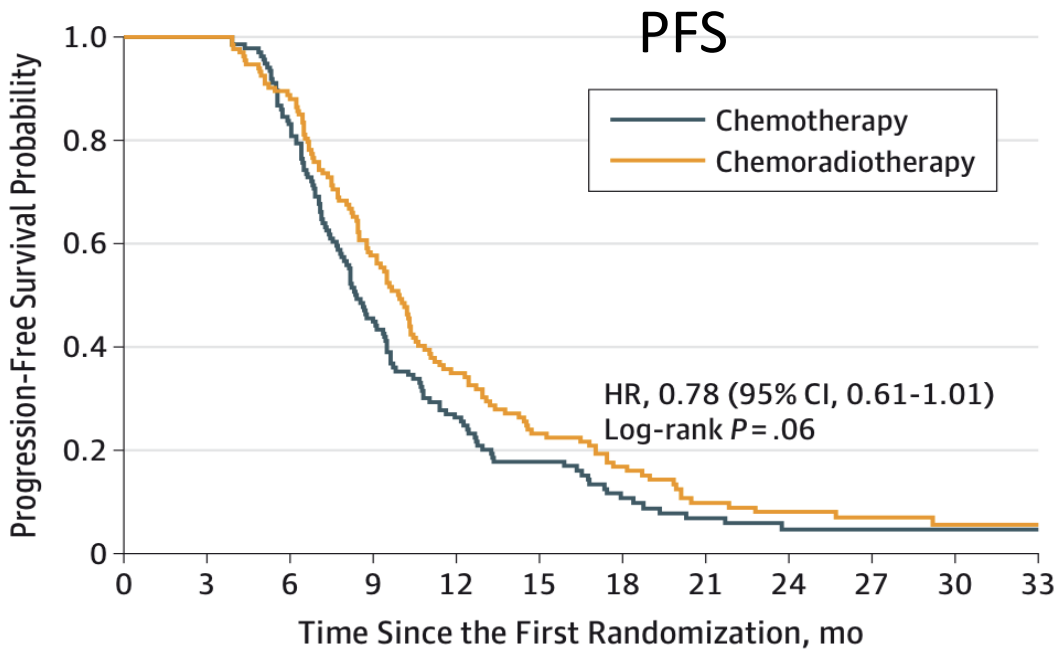
Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib
The LAP07 Randomized Clinical Trial

Time without Treatment

6.1m (4.8- 7.0) vs **3.7m** (3.0-4.6) (*P* = .02)

Local progression

32% vs **46%**, (*P* = .03)



Chemotherapy												
No. at risk	136	136	113	61	35	21	12	7	3	1	1	1
No. of events	0	0	24	76	101	112	119	124	125	125	125	125
Chemoradiotherapy												
No. at risk	133	133	117	76	45	30	21	11	8	7	4	4
No. of events	0	0	18	57	87	102	110	118	120	120	121	121

JAMA. 2016;315(17):1844-1853

Locally advanced pancreatic cancer

Radiotherapy

SBRT vs CRT

Study, Year	Median Age (Range)	SBRT Dose (Gy)	Fractions	Induction Chemotherapy	Stage	Patients	Median Follow-up (Range)	Conversion Rate	Local Control (%)	Median OS (Months)	1-Year OS (%)	Median PFS (Months)	1-Year PFS (%)	Toxicity
Jung et al., 2019 [27]	64 (38–84)	28 (24–36)	4	FOLFIRINOX/GE based	LAPC	95	15 (2–49)	7.4%	N/A	16.7	67.4	10.2	42.9	3.2% acute G3+ 3.2% late G3+
Herman et al., 2015 [33]	67 (35–87)	33	5	GE	LAPC	49	13.9 (3.9–45.2)	8.0%	78 1-year	13.9	59.2	7.8	32.7	2% acute G2+ 12% late G2+
Park et al., 2017 [34]	68.3 (45–90)	30–33	5	FOLFIRINOX/GE based/FOLFOX	LAPC	44	12.9 (1.7–107.6)	7%	N/A	15.7	56.2	N/A	N/A	0% G3+
Ryan et al., 2018 [35]	74 (68–79)	28 (25–33)	5	FOLFIRINOX/GE/GE based	LAPC	29	15 (4–18)	N/A	78 1-year	13	51.7	6	17.2	10% acute G3+ 4% late G3+
Shen et al., 2019 [36]	62 (38–84)	40 (30–50)	5	GE+capecitabine	LAPC	56	17 (3–43)	N/A	N/A	19	82.1	12	48.2	3.6% acute G3 5.4% late G3 3.6% late G4
Mellon et al., 2015 [43]	66.5 (45–85)	median 30–40	5	FOLFIRINOX/GTX/GE based	LAPC BRPC	49 110	14 (4–46)	N/A 51.0%	N/A	15 19.2	46.9 63.6	13.2 11.9	34.7 43.6	7% acute & late G3+
Hill et al., 2022 [44]	N/A	N/A	5	FOLFIRINOX/GE + nab-paclitaxel	LAPC	48	60 (14-65)	38.6%	23.9 months (median local PFS)	20.2	58	N/A	N/A	2.1% late G2+
Chuong et al., 2013 [45]	64 (38–87)	35 (25–50)	5	GTX	LAPC BRPC	16 57	11 (2.2–21) 7.8 (3.4–25.9)	N/A 56.1%	81 1-year	15 16.4	68.1 72.2	9.8 9.7	41 42.8	0% acute G3+ 5.3% late G3+
Moningi et al., 2015 [46]	67.2 (35–87)	25–33	5	FOLFIRINOX/GE/GE based	LAPC BRPC	74 14	14.5 10.3	21.6%	61% 1-year	18.4 14.4	N/A	9.8	N/A	3.4% acute G3+ 5.7% late G2+
Mahadevan et al., 2011 [51]	67 (44–88)	24–36	3	GE	LAPC	39	21 (6–36)	N/A	85 crude	20	68.1	15	55.3	9% late G3+
Zhang et al., 2018 [52]	64 (44–80)	30–36	5 or 6	N/A	LAPC	41	12.4 (2.8–24)	N/A	N/A	11.8	46.3	N/A	N/A	N/A
Kim et al., 2019 [53]	74 (56–92)	29 (25–42)	3 or 5	FOLFIRINOX	LAPC	27	9 (3–32.7)	N/A	61 1-year	11.6	40.7	N/A	N/A	22% G3 22% G2 0% G4
Song et al., 2015 [54]	62 (28–86)	45 (35–50)	3–8	N/A	LAPC	59	10.9 (3.2–48.7)	N/A	90.8% 1-year	12.5	53.9	13.9	N/A	1.7% late G3 0% late G4

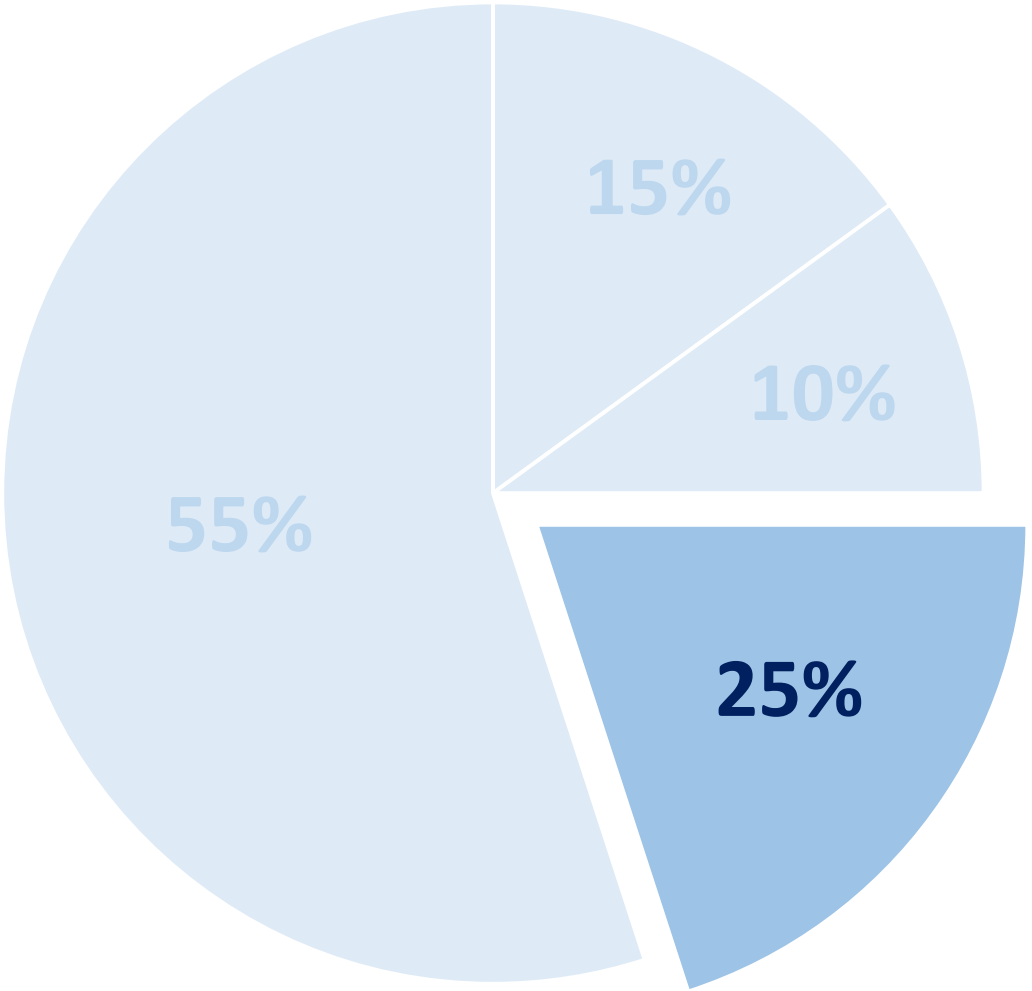
Locally advanced pancreatic cancer

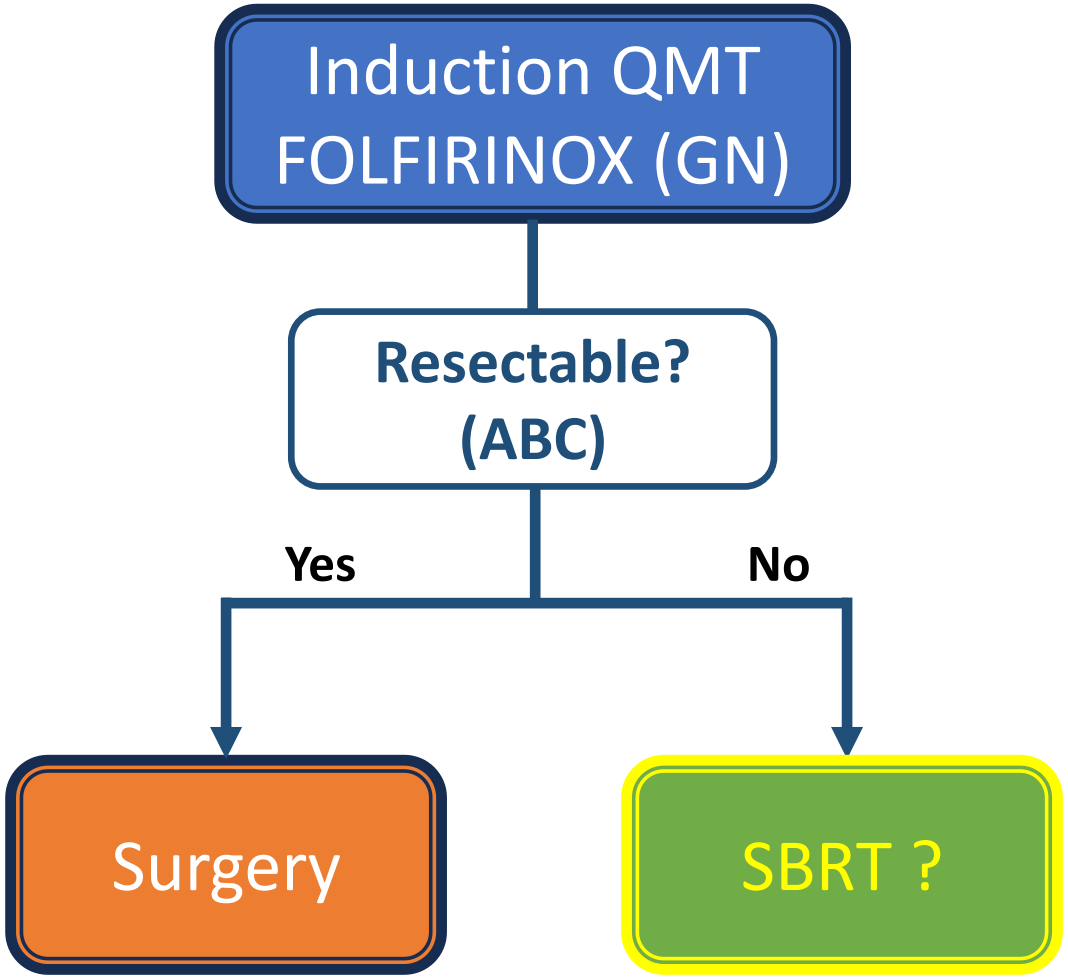
Radiotherapy	SBRT vs CRT

- Higher biological equivalent dose
- Reduced volumen
- Shortened treatment time
- Better pain relief
- Improved survival ?

