Biomarkør-drevet medicinsk behandling af pankreascancer

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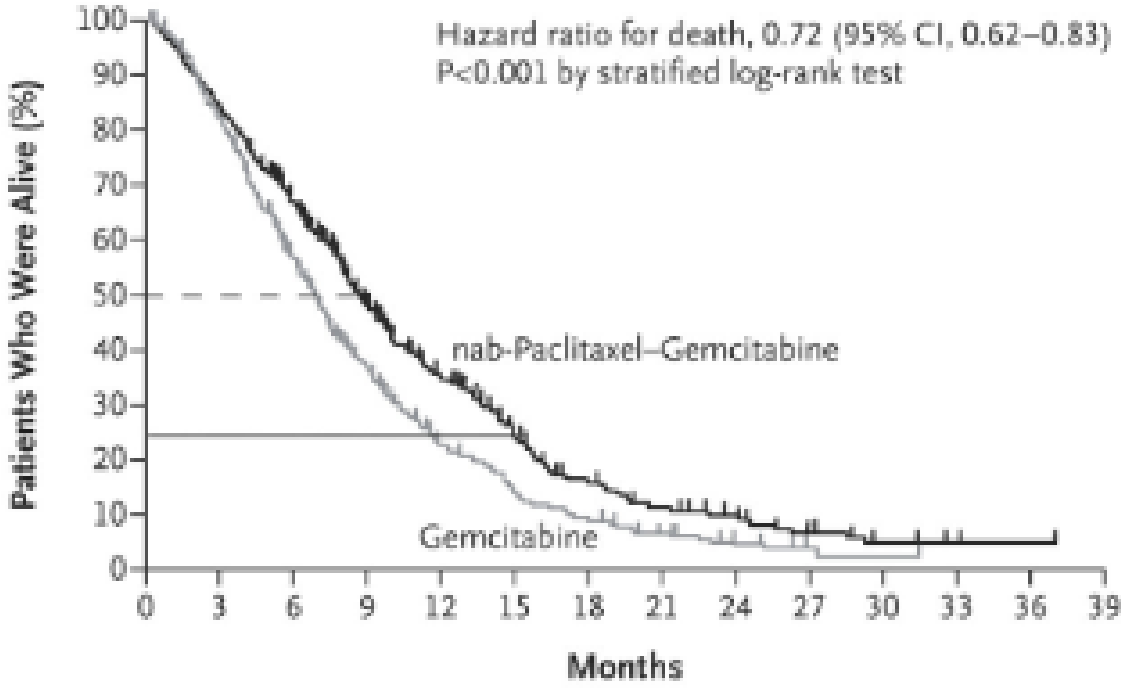
Valg af kemoterapi

- Performance status (0-2)
- Alder
- Specifik komorbiditet
- Præferencer (patient/læge)
- Compliance/logistik
- Fragility

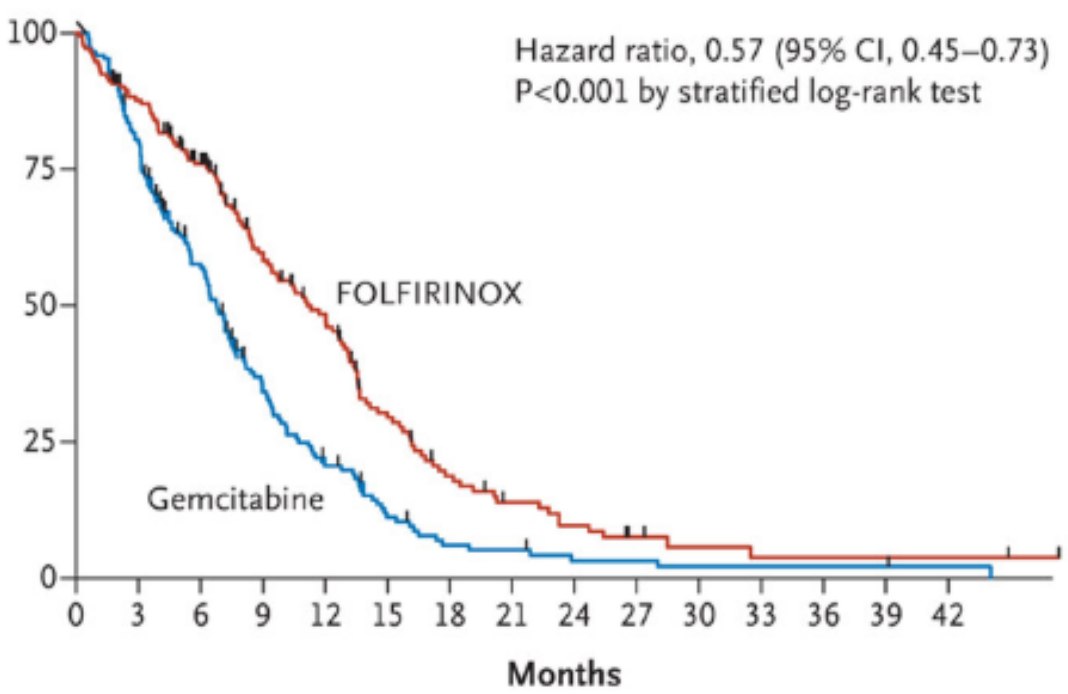
- Gemcitabin
- Gemcitabin/*nab*-paclitaxel
- Folfirinox
- Gemcitabin/flouracil (S1/cap)
- (Nalirifox)

- QoL/tid til forværring
- Livslængde
- (Neo)adjuverende
- Downstaging (respons)
- Bivirkninger

Gem-nab vs gem



Folfirinox vs gem



QoL og tid til forværring er også bedre ved kombinationskemoterapi vs gem

Gem-nab vs gem

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

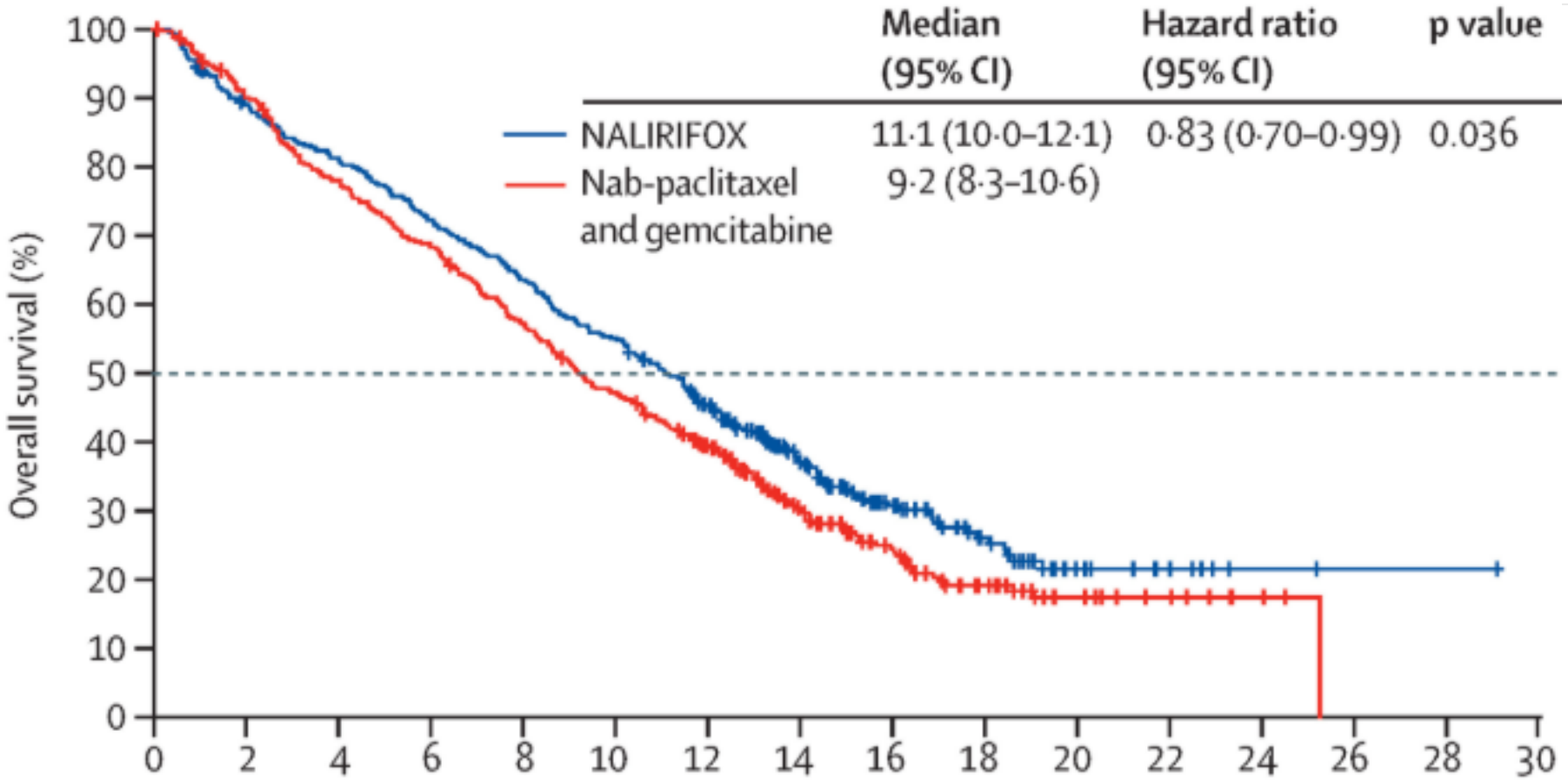
Event	nab-Paclitaxel plus Gemcitabine (N=421)	Gemcitabine Alone (N=402)
Adverse event leading to death — no. (%)	18 (4)	18 (4)
Grade ≥3 hematologic adverse event — no./total no. (%)†		
Neutropenia	153/405 (38)	103/388 (27)
Leukopenia	124/405 (31)	63/388 (16)
Thrombocytopenia	52/405 (13)	36/388 (9)
Anemia	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