Biomedicines 2022, 10, 2480

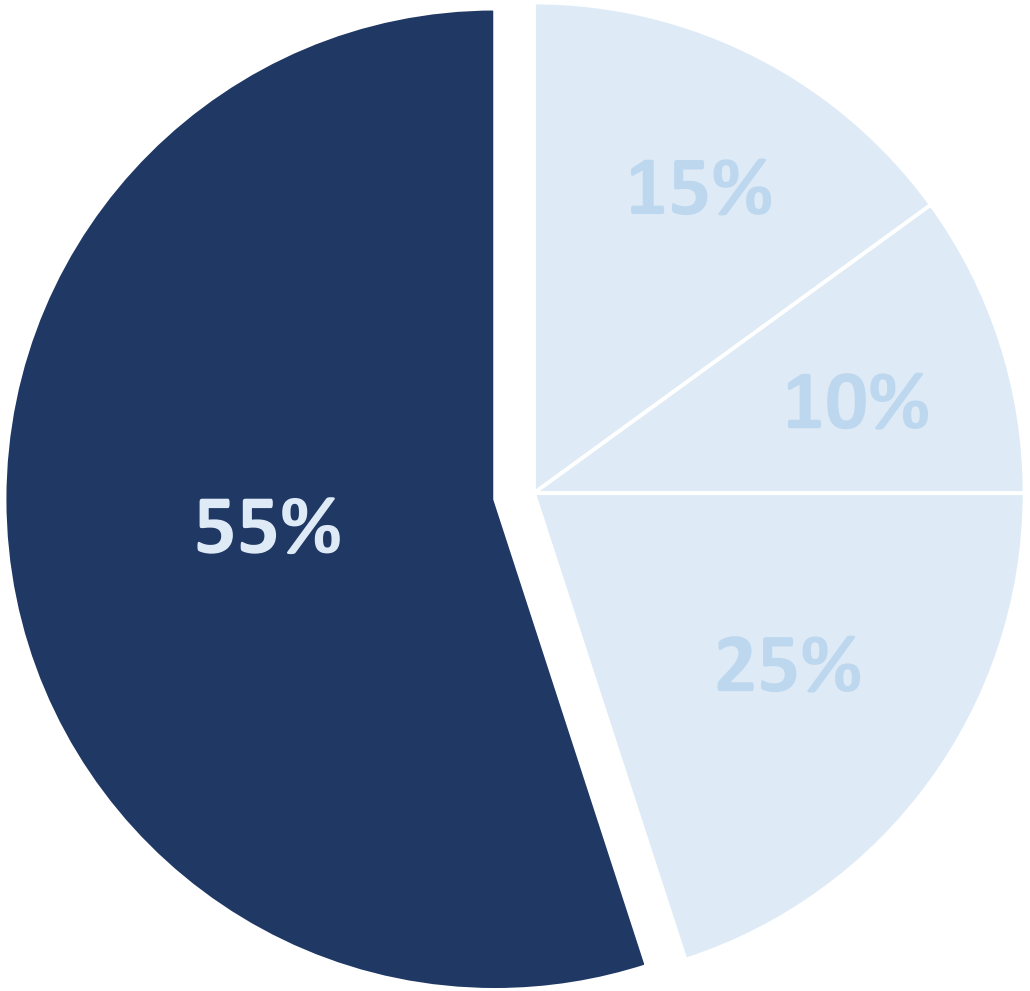
Locally advanced pancreatic cancer





Adapted from ESMO guidelines

Metastatic pancreatic cancer



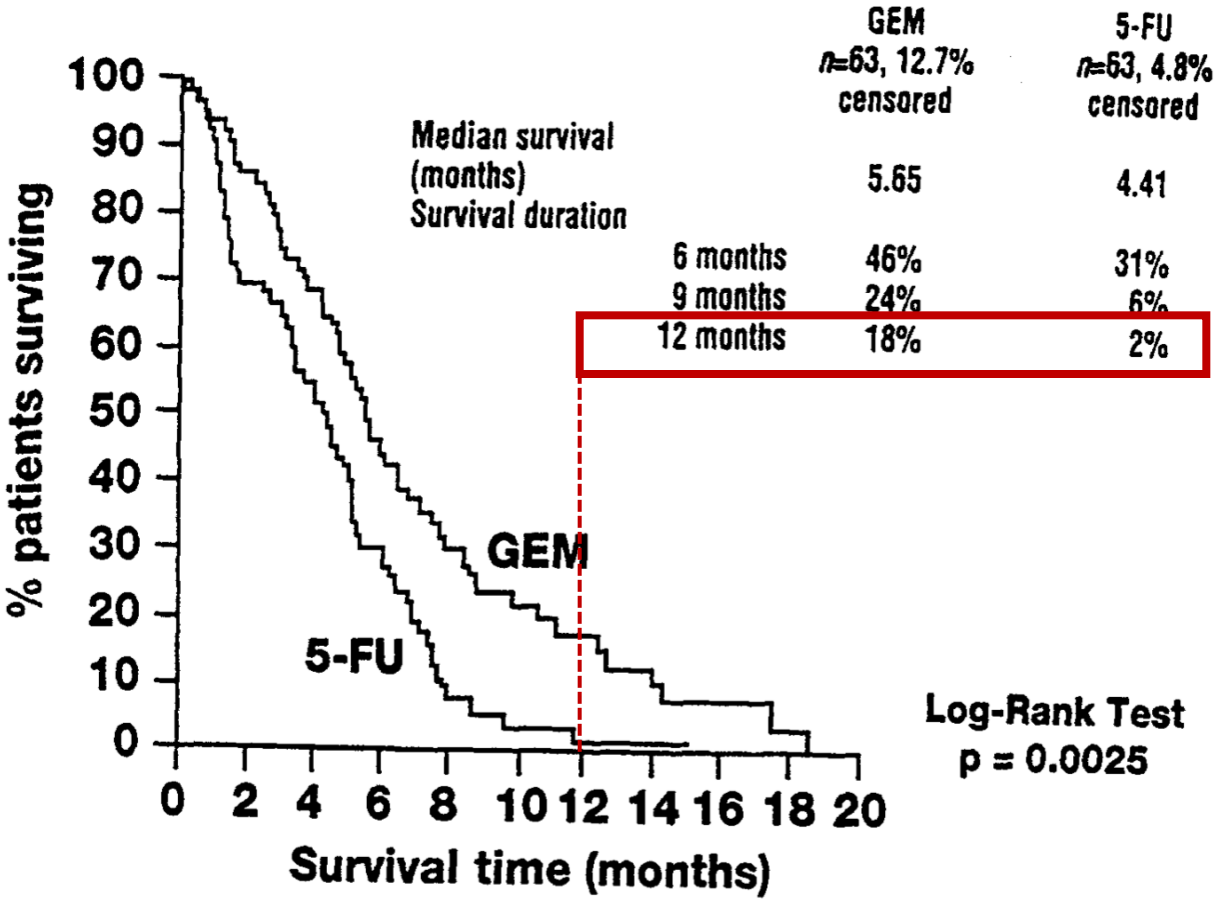
Palliative QMT

Adapted from ESMO guidelines

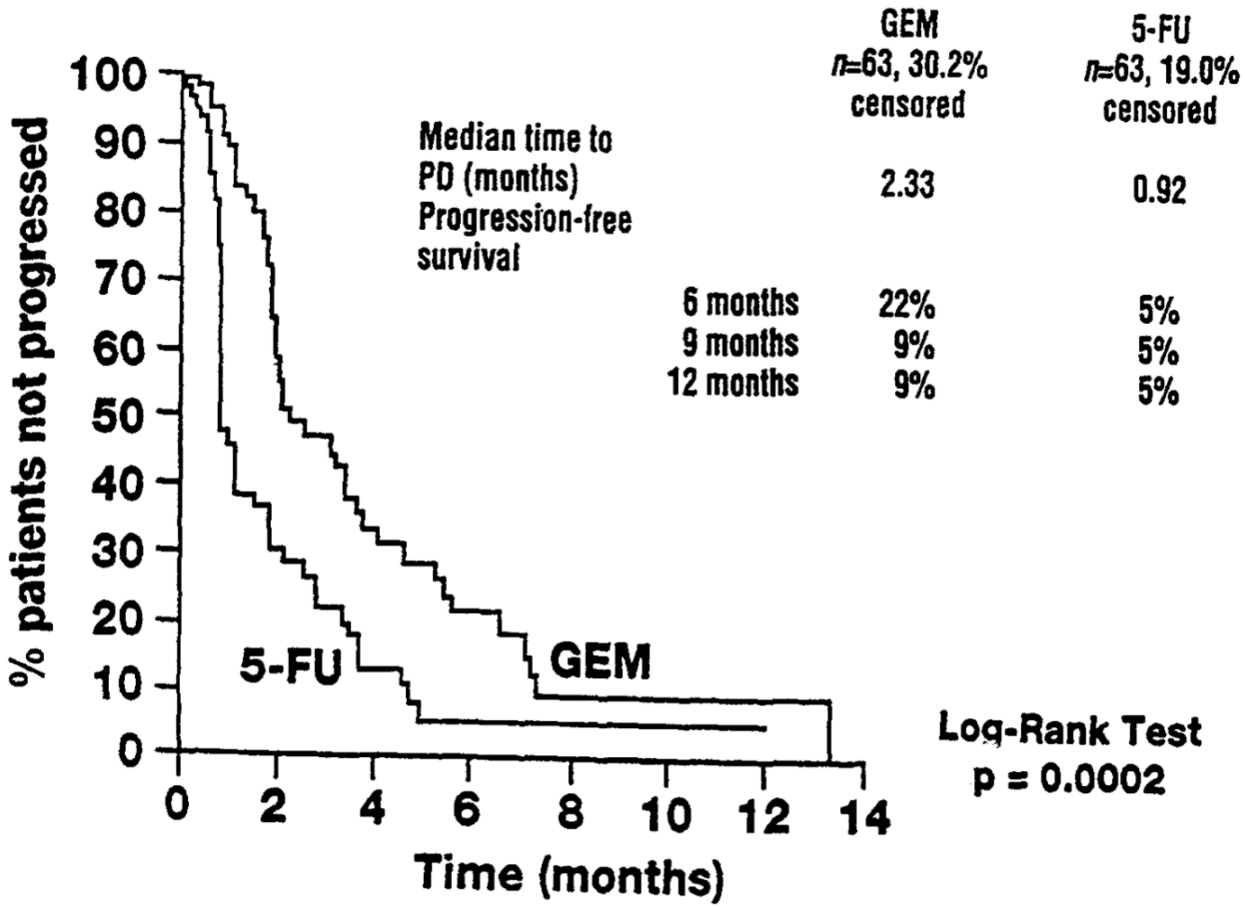
Metastatic pancreatic cancer

Systemic chemotherapy	Gemcitabine > 5-FU, 1997

OS



PFS



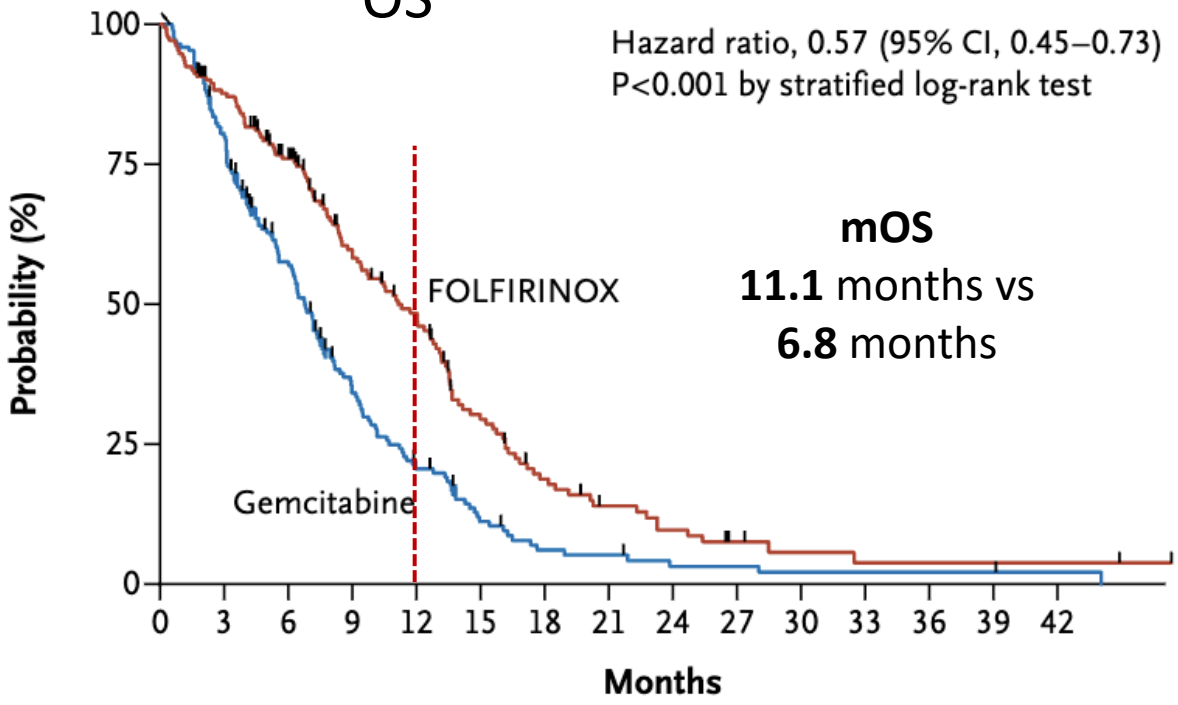
JCO 1997

Metastatic pancreatic cancer

Systemic chemotherapy | FOLFIRINOX > Gemcitabine, 2011

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

OS

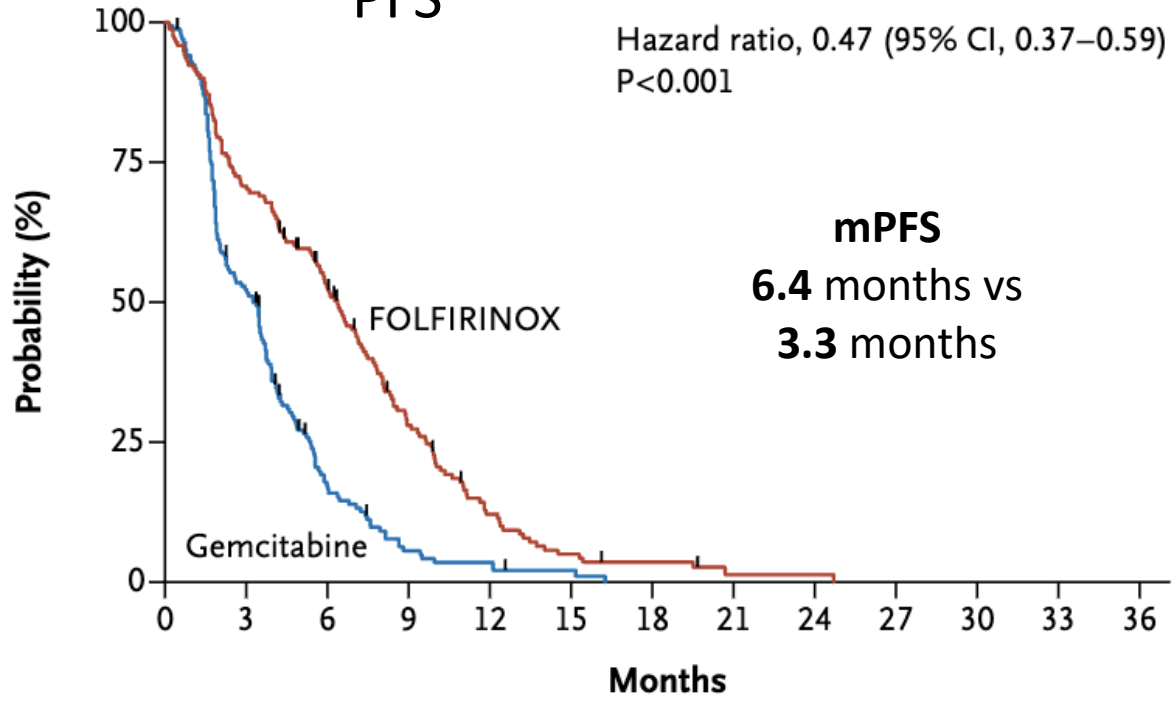


mOS
11.1 months vs
6.8 months

No. at Risk

Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2

PFS



mPFS
6.4 months vs
3.3 months

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

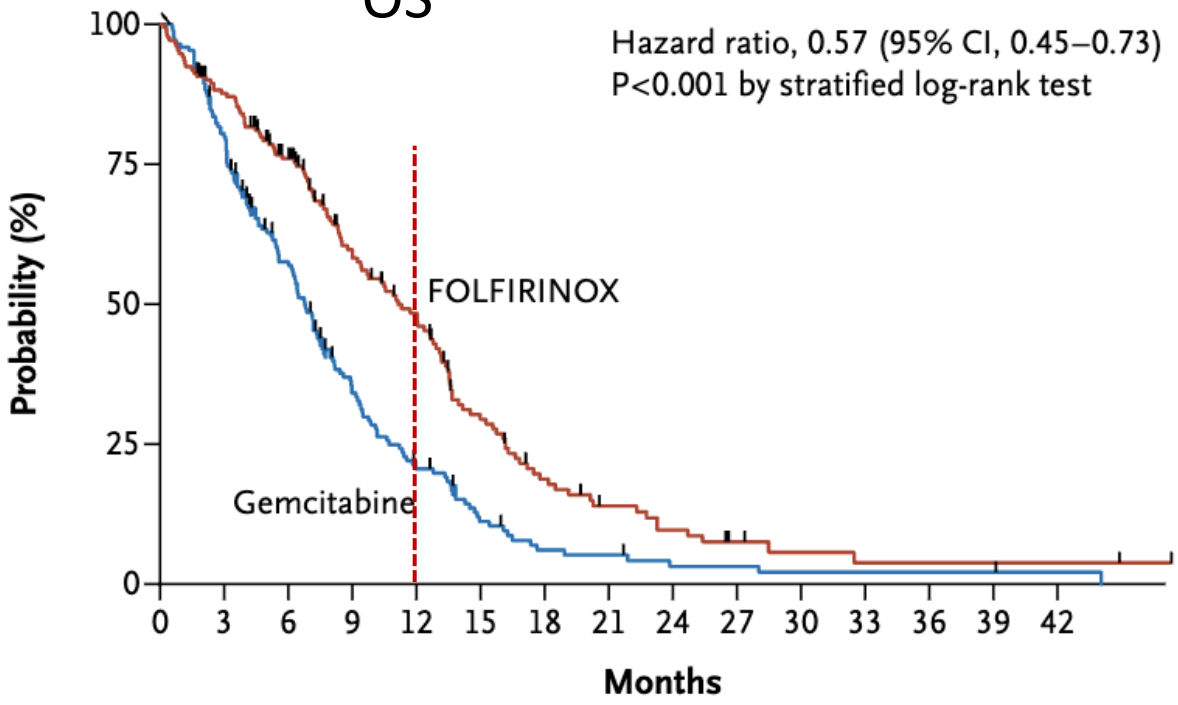
Conroy, NEJM 2011

Metastatic pancreatic cancer

Systemic chemotherapy | FOLFIRINOX > Gemcitabine, 2011

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

OS

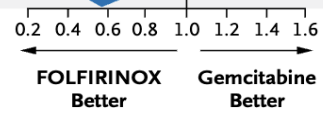


No. at Risk

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

Conroy, NEJM 2011

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	

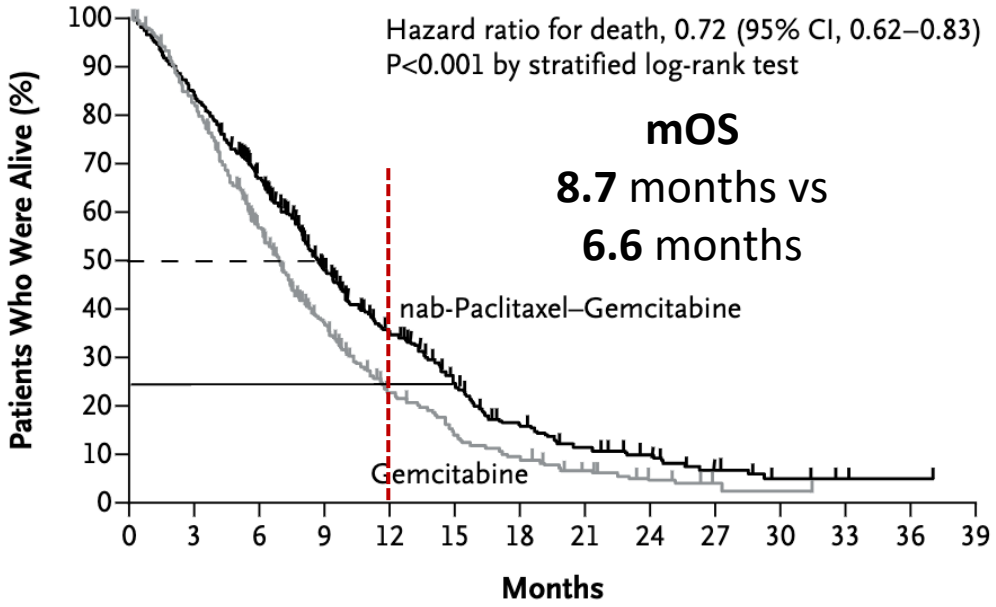


Metastatic pancreatic cancer

Systemic chemotherapy | Gemcitabine + nab-Paclitaxel > Gemcitabine, 2013

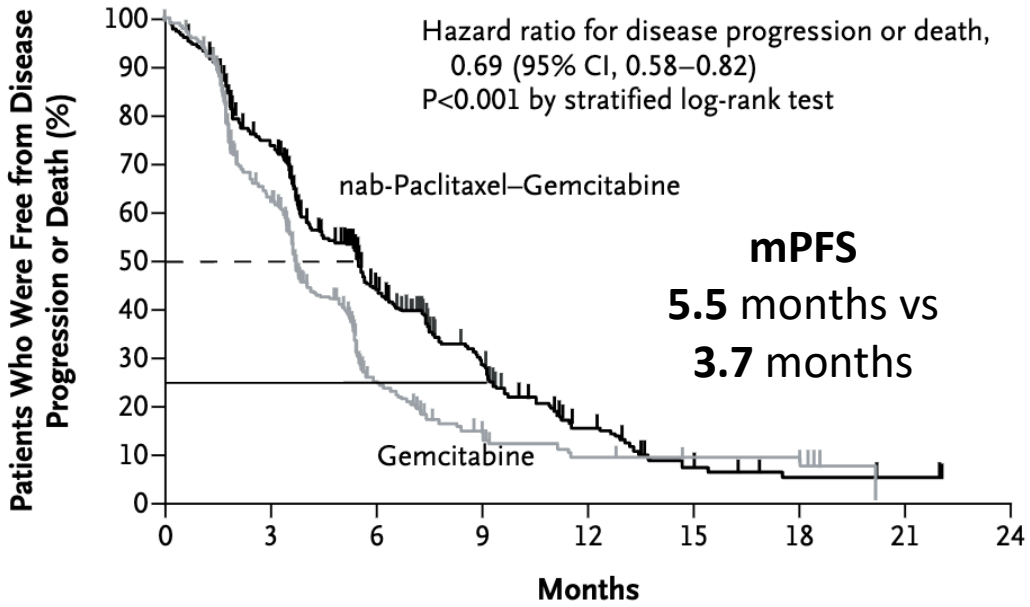
Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

OS



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

PFS



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

NEJM 2013

Metastatic pancreatic cancer

Systemic chemotherapy	FOLFIRINOX vs Gemcitabine + nab-Paclitaxel ?

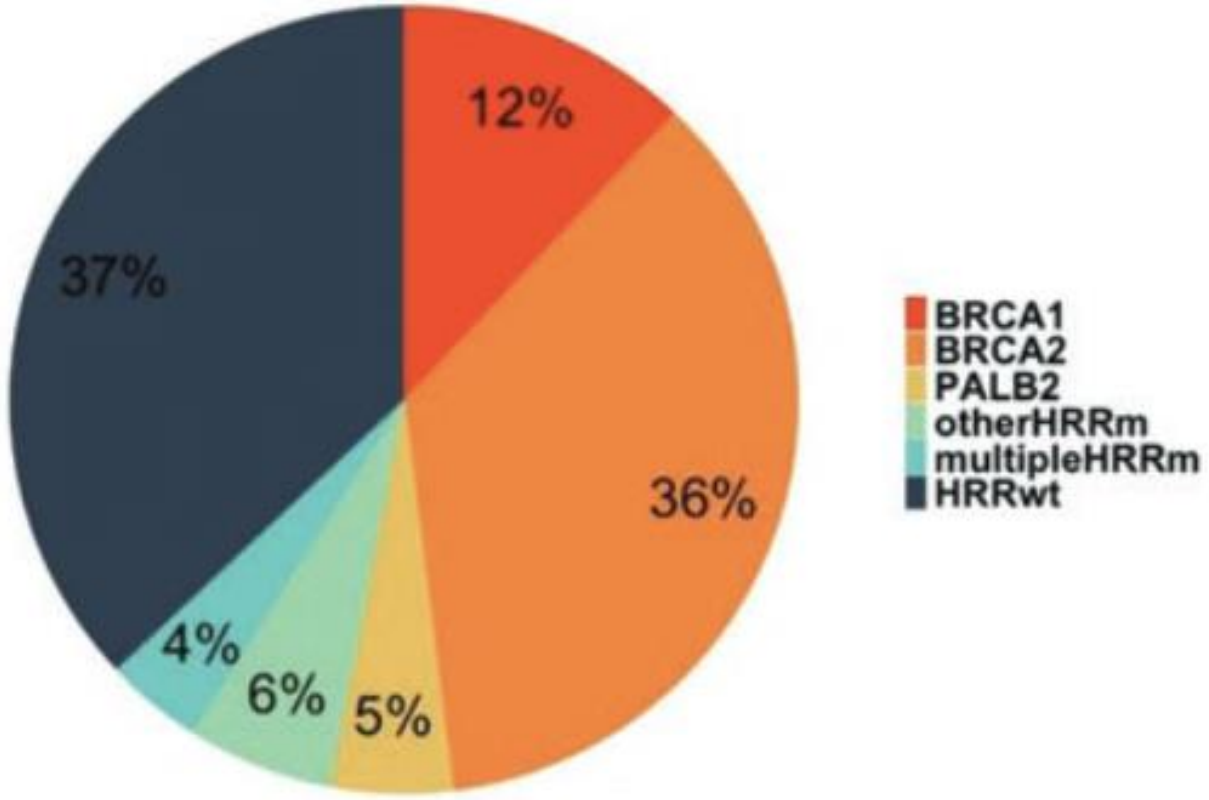
A Novel HRD Signature Is Predictive of FOLFIRINOX Benefit in Metastatic Pancreatic Cancer

Kuei-Ting Chen[1], Russell Madison[1], Jay Moore[1], Dexter Jin[1], Zoe Fleischmann[1], Justin Newberg[1], Alexa Schrock[1], Neeru Bhardwaj[1], Katherine T. Lofgren[1], Jie He[1], Garrett Frampton[1], Priti Hegde[1], David Fabrizio[1], Michael J. Pishvaian[2], Ericka Ebot[1], Aatur Singhi[*,3,‡], Ethan Sokol[*,1,‡]

(n = 8358)

9%

HRD



The Oncologist, 2023

Metastatic pancreatic cancer

Systemic chemotherapy	FOLFIRINOX vs Gemcitabine + nab-Paclitaxel ?

A Novel HRD Signature Is Predictive of FOLFIRINOX Benefit in Metastatic Pancreatic Cancer

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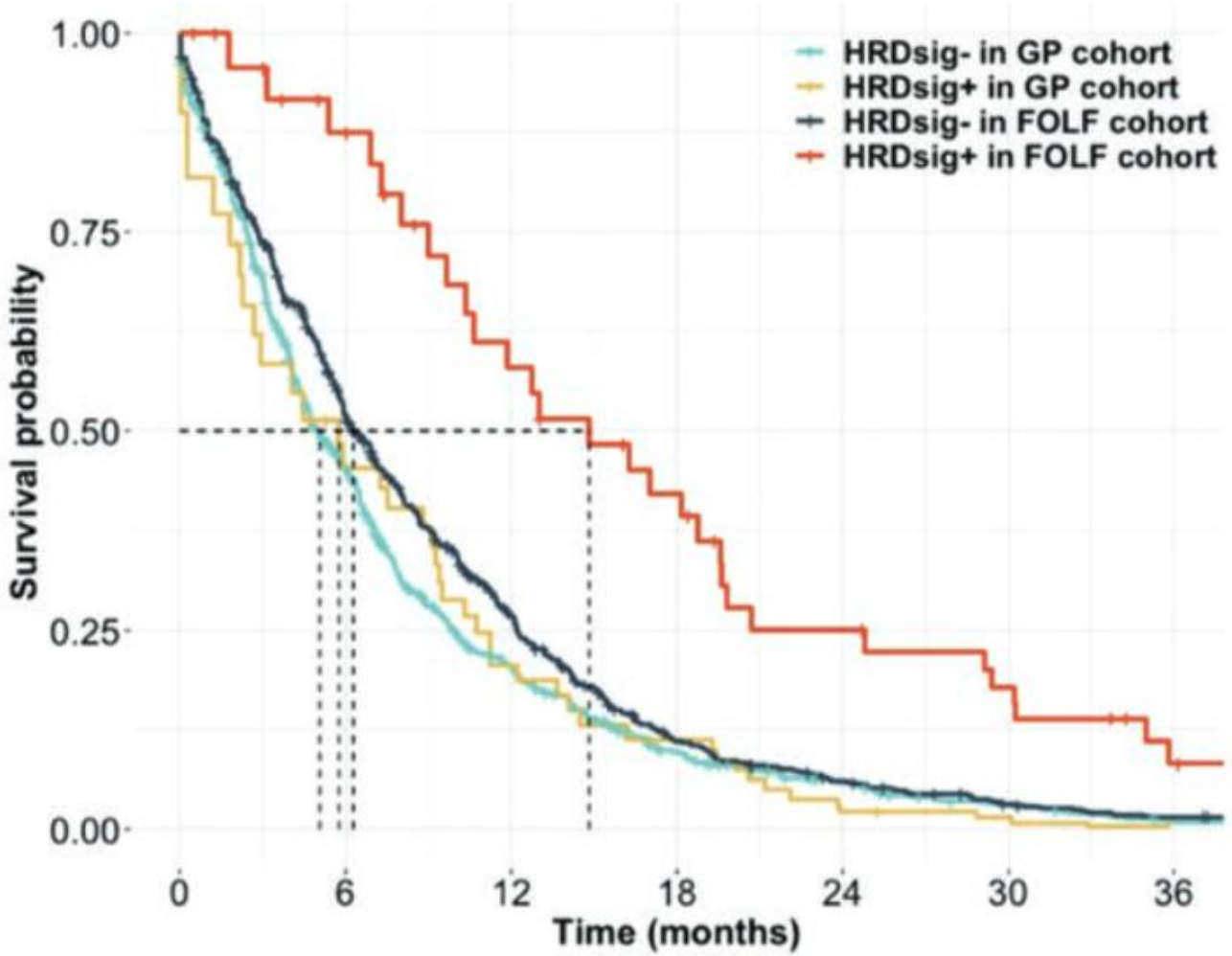
9%