Folfirinox vs gem

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

Nalirifox vs gem-nab



Nalirifox vs gem-nab

	NALIRIFOX (n=370)	Nab-paclitaxel and gemcitabine (n=379)
Median duration of treatment, weeks	24·3 (0·4–100·9; 8·4–42·1)	17·6 (0·7–81·7; 8·1–30·1)
Median number of treatment cycles	5·0 (1–24; 2–10)	4·0 (1–20; 2–7)
Any dose reductions	220 (60%)	204 (54%)
TEAEs of grade 3–4 occurring in ≥5% of patients in either treatment arm		
Diarrhoea	75 (20%)	17 (5%)
Nausea	44 (12%)	10 (3%)
Vomiting	26 (7%)	8 (2%)
Decreased appetite	32 (9%)	10 (3%)
Hypokalaemia	56 (15%)	15 (4%)
Fatigue	23 (6%)	20 (5%)
Asthenia	33 (9%)	19 (5%)
Neutropenia	52 (14%)	93 (25%)
Neutrophil count decreased	36 (10%)	51 (14%)
Anaemia	39 (11%)	66 (17%)
Peripheral neuropathy	12 (3%)	22 (6%)
Increased γ-glutamyltransferase	23 (6%)	21 (6%)

SÅ HVAD ER BEDST

Gem-nab eller Folfirinox ?

Nalirifox eller Folfirinox ?

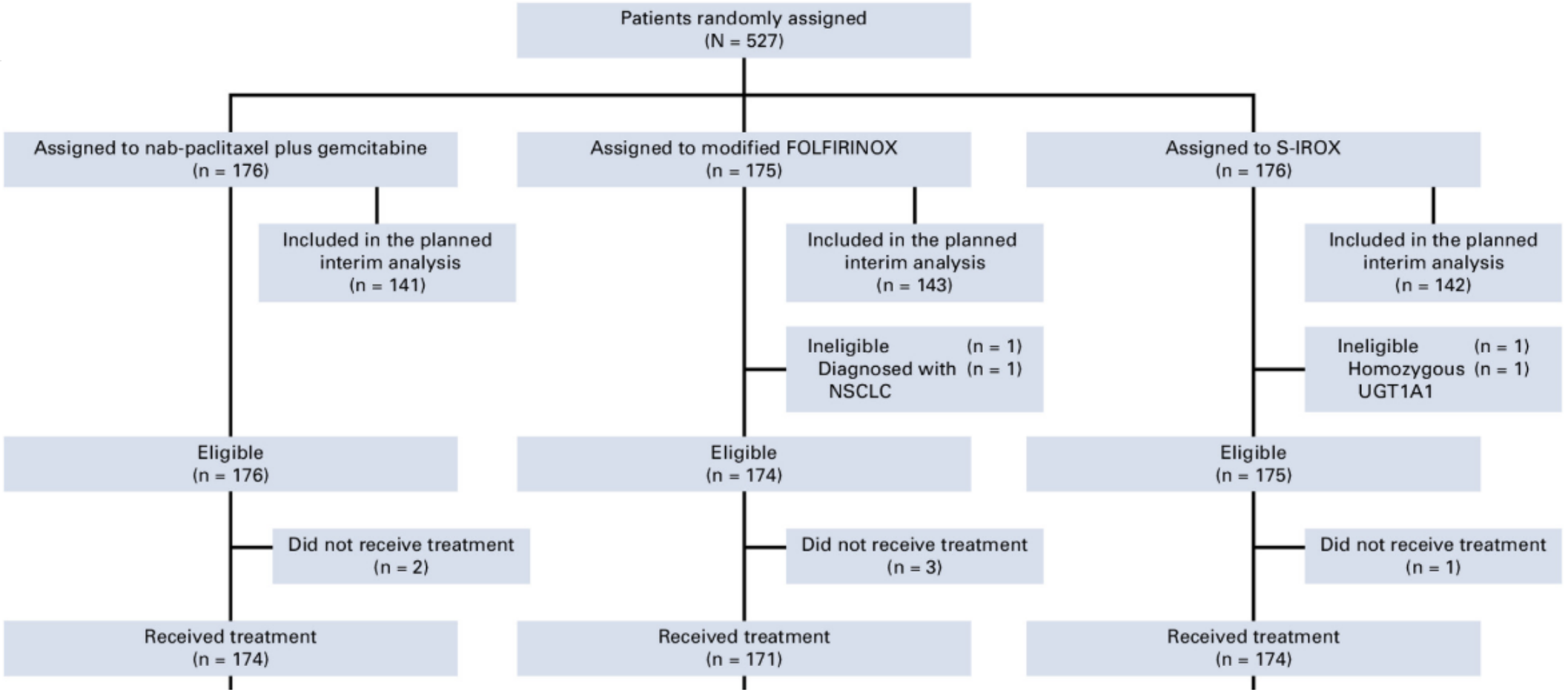
EDITORIALS | October 01, 2025

Personalizing Chemotherapy in Metastatic Pancreatic Cancer

Author: Thomas Seufferlein, MD, PhD AUTHORS INFO & AFFILIATIONS

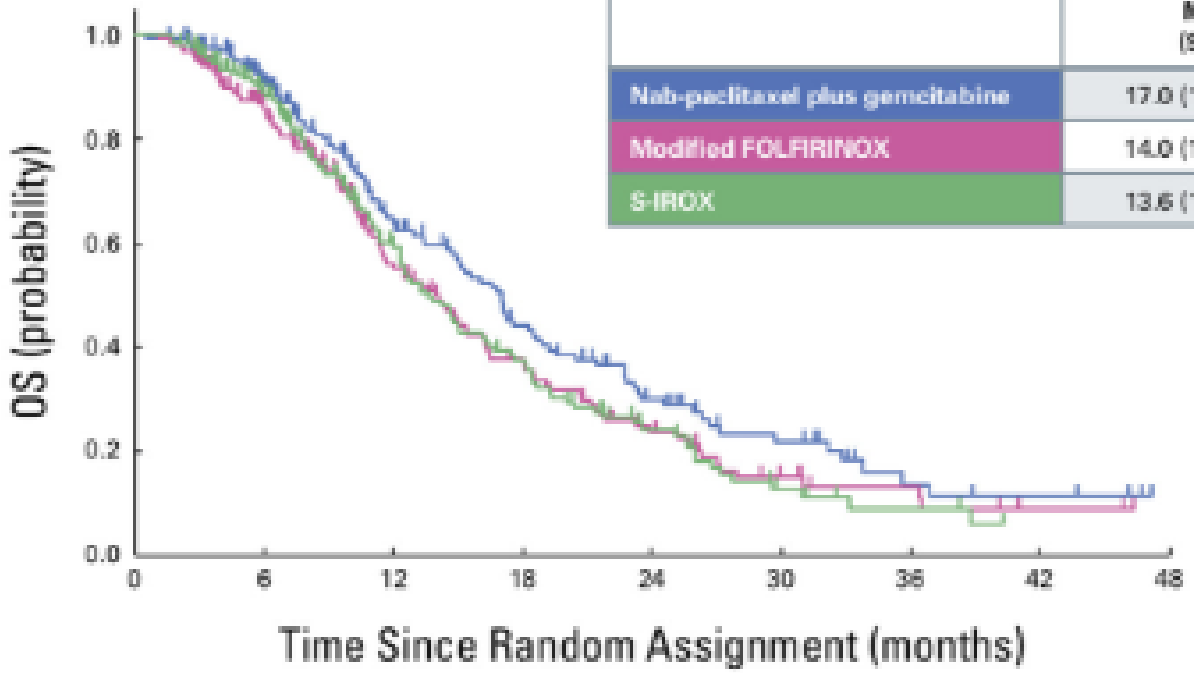
J Clin Oncol **43**, 3327-3330(2025) • Volume 43, Number 31 • DOI: 10.1200/JCO-25-01786