HRD



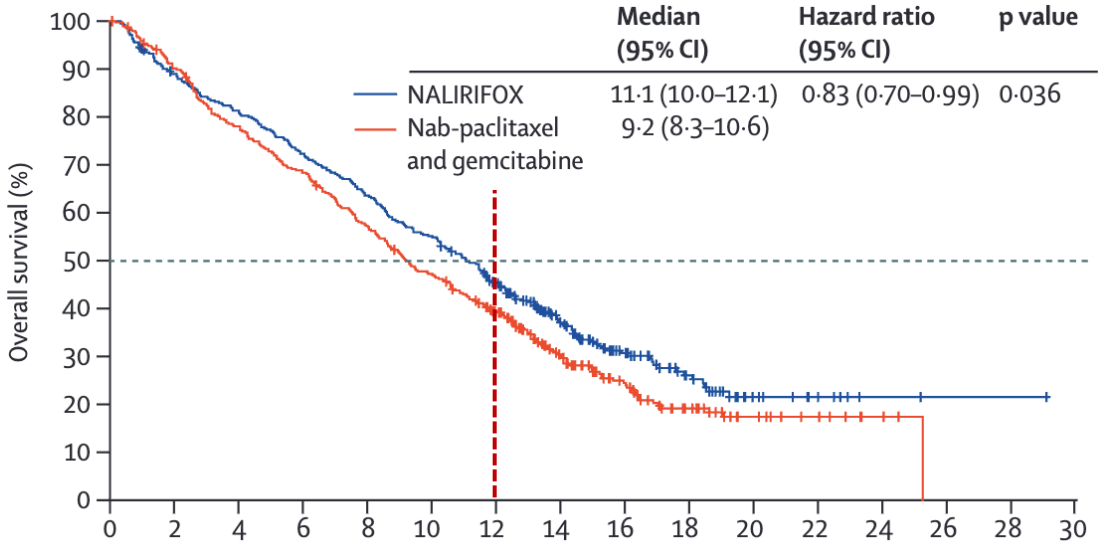
The Oncologist, 2023

Metastatic pancreatic cancer

Systemic chemotherapy | NALIRIFOX > Gemcitabine + nab-Paclitaxel, 2023

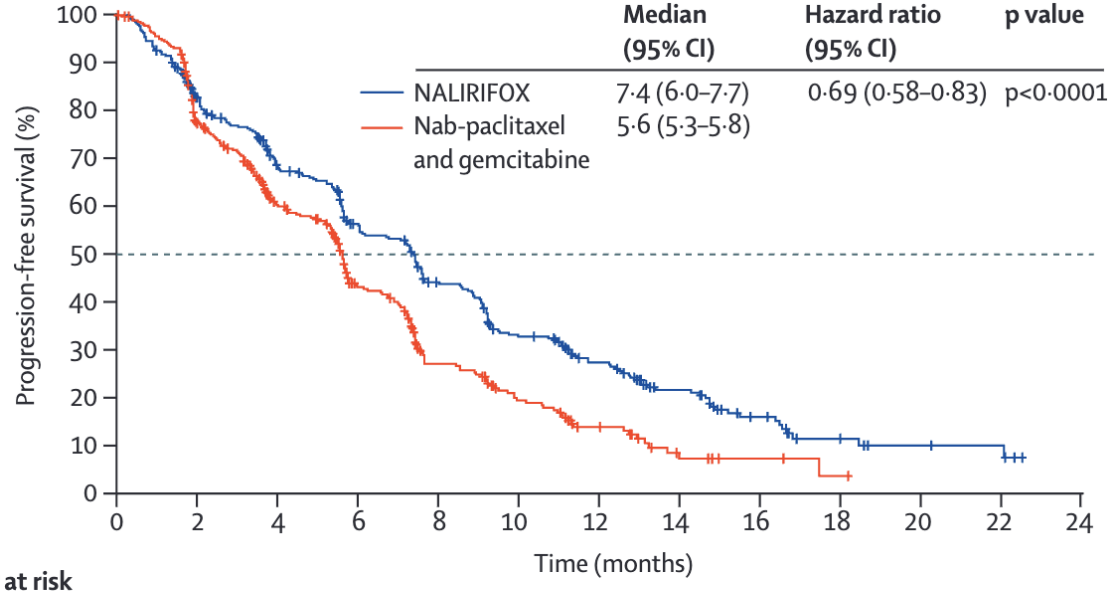
NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial

OS



Number at risk (number censored)																
NALIRIFOX	383	337	308	274	241	209	162	98	59	32	13	7	2	1	1	0
	(0)	(4)	(4)	(4)	(4)	(4)	(15)	(53)	(77)	(97)	(111)	(117)	(122)	(123)	(123)	(124)
Nab-paclitaxel and gemcitabine	387	345	298	261	218	179	140	80	50	28	15	10	3	0	0	0
	(0)	(4)	(5)	(5)	(6)	(7)	(17)	(48)	(65)	(77)	(88)	(93)	(100)	(102)	(102)	(102)

PFS



Number at risk (number censored)													
NALIRIFOX	383	271	210	164	122	87	61	39	20	9	5	4	0
	(0)	(52)	(68)	(77)	(84)	(88)	(101)	(111)	(121)	(127)	(130)	(131)	(134)
Nab-paclitaxel and gemcitabine	387	267	182	112	60	38	19	6	3	1	0	0	0
	(0)	(40)	(68)	(89)	(102)	(108)	(117)	(123)	(126)	(127)	(128)	(128)	(128)

Wainberg, Lancet 2023

Metastatic pancreatic cancer

Systemic chemotherapy | NALIRIFOX > Gemcitabine + nab-Paclitaxel, 2023

NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial

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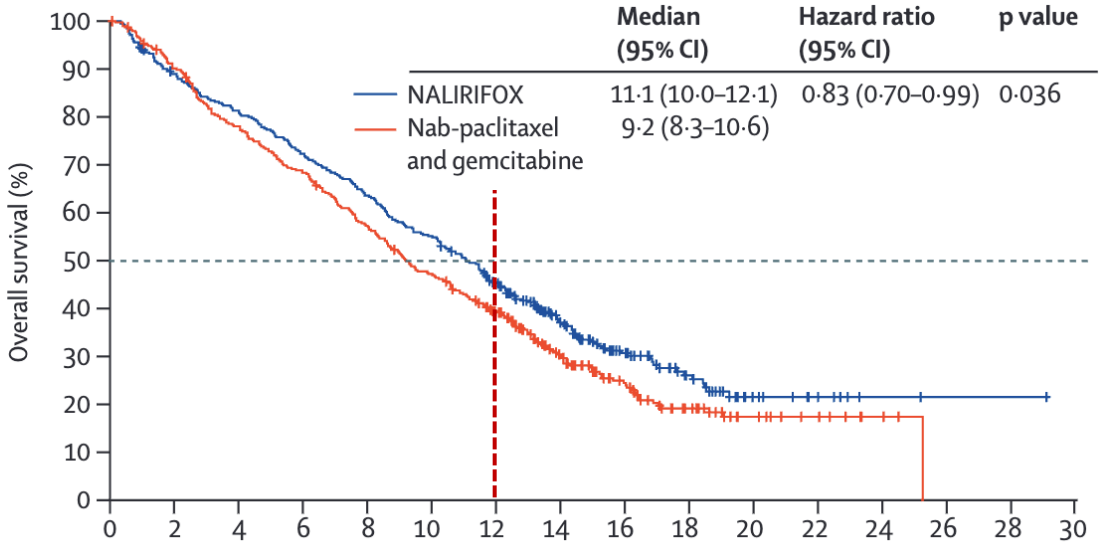
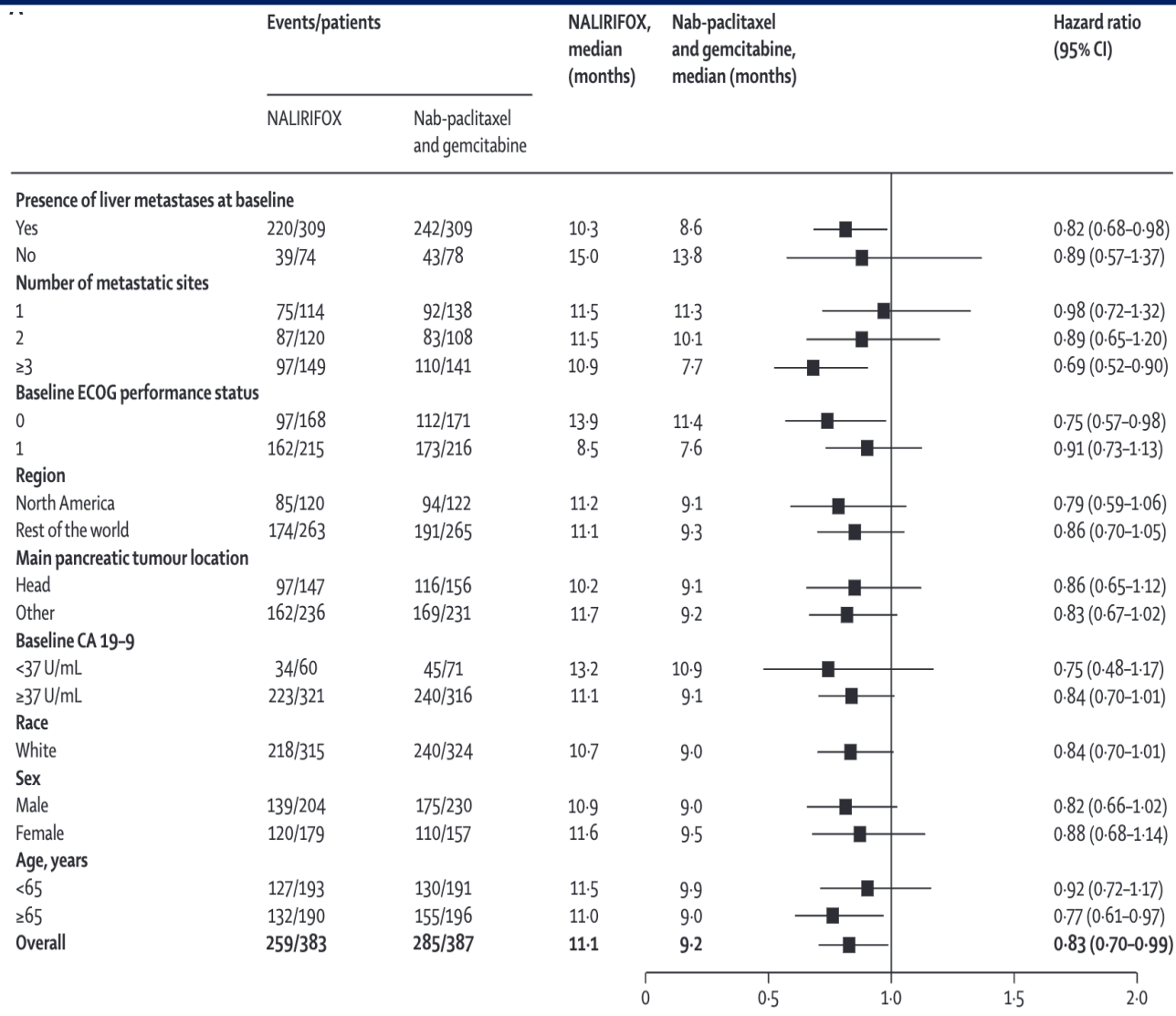


Number at risk (number censored)

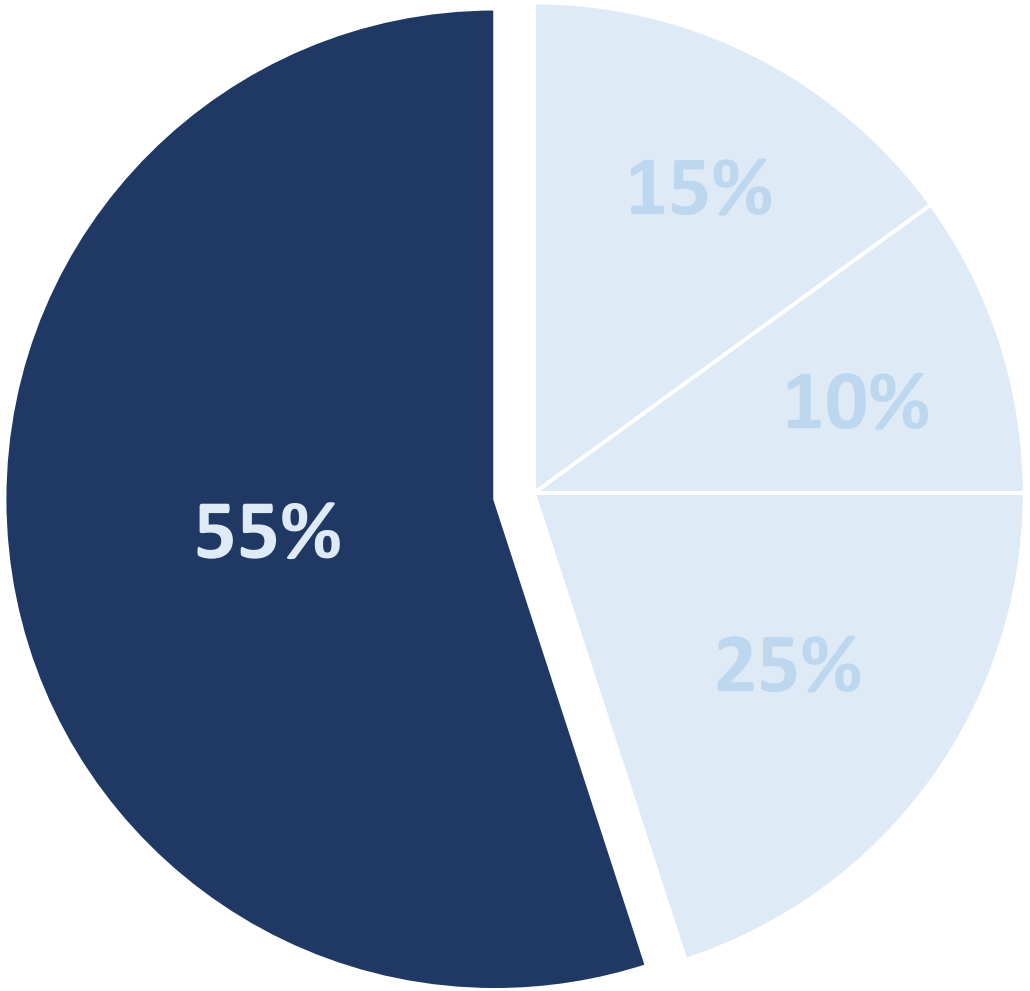
NALIRIFOX	383 (0)	337 (4)	308 (4)	274 (4)	241 (4)	209 (4)	162 (15)	98 (53)	59 (77)	32 (97)	13 (111)	7 (117)	2 (122)	1 (123)	1 (123)	0 (124)
Nab-paclitaxel and gemcitabine	387 (0)	345 (4)	298 (5)	261 (5)	218 (6)	179 (7)	140 (17)	80 (48)	50 (65)	28 (77)	15 (88)	10 (93)	3 (100)	0 (102)	0 (102)	0 (102)

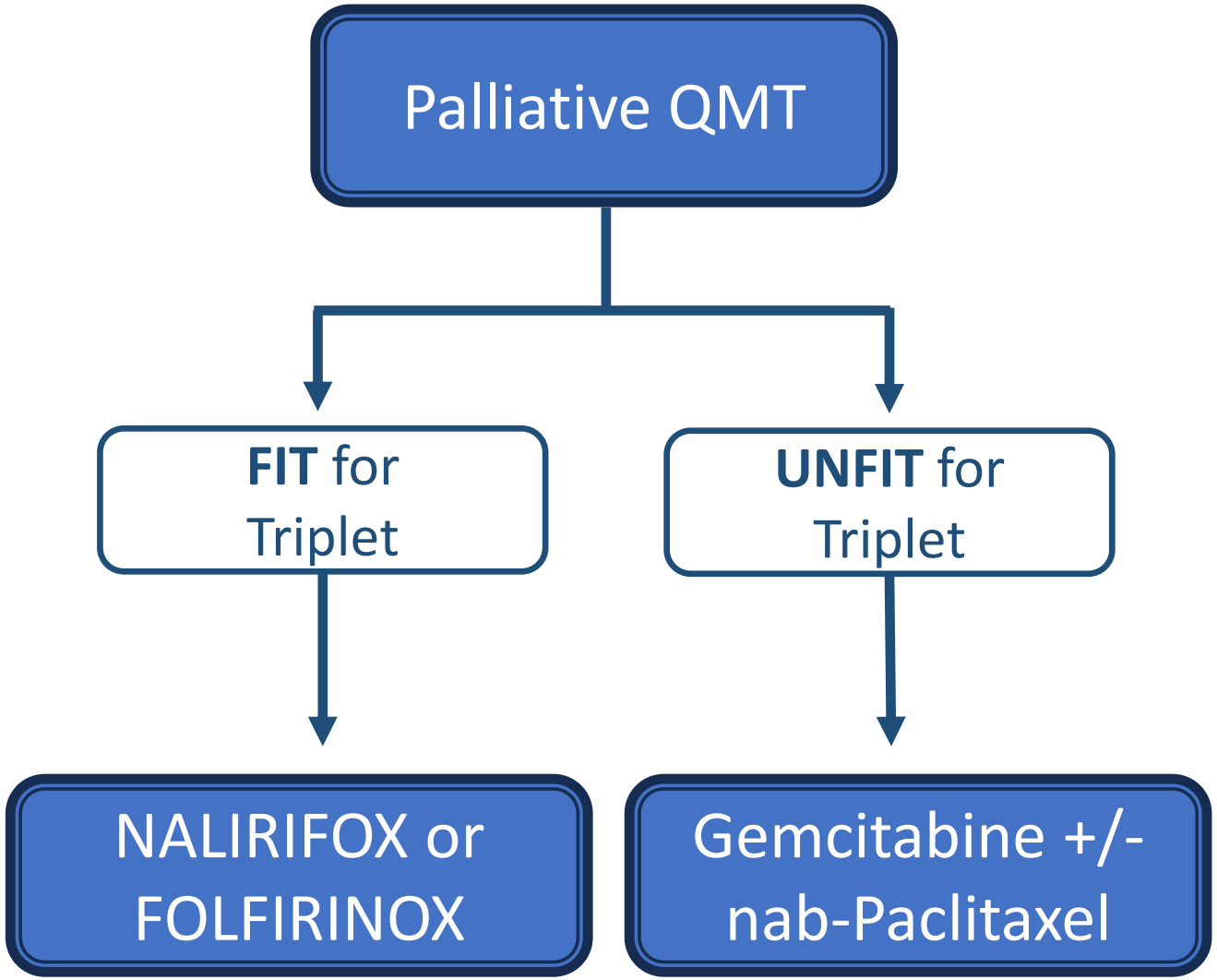


Wainberg, Lancet 2023

	Gemcitabine	Gemcitabine Nab-Paclitaxel	FOLFIRINOX	NALIRIFOX
Median OS	6.7 months	9 months	11.1 months	11.1 months
12m OS rate	20.6%	39.5%	48.4%	45.6%
18m OS rate	6.0%	19.3%	18.6%	26.2%
Median PFS	3.5 months	5.6 months	6.4 months	7.4 months
12m PFS rate	6%	14%	12.1%	27.4%
18m PFS rate	0%	3.6%	3.3%	11.4%
ORR	7%	23%	31.6%	41.8%
Grade 3/4 AEs				
Neutropenia	25%	38%	46%	24%
Diarrea	2%	6%	13%	20%

Metastatic pancreatic cancer



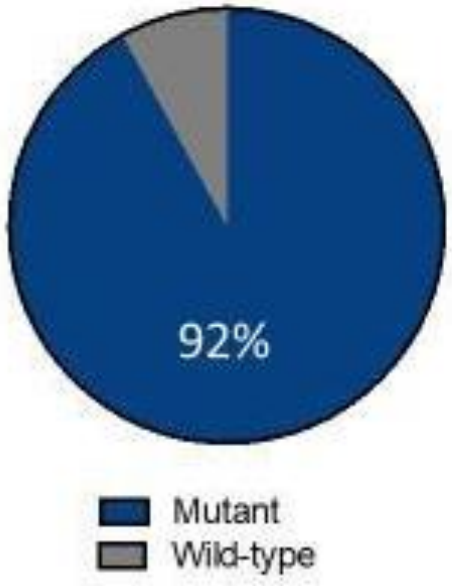


Adapted from ESMO guidelines

Metastatic pancreatic cancer

Targeted therapies	Promising targets

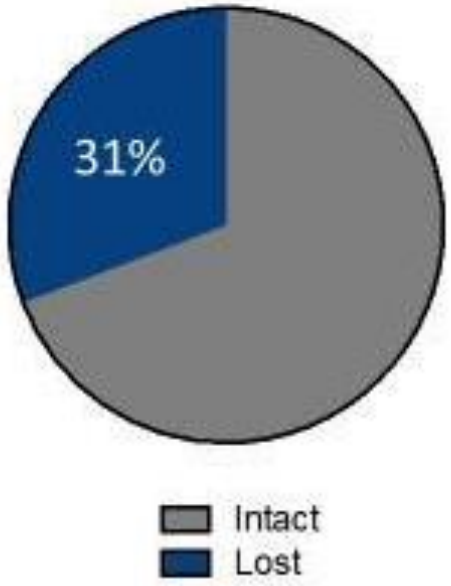
KRAS Mutation



TCGA, Cancer Cell 2017
Singhe et al. CCR 2023

KRAS inhibitors

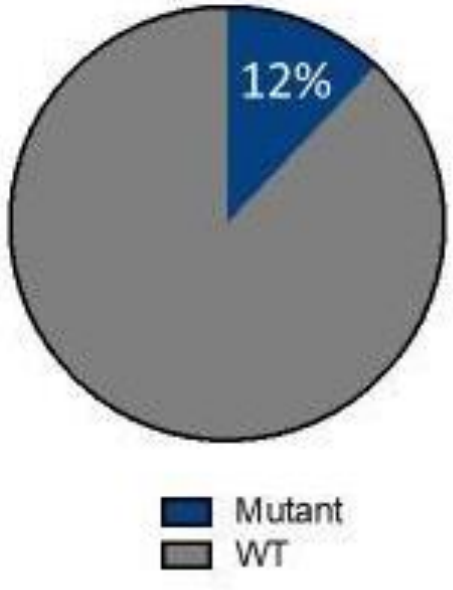
MTAP Loss



Vayrynen et al. in prep

PRMT5 inhibitors

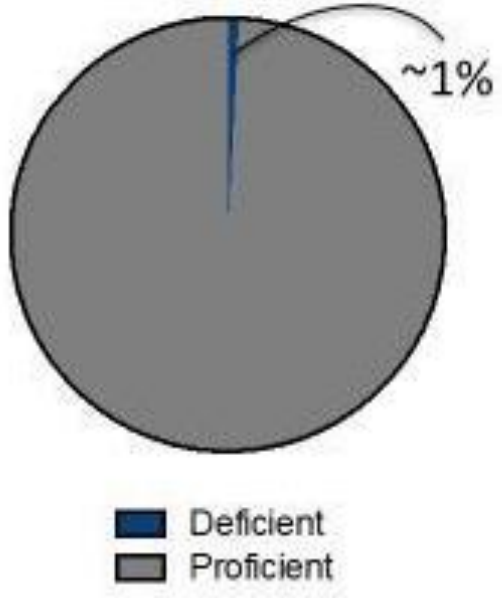
BRCA1, BRCA2, PALB2



Park et al. CCR 2020

PARP inhibitors

Mismatch Repair Deficient



Hu et al. CCR 2018

Immunotherapy
WRN inhibitors

Metastatic pancreatic cancer

Targeted therapies	Promising targets

KRAS Mutation

TCGA, Cancer Cell 2017
Singhe et al. CCR 2023

KRAS inhibitors

MTAP Loss

Vayrynen et al. in prep

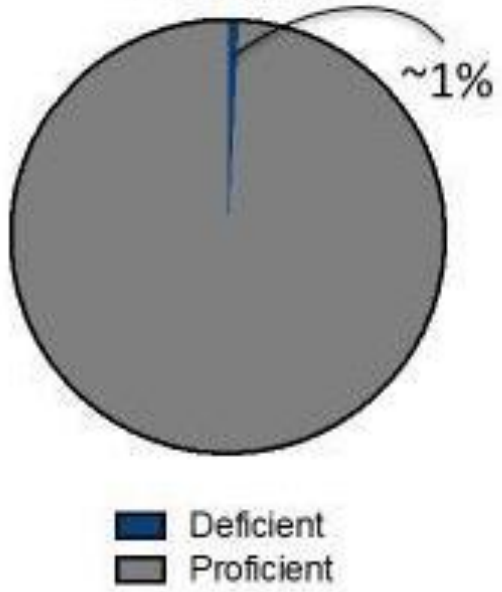
PRMT5 inhibitors

BRCA1, BRCA2, PALB2

Park et al. CCR 2020

PARP inhibitors

Mismatch Repair Deficient



Hu et al. CCR 2018

Immunotherapy
WRN inhibitors

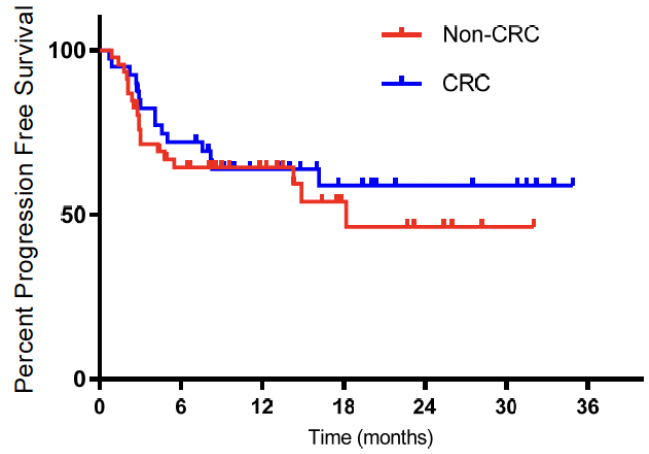
Metastatic pancreatic cancer

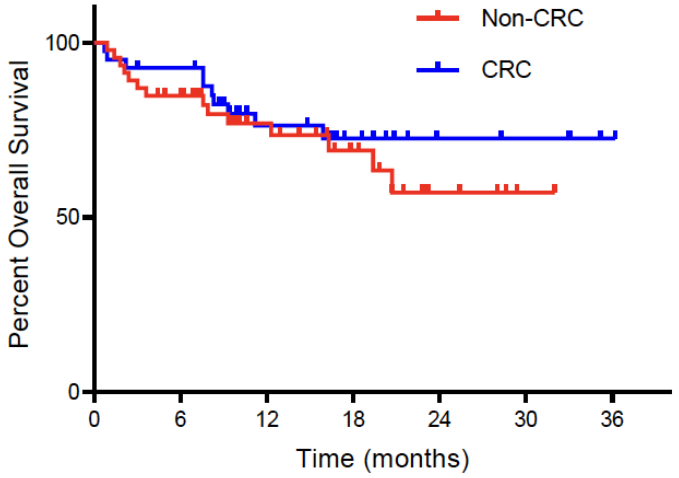
Targeted therapies

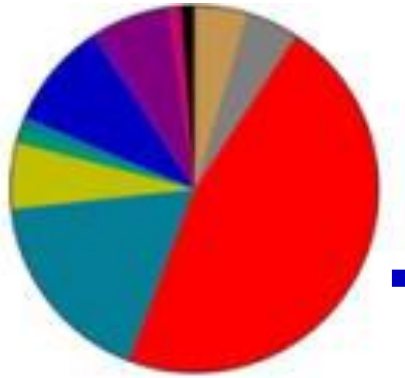
Checkpoint inhibitor in dMMR/MSI

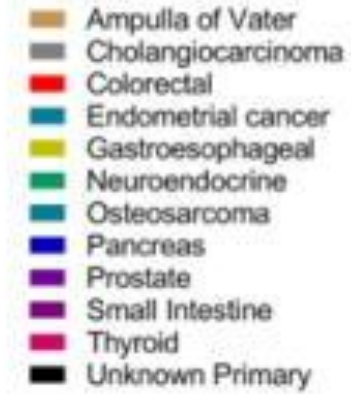
Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