GENERATE, JCOG1611 phase II/IIItrial



DOI: 10.1200/JCO.24.00936

GENERATE, JCOG1611 trial



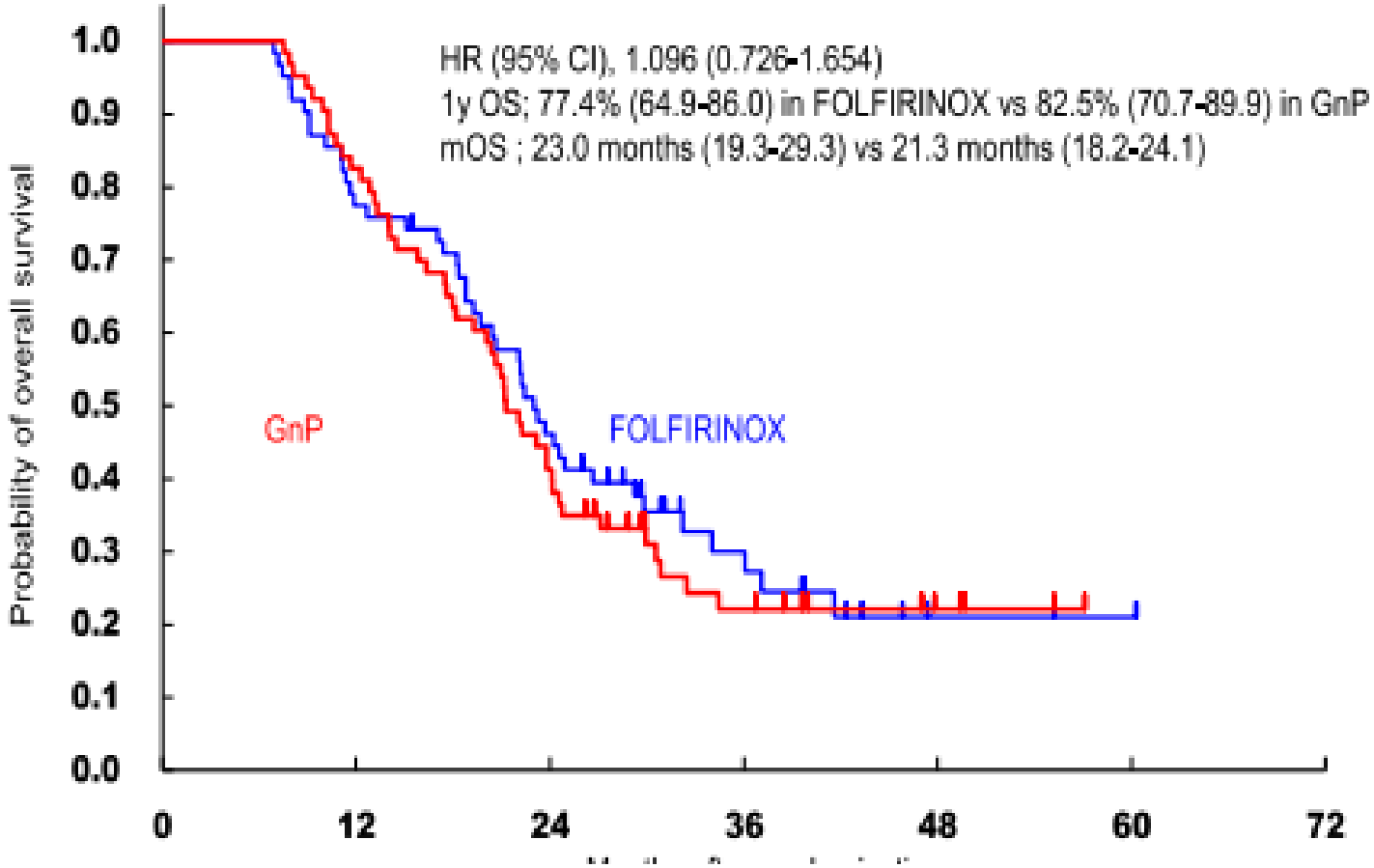
	Median (95% CI)	Hazard Ratio (95% CI)
Nab-paclitaxel plus gemcitabine	17.0 (14.5 to 18.9)	–
Modified FOLFIRINOX	14.0 (11.4 to 16.3)	1.29 (0.98 to 1.70)
S-IROX	13.6 (12.3 to 16.3)	1.29 (0.98 to 1.70)

PFS1 var ens, men PFS2 var bedre ved gem-nab (irinotecanresistens ved tidligere behandling med Folfirinox eller S-Irifox?)

In conclusion, mFOLFIRINOX or S-IROX did not appear to show superiority compared with nab-paclitaxel + gemcitabine as the first-line treatment for metastatic or recurrent pancreatic cancer.

DOI: 10.1200/JCO.24.00936

A randomised phase II study of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel for locally advanced pancreatic cancer (JCOG1407)☆

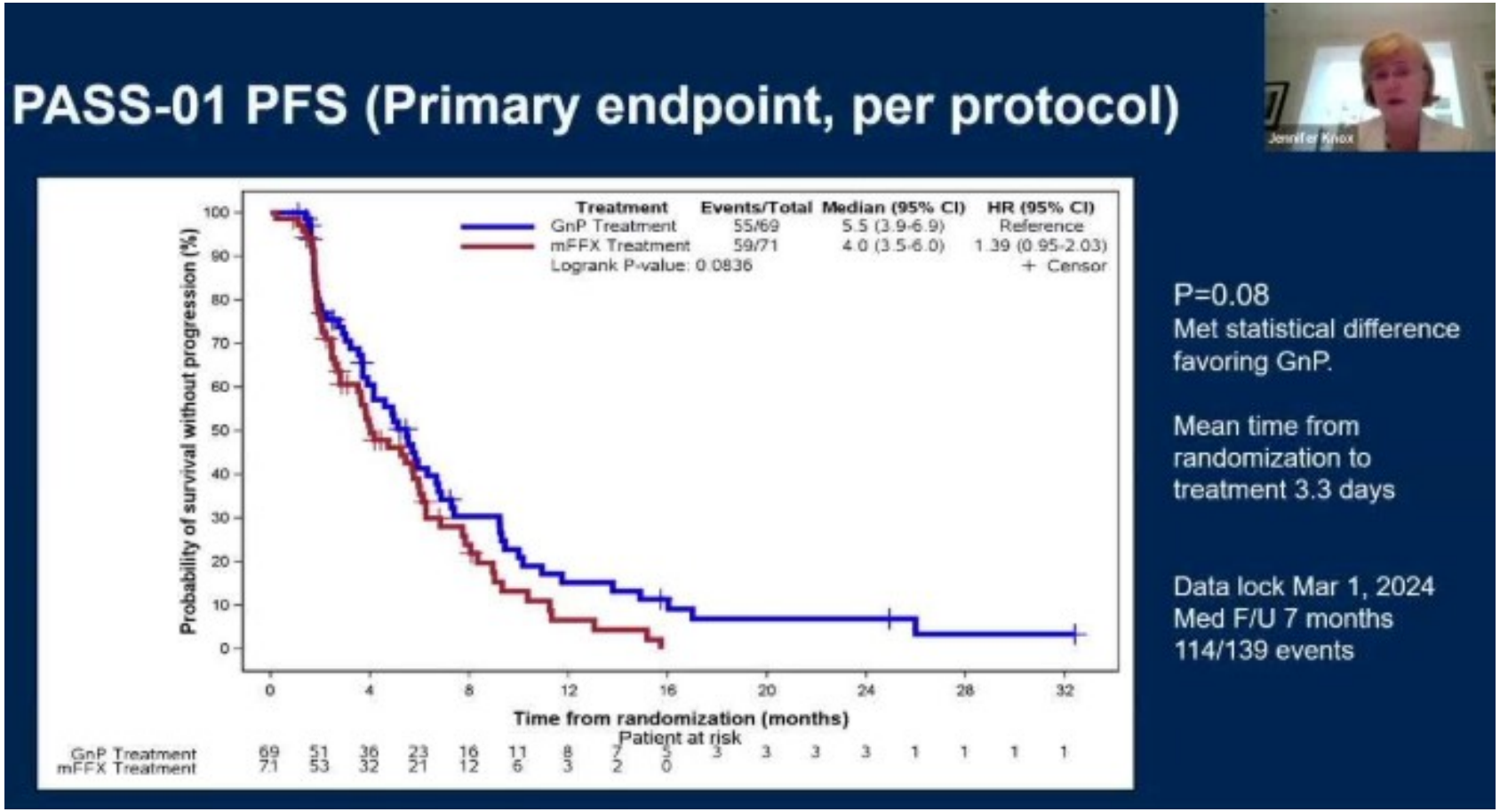


In conclusion, mFOLFIRINOX and GnP displayed comparable efficacy and safety for LAPC. We considered GnP as the candidate for the subsequent phase III trial because of its better RR, DCR, and CA19-9 response and mild gastrointestinal toxicities.