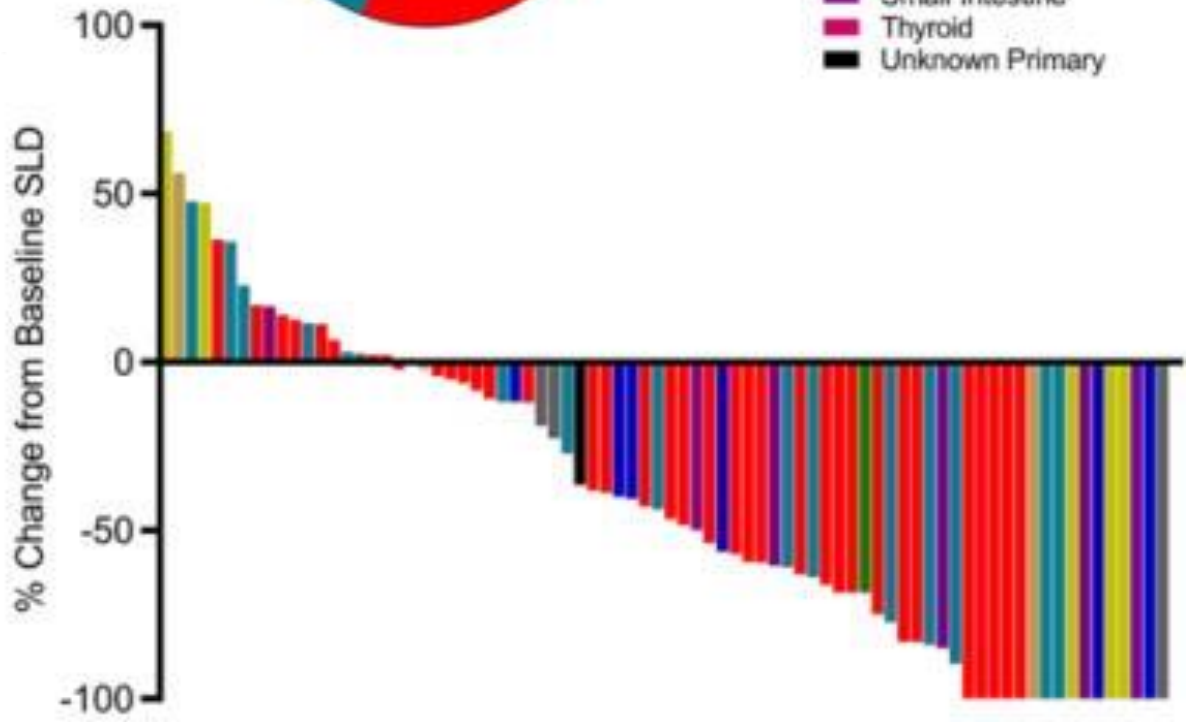
Type of Response-no (%)	Colorectal cancers n=40	Non-colorectal cancers n=46	Pancreas n=8
Complete Response	5 (12)	13 (28)	2 (25)
Partial Response	16 (40)	12 (26)	3 (37)
Stable Disease	12 (30)	8 (17)	1 (12)
Progressive Disease	4 (10)	8 (17)	0 (0)
Not Evaluable[1]	3 (8)	5 (11)	2 (25)
Objective Response Rate (%)	52	54	62
95% CI	36, 68	39, 69	75











Le DT, Science. 2017 Jul 28; 357(6349): 409–413

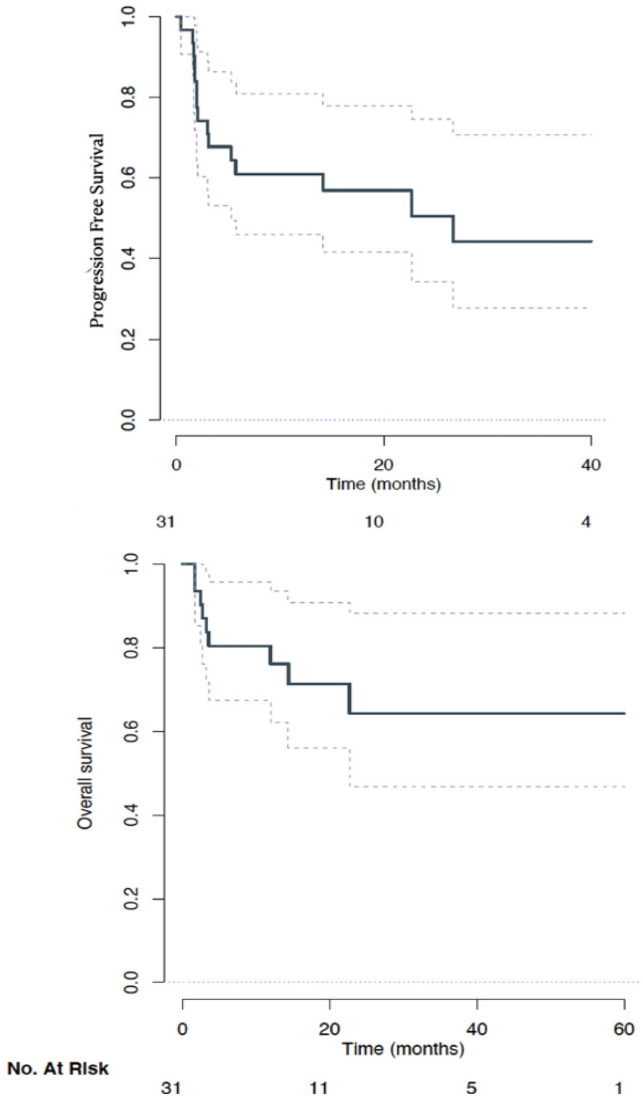
Metastatic pancreatic cancer

Targeted therapies

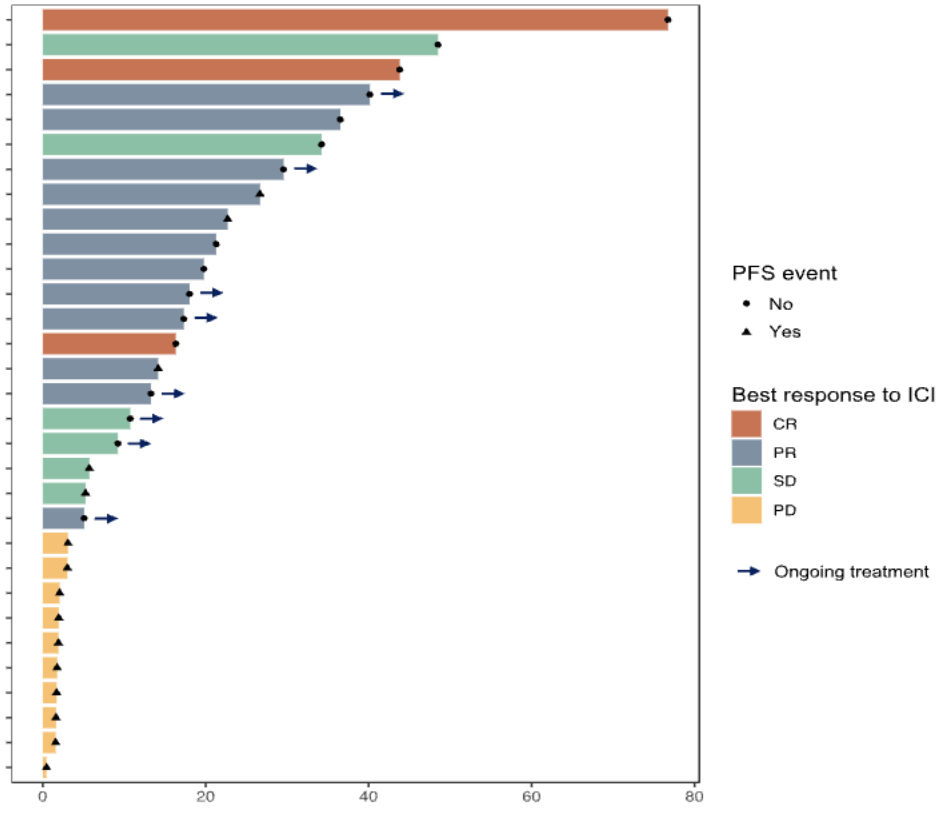
Checkpoint inhibitor in dMMR/MSI

Characteristics (n or %)	N = 31
Gender (M / F)	17/ 14
Median age (IQ range)	62.1 (37–82)
ECOG PS (0 /1 /2/NA)	17 / 9 / 4/1
Metastatic sites n (%)	
Liver	16 (51.6%)
Nodes	16 (51.6%)
Peritoneal	11 (35.5%)
Lung	9 (29.0%)
Other	6 (19.3%)
Number of metastatic sites (%)	
≤1	13 (41.9%)
> 1	18 (58.1%)
Number of prior regimens	
0	5
1	12
> 1	14
Baseline CA 19.9 (IU/L-range)	3833 (0.8–55400)
Prior systemic anticancer treatment	(%)
Fluoropyrimidine	77.4
Oxaliplatin	67.8
Irinotecan	51.6
Gemcitabine	48.4
Taxanes	45.2
Techniques for MSI/dMMR diagnosis	
Immunohistochemistry/PCR/Both	27/24/20
Germline mutations	
(searched/Identified)	20/8

J. Taïeb et al. / European Journal of Cancer 188 (2023) 90–97



Efficacy of immune checkpoint inhibitors in microsatellite unstable/mismatch repair-deficient advanced pancreatic adenocarcinoma: an AGEO European Cohort