https://doi.org/10.1016/j.ejca.2022.12.014

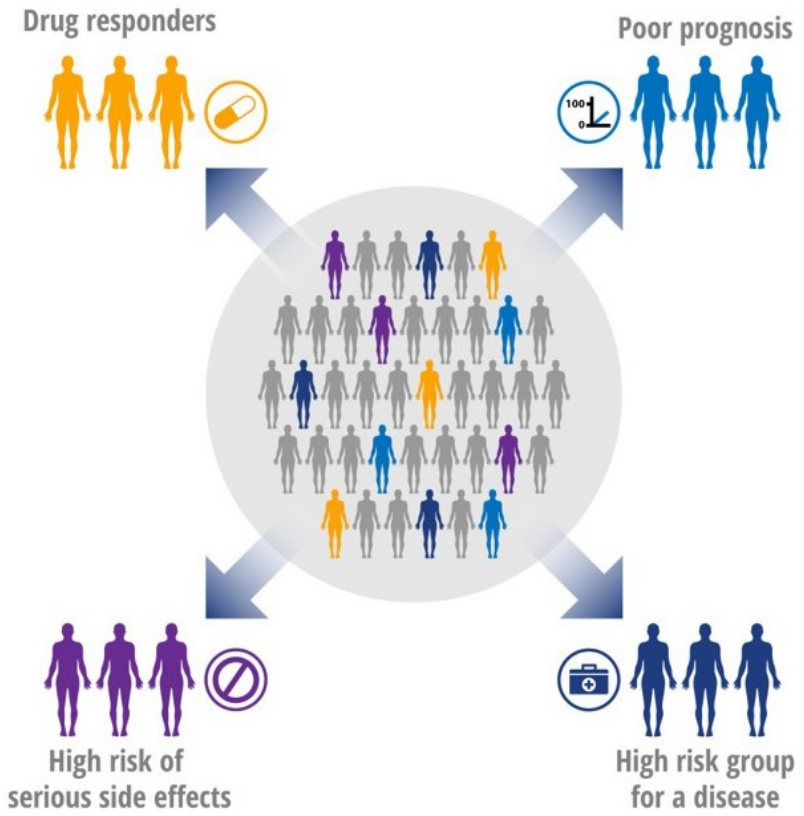
Gem-nab vs mFolfirinox

PASS-01: Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer



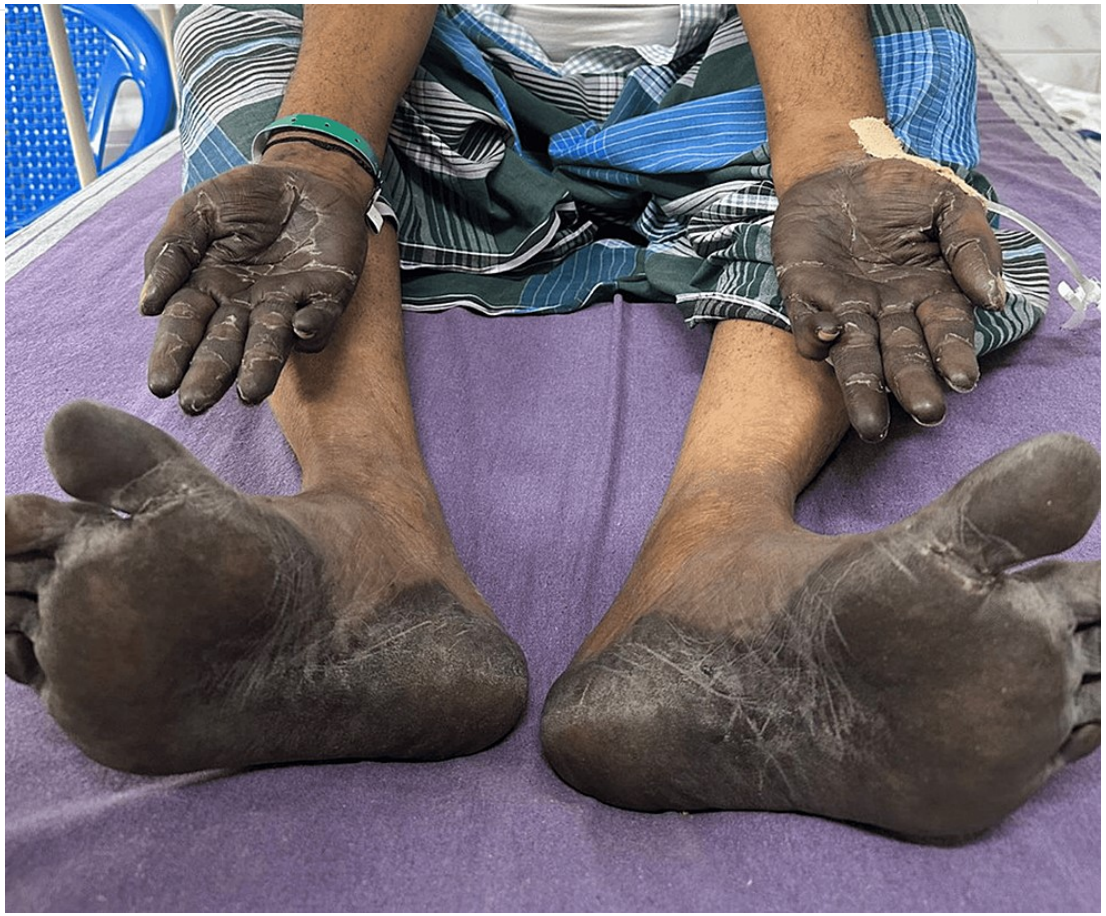
DOI: 10.1200/JCO-25-00436

Biomarkører for kemoterapivalg udover ECOG performance status



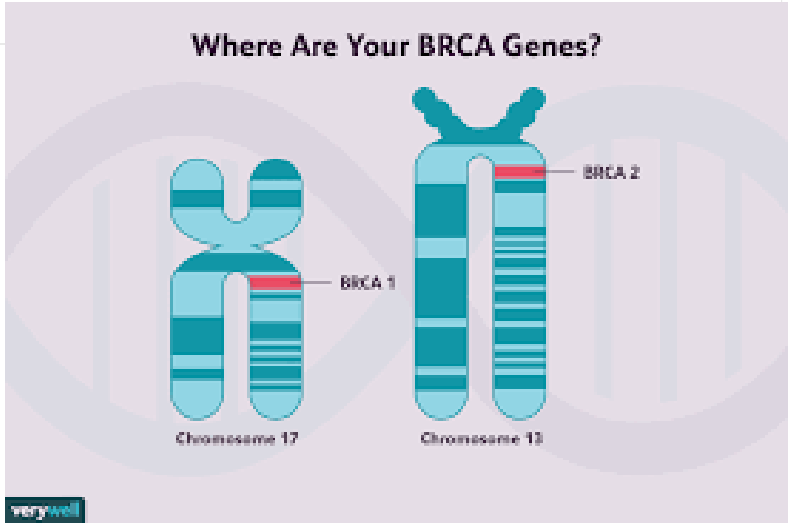
Dihydropyrimidine dehydrogenase deficiency

- DPD mangel-test er obligatorisk i DK
- Tester specifikke gen-varianter og p-uracil (fænotype)
- Nedsat DPD-enzymaktivitet medfører øget toksicitet af flouropyrimidiner
- 6-10% er heterozygote

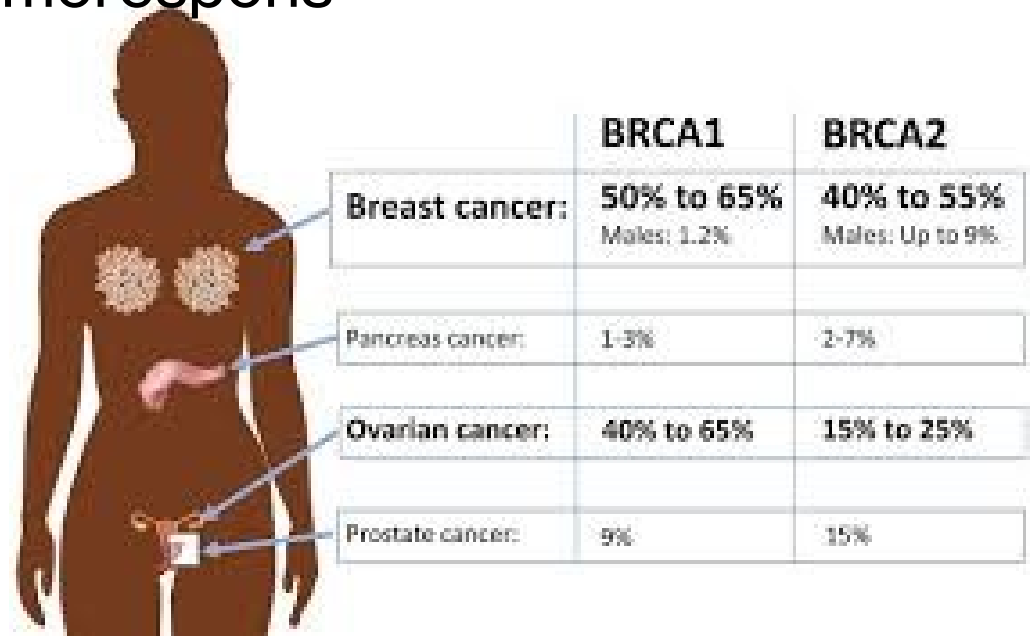


Biomarkører, kemoterapi - BRCA

- Germline *BRCA1/2* mutationer forårsager 5-7% af PC tilfælde
- Livsrisiko for PC er 5-10%
- Mistænkes hos yngre patienter, typisk historik, kraftig kemorespons



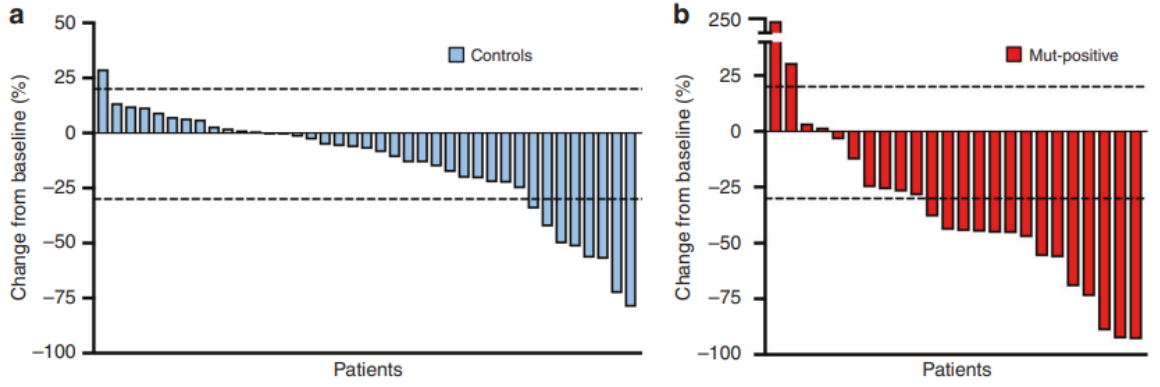
Dominant arvelig med nedsat penetrans

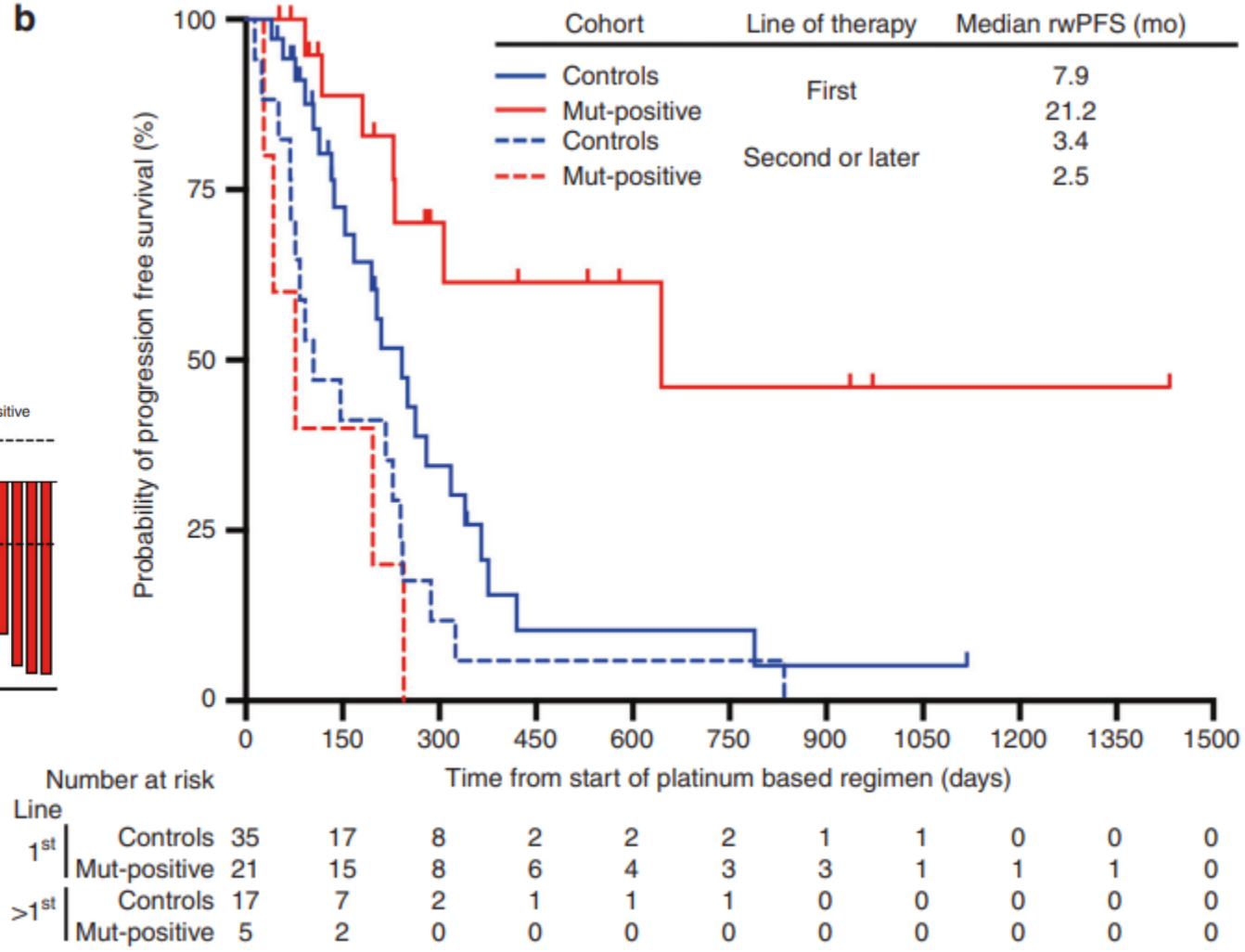


	BRCA1	BRCA2
Breast cancer:	50% to 65% Males: 1.2%	40% to 55% Males: Up to 9%
Pancreas cancer:	1-3%	2-7%
Ovarian cancer:	40% to 65%	15% to 25%
Prostate cancer:	9%	15%

Biomarkører, kemoterapi - BRCA

BRCA-muterede lever 2½ gange længere end ikke-muterede ved platinbaseret 1.-linje kemoterapi





British Journal of Cancer (2020) 122:333–339; https://doi.org/10.1038/s41416-019-0582-7

45-årig kvinde med non-resektabel, lokalt-avanceret PC. Ni år tidligere mammacancer og bilateralt mastektomeret efter påvisning af g*BRCA1* mutation.

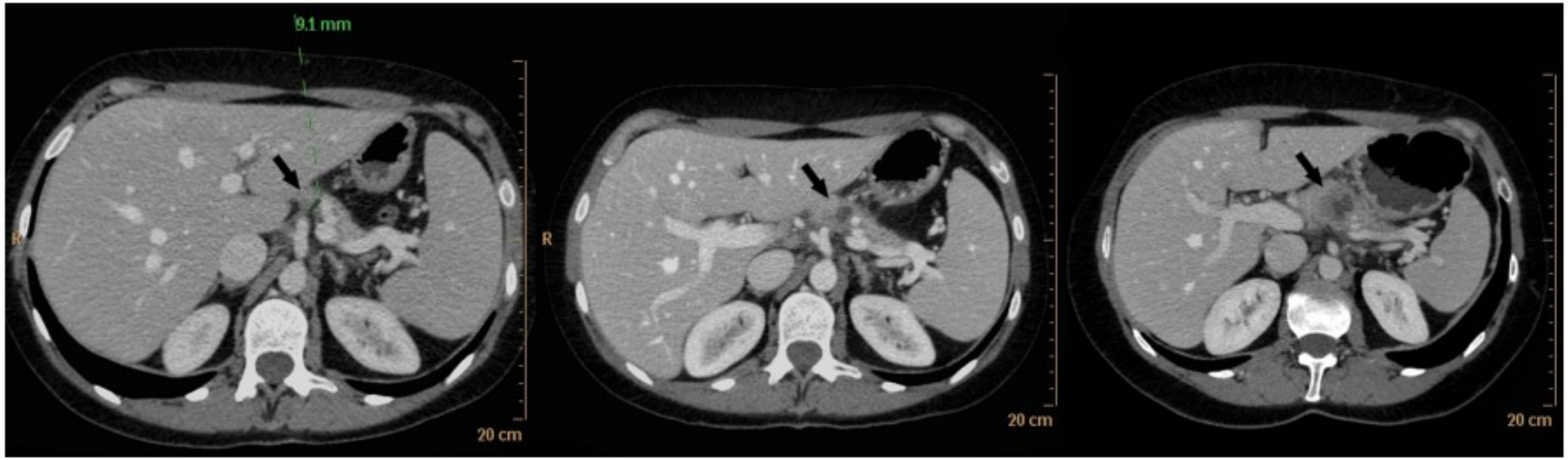
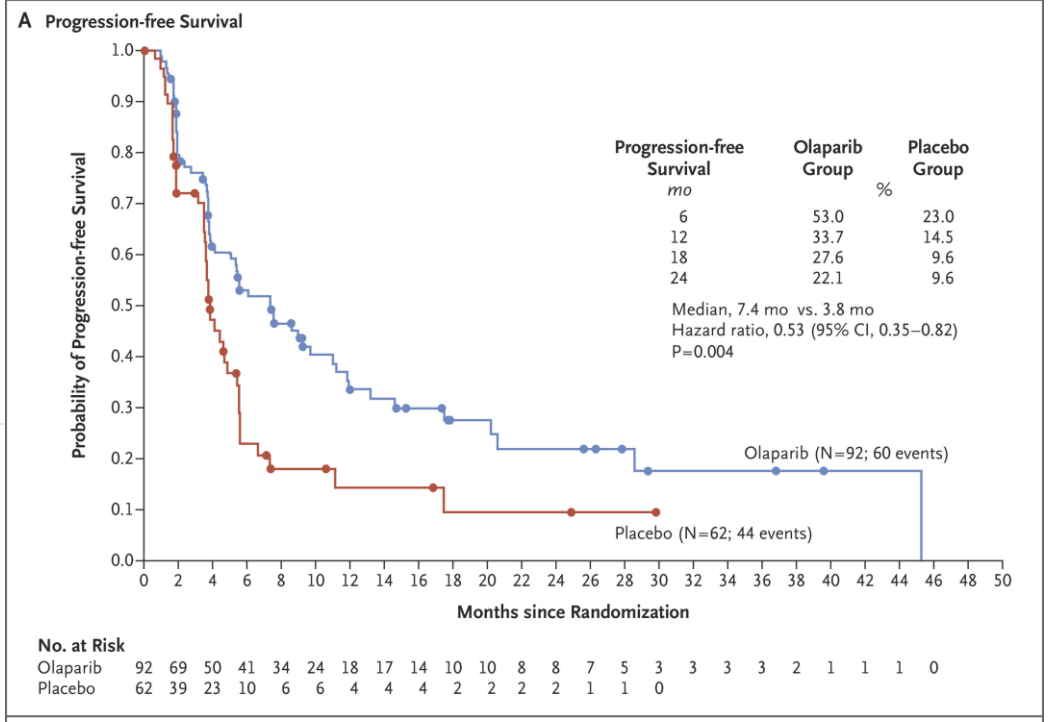