Metastatic pancreatic cancer

Targeted therapies	Promising targets

KRAS Mutation

TCGA, Cancer Cell 2017
Singhe et al. CCR 2023

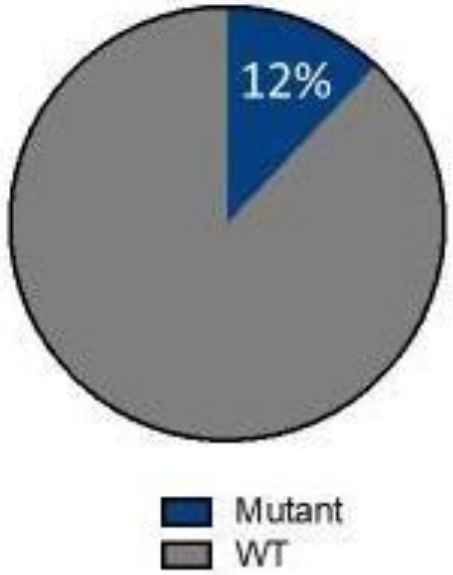
KRAS inhibitors

MTAP Loss

Vayrynen et al. in prep

PRMT5 inhibitors

BRCA1, BRCA2, PALB2



Park et al. CCR 2020

PARP inhibitors

Mismatch Repair Deficient

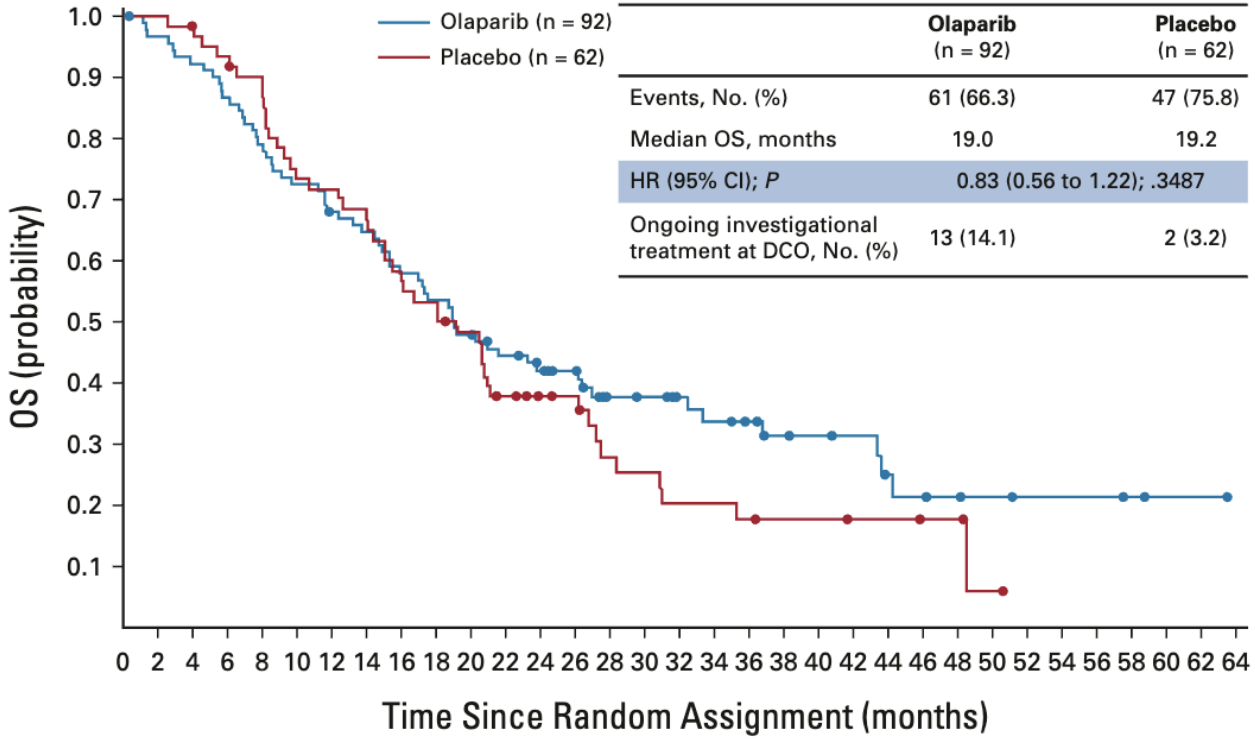
Hu et al. CCR 2018

Immunotherapy
WRN inhibitors

Metastatic pancreatic cancer

Targeted therapies | Promising targets: BRCA and HRDs

OS

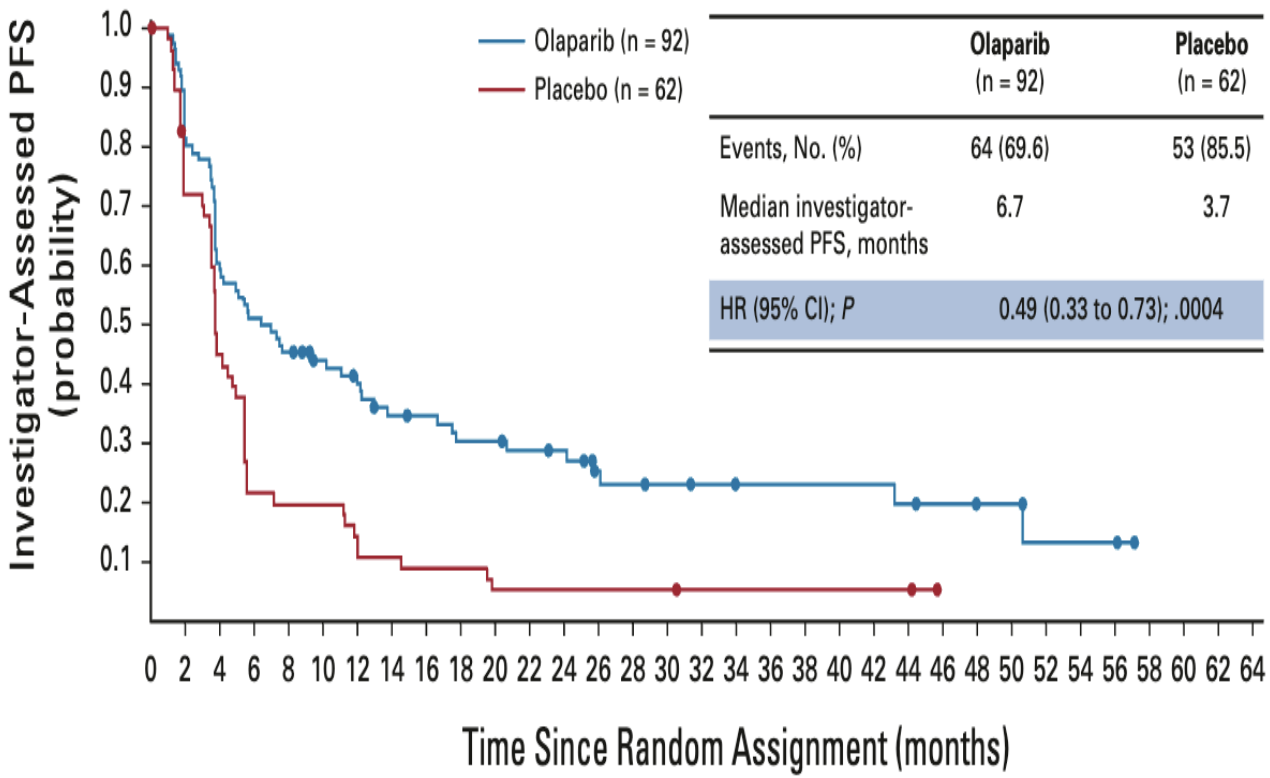


	Olaparib (n = 92)	Placebo (n = 62)
Events, No. (%)	61 (66.3)	47 (75.8)
Median OS, months	19.0	19.2
HR (95% CI); *P*	0.83 (0.56 to 1.22); .3487	
Ongoing investigational treatment at DCO, No. (%)	13 (14.1)	2 (3.2)

No. at risk:

Olaparib	92	88	84	79	72	66	61	58	52	48	43	38	34	31	23	22	19	17	15	12	11	10	7	6	5	4	3	3	3	2	1	1	0
Placebo	62	62	60	57	53	44	43	40	34	32	28	21	17	16	11	10	8	8	7	6	6	5	5	4	4	1	0						

PFS



	Olaparib (n = 92)	Placebo (n = 62)
Events, No. (%)	64 (69.6)	53 (85.5)
Median investigator-assessed PFS, months	6.7	3.7
HR (95% CI); *P*	0.49 (0.33 to 0.73); .0004	

No. at risk:

Olaparib	92	69	51	44	39	34	30	25	24	21	21	19	17	12	11	10	8	7	7	7	7	7	6	5	4	4	2	2	2	0
Placebo	62	40	25	12	11	11	6	6	5	5	3	3	3	3	3	3	2	2	2	2	2	2	2	0						

Golan T, NEJM 2019; Kindler, JCO 2022

Metastatic pancreatic cancer

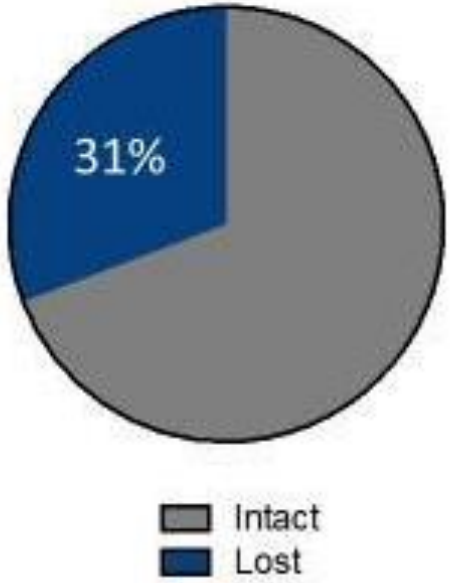
Targeted therapies	Promising targets

KRAS Mutation

TCGA, Cancer Cell 2017
Singhe et al. CCR 2023

KRAS inhibitors

MTAP Loss



Vayrynen et al. in prep

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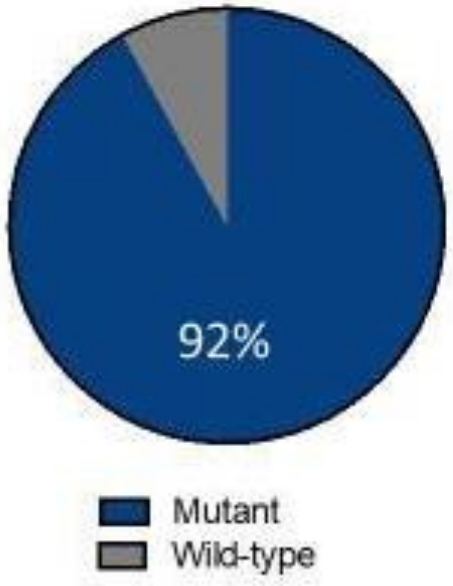
Immunotherapy
WRN inhibitors

Metastatic pancreatic cancer

Targeted therapies	Promising targets

KRAS Mutation



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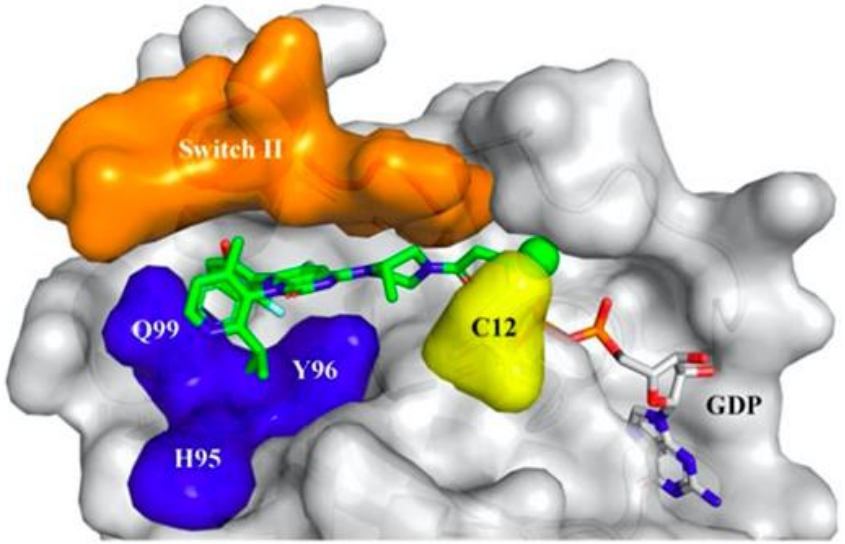
Metastatic pancreatic cancer

Targeted therapies | KRAS inhibitors

2013 bolsillo en G12C pasible de ser bloqueado

RESOLVER EL PROBLEMA DE RAS TIENE ALTA PRIORIDAD EN INVESTIGACIÓN ONCOLÓGICA



KRAS
Carece de bolsillos de U (accesibles como TK)
Alta afinidad por GPT (1 millón de veces superior vs BRAF-ATP)
ON-OFF state

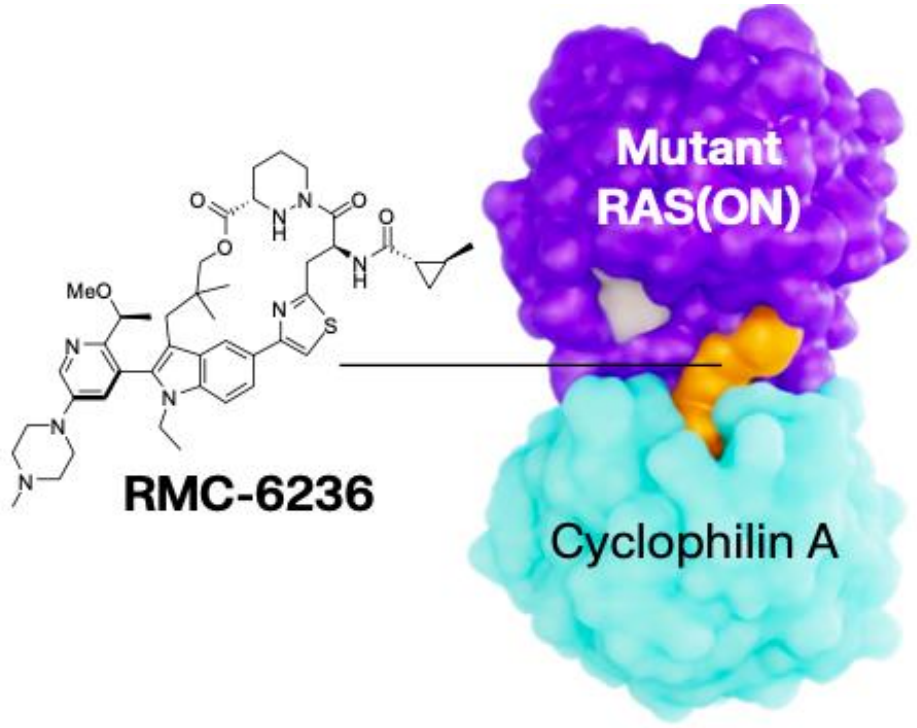
Residuos cisteína en bolsillo de unión
PASIBLE DE MODIFICACIÓN COVALENTE

Metastatic pancreatic cancer

Targeted therapies | KRAS inhibitors

- iKRASG12 D

Molecule	MoA	Company	Status
MRTX1133	Direct G12D Inhibitor	Mirati Therapeutics	Phase 1/2[1]
ASP3082	G12D protein degrader	Astellas Pharma	Phase 1[2]
HRS-4642	Direct G12D Inhibitor	Jiangsu HengRui Medicine	Phase 1[3]
INCB161734	Direct G12D Inhibitor	Incyte	Phase I
RMC-9805	Direct G12D Inhibitor	Revolution Medicines	Phase I



- Inhibidores TRICOMPLEX

-RMC 7977: pre-clínico

-RMC 6236 (The first!)