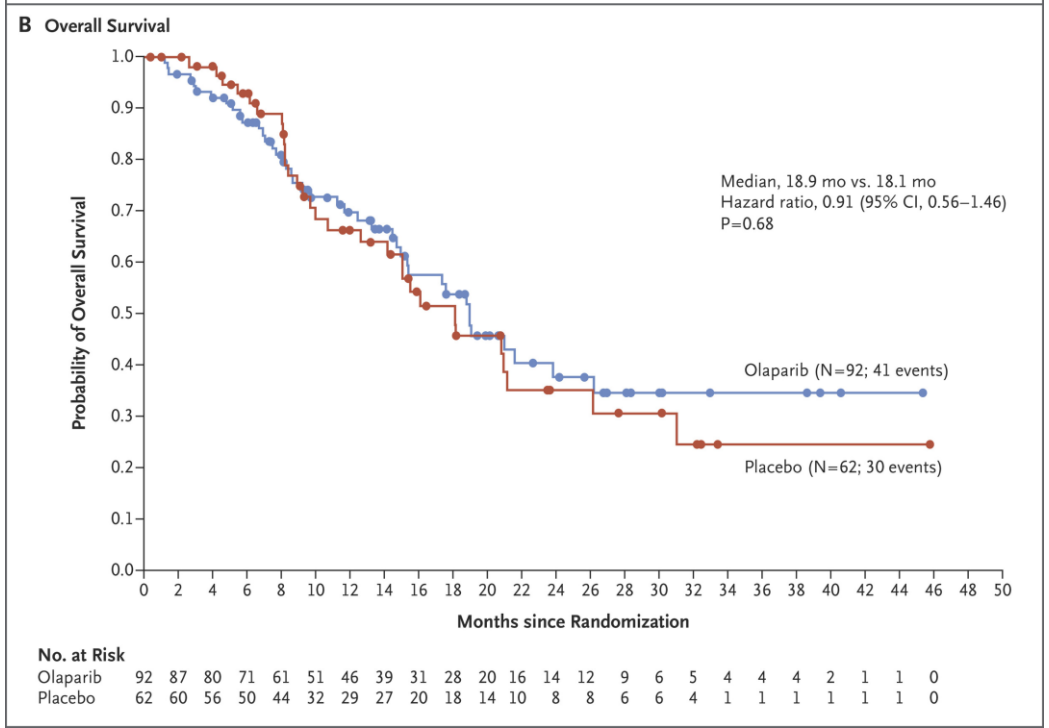
Figure 1. CT images of locally advanced pancreatic adenocarcinoma (arrow) at baseline (right), after four cycles of Folfirinox (middle), and after eight cycles with tumor shrinkage to 9 mm in a 45-year-old female (Case 1) with BRCA1 germline mutation, showing complete pathological response after radical pancreatectomy.

Acta Oncologica, 2016; 55: 377–381

Biomarkører - BRCA

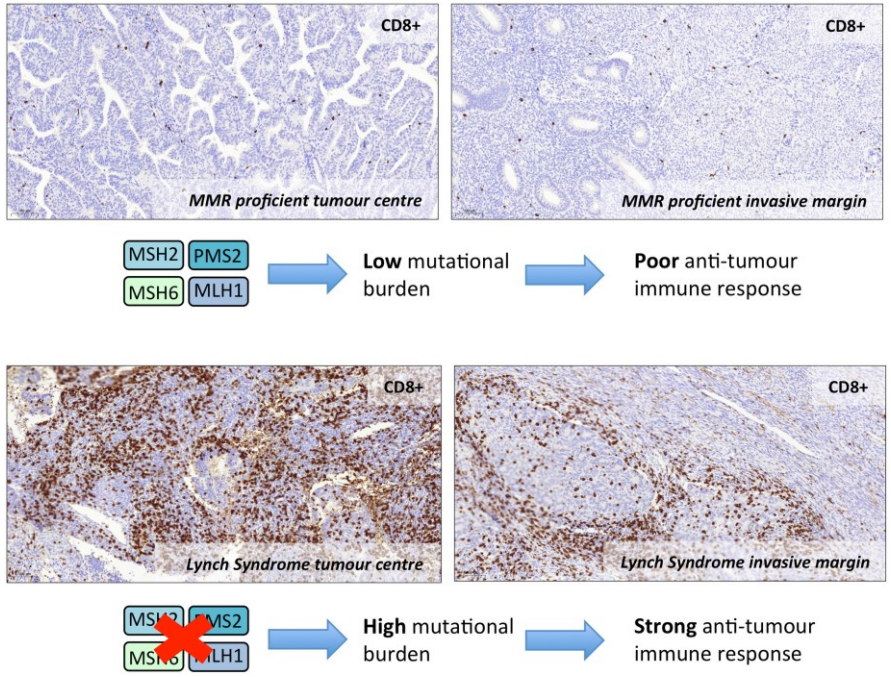
BRCA-mutationer medfører defekt reparation af dobbeltstrengsbrud i DNA, hvorfor cellerne er ekstra følsomme overfor DNA-skadende stoffer, herunder platin og PARP-inhibitorer

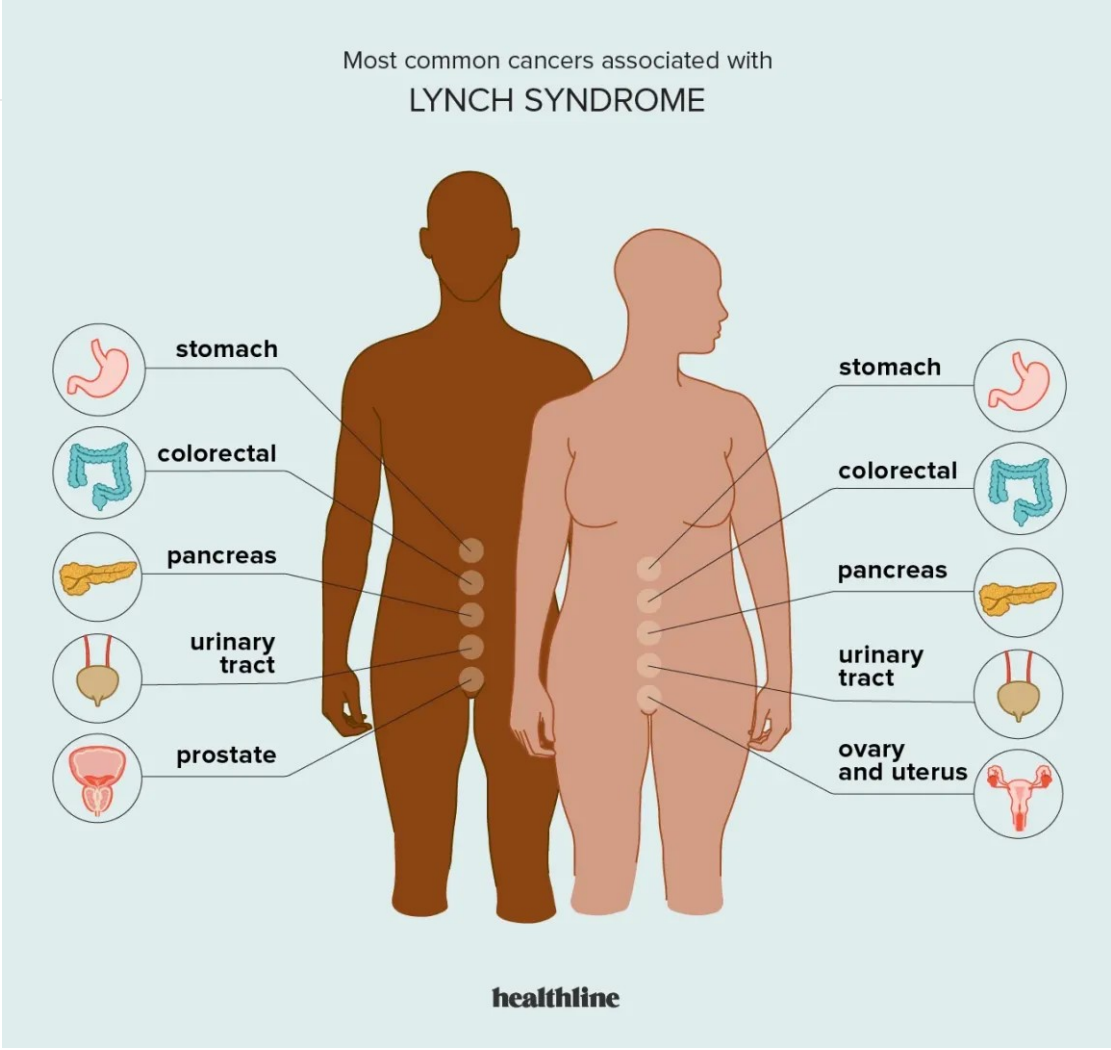




Biomarkør for immunterapi – MSI/dMMR

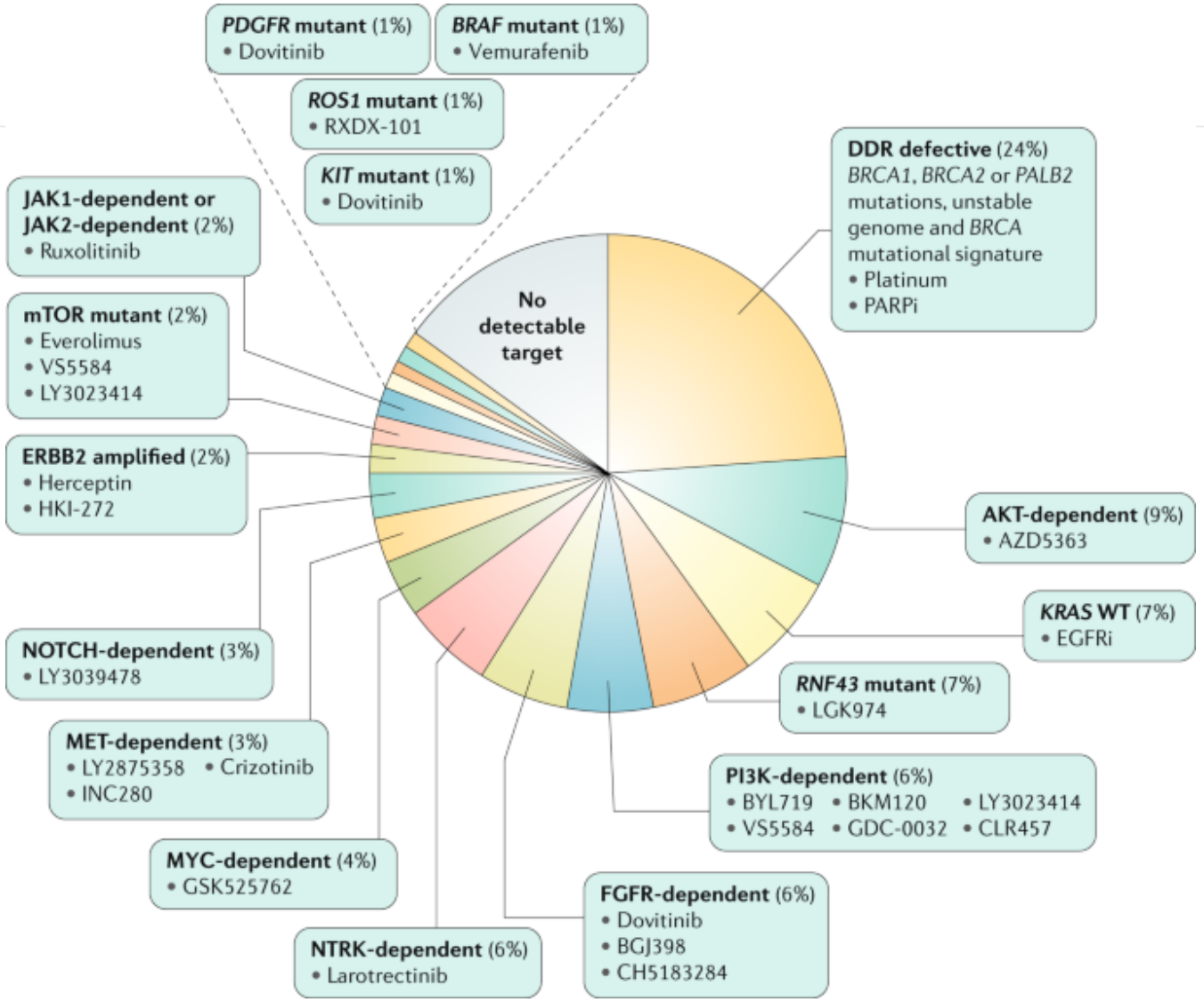
- MSI/dMMR hos 1-2%
- Herunder ved Lynch syndrom
  - 8 x øget risiko for PC
  - Obs. ved ung alder, medullær PC, historik



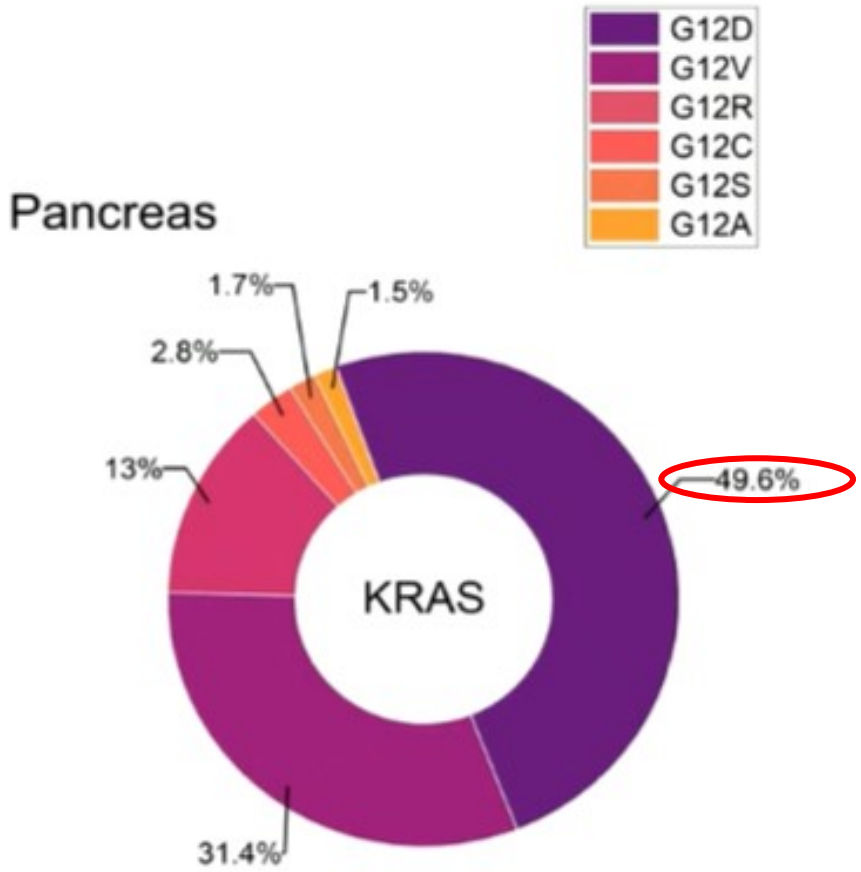


6000 familier i HNPCC-registeret i DK

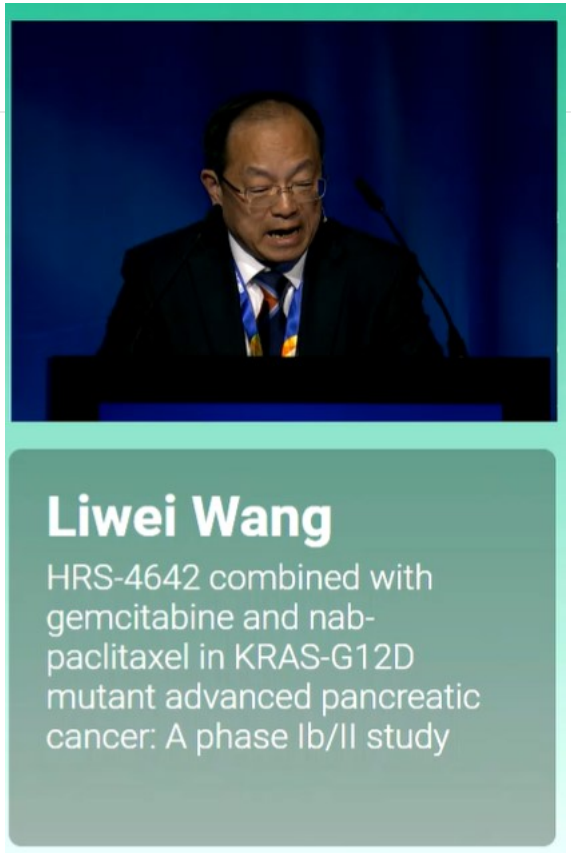
Biomarkører for molekylært målrettet behandling



Målrettet behandling af KRAS på vej



The distribution of distinct KRAS mutations for pancreatic cancer [3]

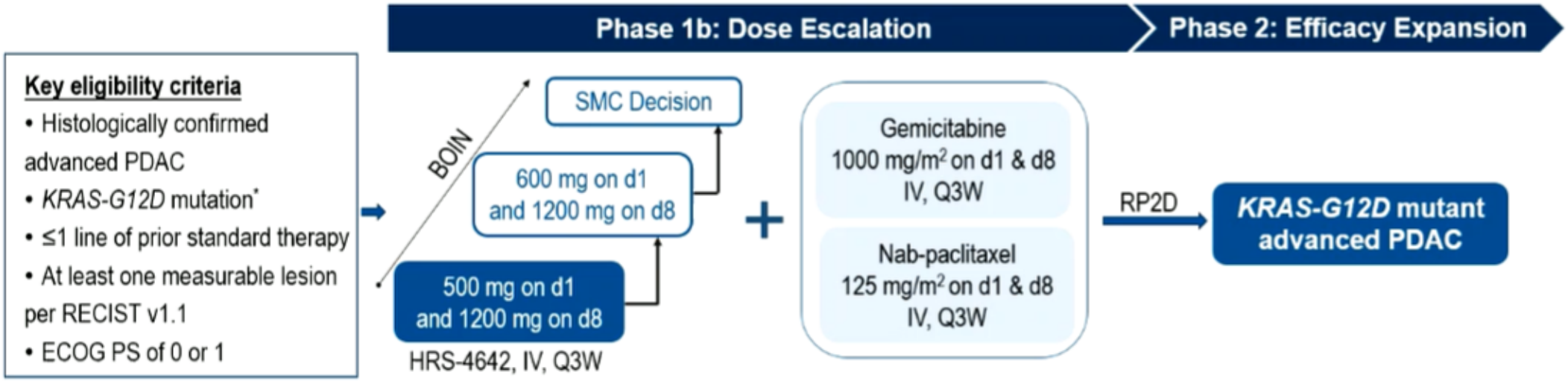


Liwei Wang

HRS-4642 combined with gemcitabine and nab-paclitaxel in KRAS-G12D mutant advanced pancreatic cancer: A phase Ib/II study

Study design

- **A phase 1b/2 study to assess HRS-4642 combined with GA in patients with *KRAS-G12D* mutant advanced PDAC (NCT05533463).**



*KRAS-G12D mutation was centrally assessed.