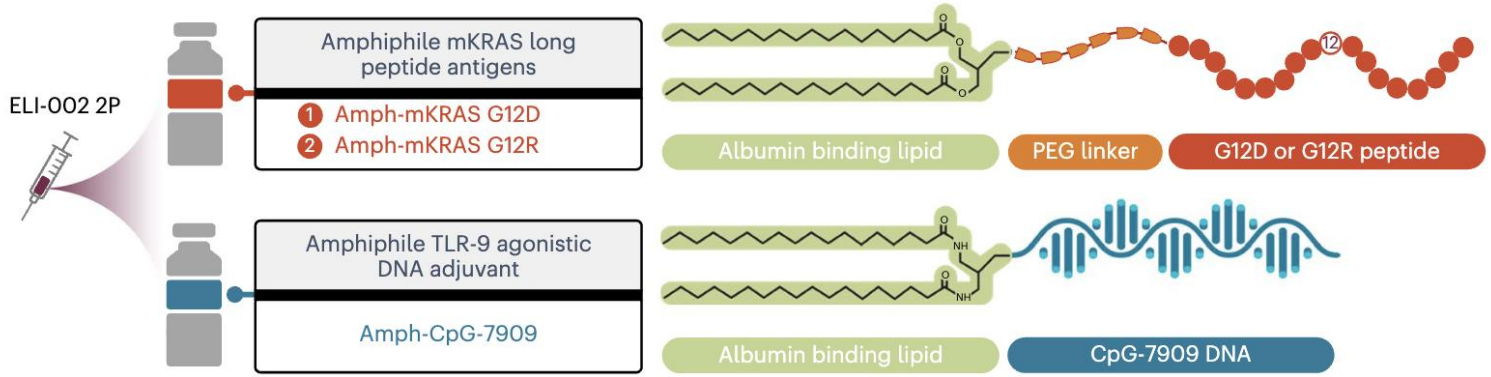
RMC 6236001. ESMO 2023

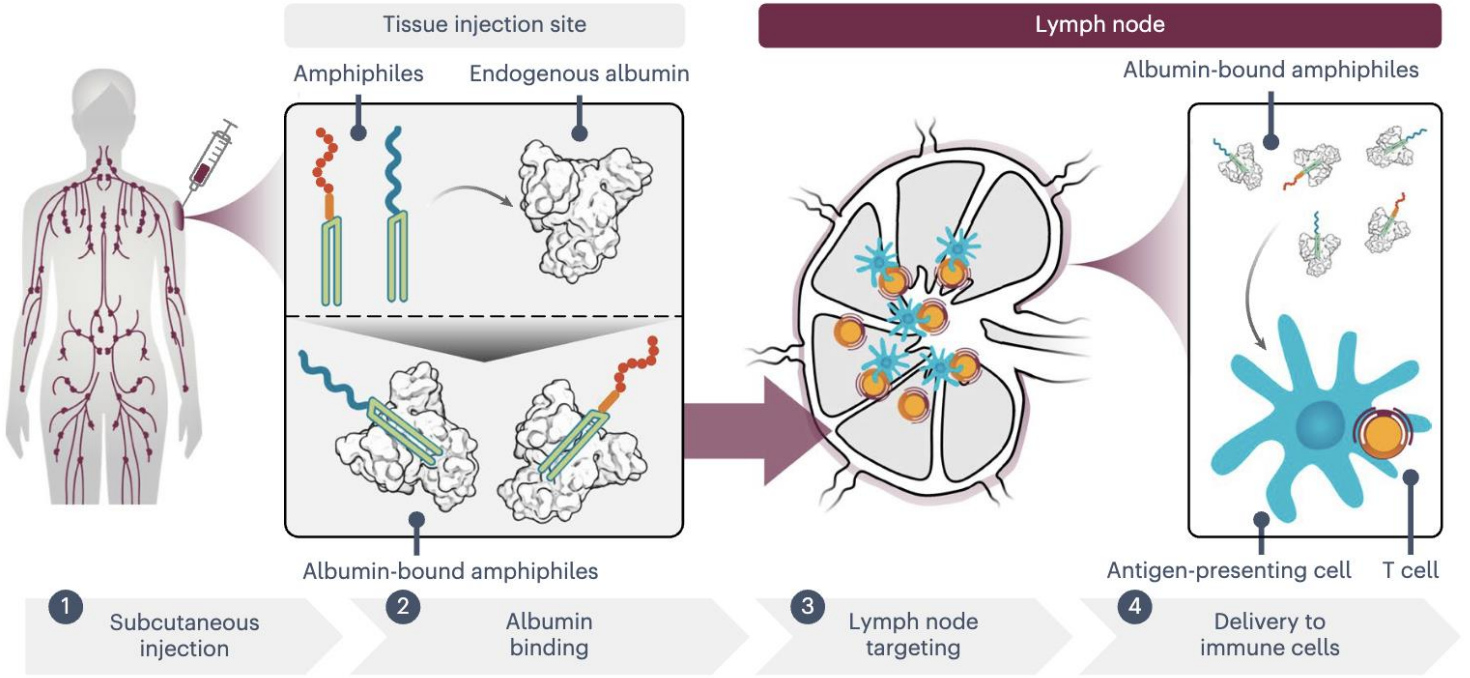
Is there a place for immunotherapies in the management of pancreatic cancer?

Vaccination & PDAC | Shared neoantigens vaccines

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

Nature 2024

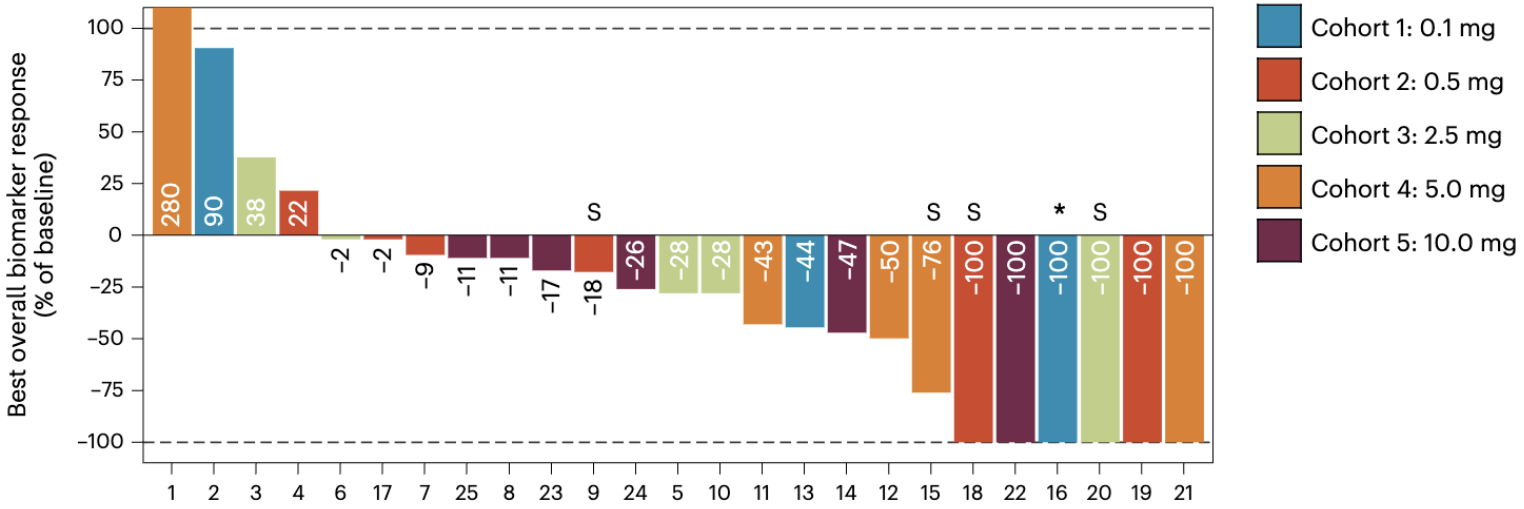


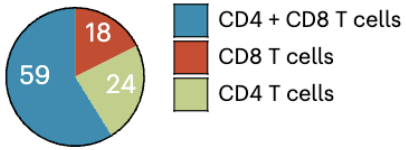


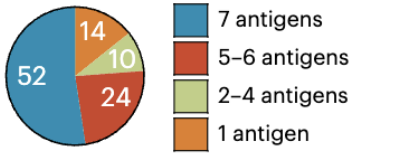
Pant S, Nature Medicine | Volume 30 | February 2024 | 531–542

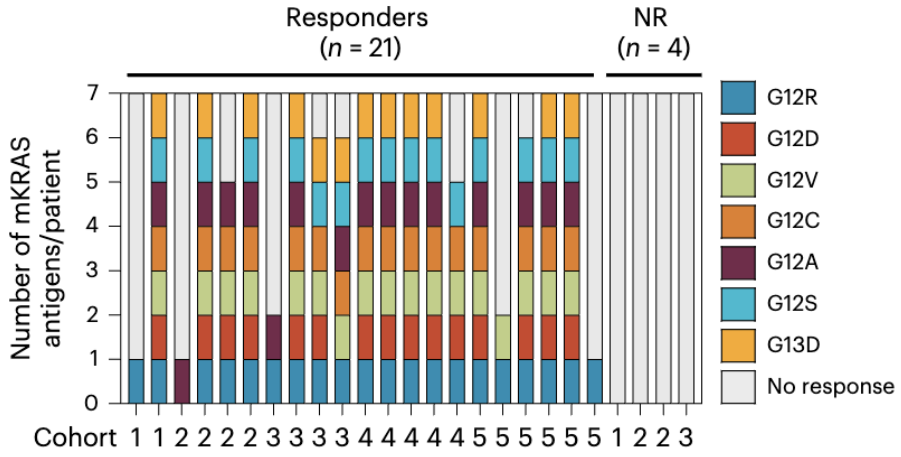
Is there a place for immunotherapies in the management of pancreatic cancer?

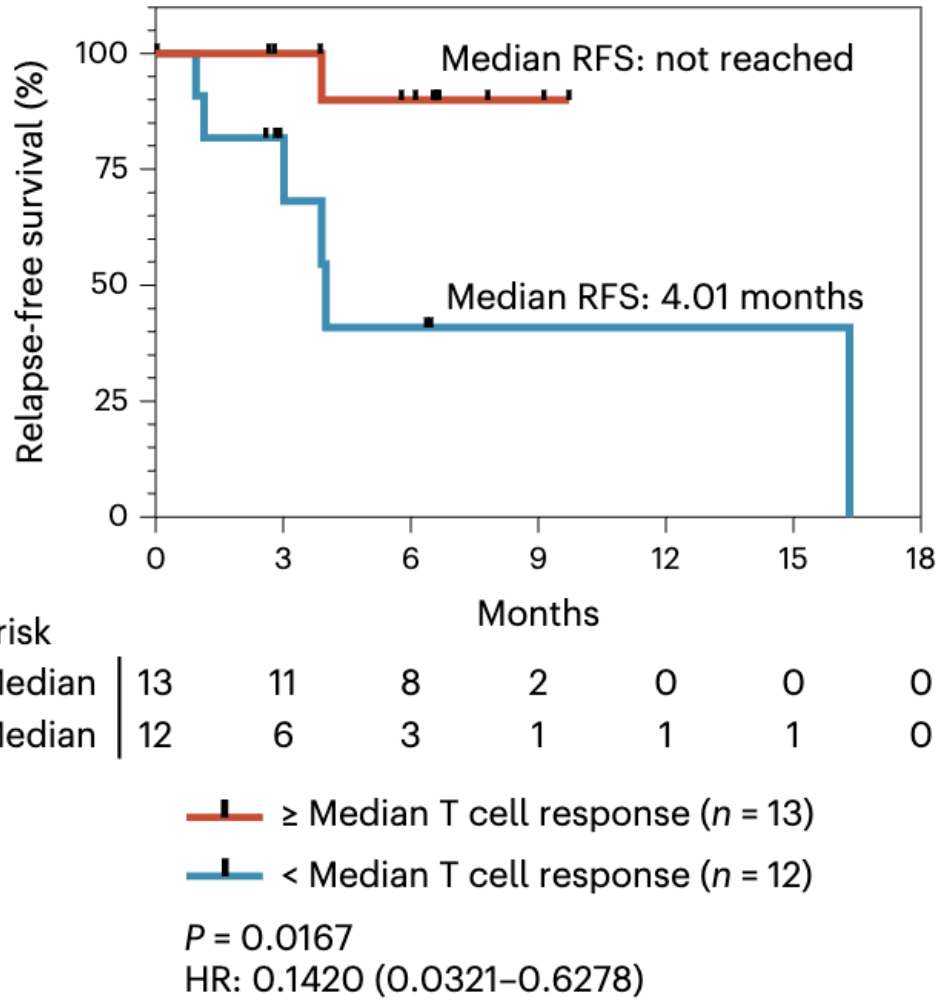
Vaccination & PDAC | Shared neoantigens vaccines





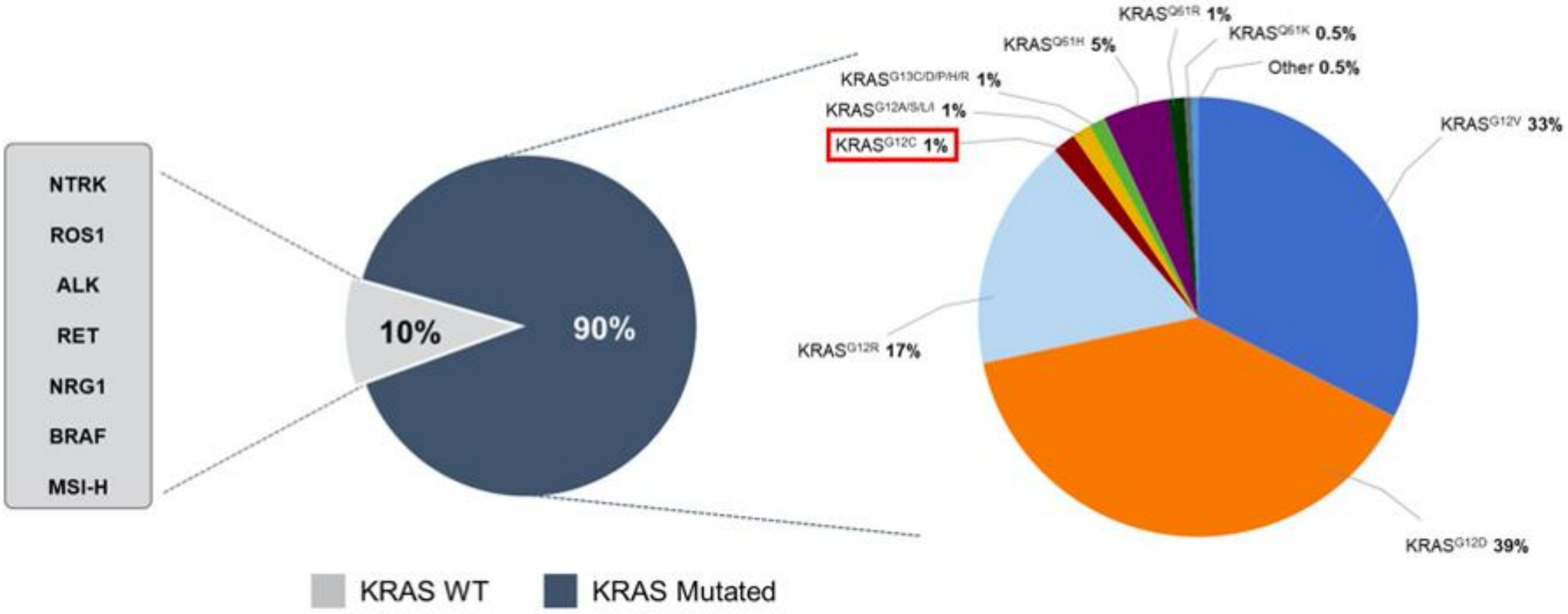






Metastatic pancreatic cancer

Targeted therapies	Promising targets



Qué podemos ofrecer ante un hallazgo?

TRATAMIENTOS APROBADOS (agnóstico / páncreas)
MSI H: pembrolizumab (1%): KN168. SVm 4 m→ NO les va tan bien/ Nivo-Ipi / Dostarlimab
NTRK (1%): 3 ptes tratados con entrectinib con RP (entrectinib, larotrectinib)
BRCA mut (germinal): 6-7% (hasta 15% en ciertas etnias) → mejor Px, sensibilidad a platino

ATM, ATR, ATRX, or BAP1, BARD1, BRIP1, CHEK1/2, RAD50/ 51/51B o FANCA/C/D2/F/G/L

KRAS WT 10% (hasta 38% de hallazgos de mut accionables)
BRAF 10% (vs 1-2%) dabrafenib-trametinib
HER2. 2.5% amp, 16-39% sobreexp, 1% mut (DESTINY PAN TUMOR) Trastu Deruxtecan
ALK 1.3% (vs 0.16%)
RET 1.35% (vs 0.6%): Libretto 001 Selpercatinib (n 45 PDAC pre-tratados→ TR 54%)
NRG1 17% (vs 0.6%) en pacientes jóvenes: Seribantumab , Zenocutuzumab

CDKN2 16% (on trial PI3K + iciclinas)

FUNDACION MARIE CURIE
Córdoba - Argentina

Congreso sobre Avances Integrados en Oncología, Radiocirugía y Física Médica: Innovación y Precisión en el tratamiento del cáncer

Gracias

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