☐**Primary endpoints**: Safety, DLT

☐**Secondary endpoints**: ORR, DCR, DoR, PFS, OS.

☐**Primary endpoint**: ORR.

☐**Secondary endpoints**: DCR, DoR, PFS, OS.

Data cutoff: Jul 8, 2025

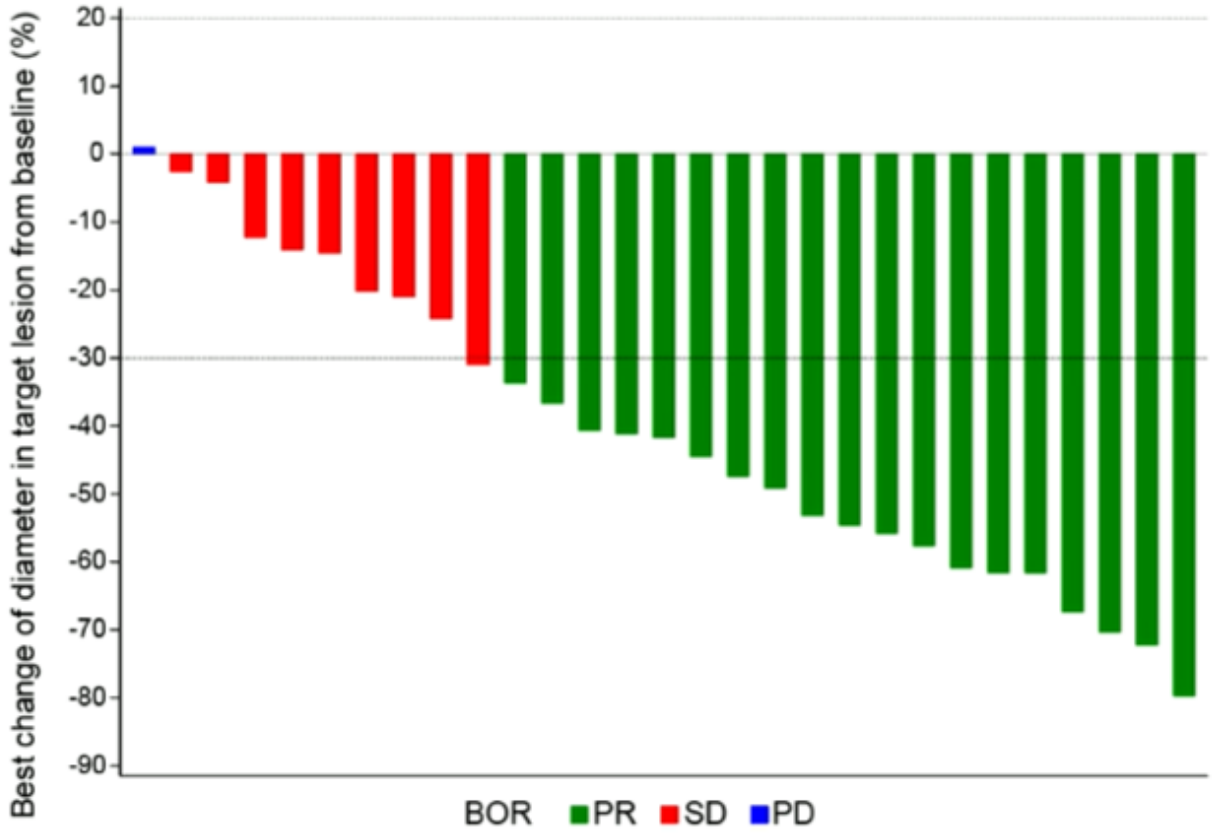
- 4 patients enrolled during dose escalation (HRS-4642 500 mg on d1 and 1200 mg on d8, IV, Q3W).
- No DLTs occurred.
- The median follow-up duration was 7.5 months (IQR: 7.2, 8.2).

ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; BOIN, Bayesian optimal interval; SMC, Safety Monitoring committee; RP2D, recommended phase 2 dose; DLT, dose-limiting toxicity; ORR, objective response rate; DCR, disease control rate; DoR, duration of response; PFS, progression-free survival; OS, overall survival.

Tumor response in previously untreated patients

	HRS-4642 + GA Previously untreated patients (n = 30)
ORR*, % (95% CI)	63.3 (43.9, 80.1)
DCR, % (95% CI)	93.3 (77.9, 99.2)
BOR, n (%)	
PR*	19 (63.3)
SD	9 (30.0)
PD	1 (3.3)
No post-baseline assessment	1 (3.3)

*Confirmed



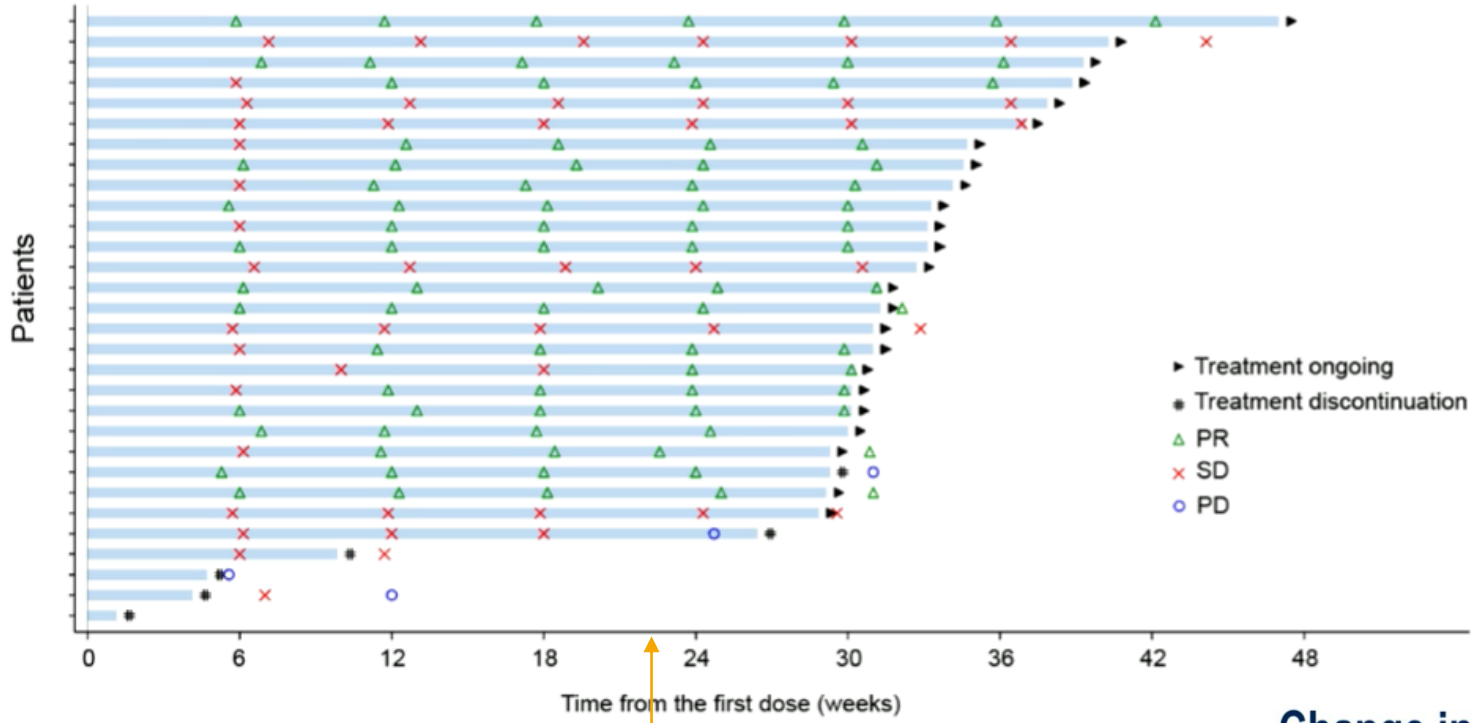
- The previously treated patient had stable disease after the study treatment.

Pro. Liwei Wang

BOR, best overall response; PR, partial response; SD, stable disease; PD, progressive disease.

ORR with gemcitabine and *nab*-paclitaxel in mPC is 23%

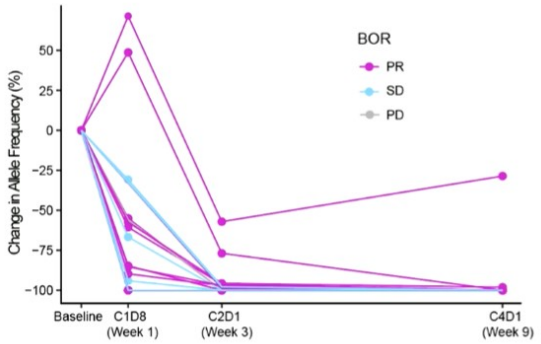
Tumor response over time in previously untreated patients



- Response was ongoing in 18 of the 19 responders; the median duration of response was not reached.

mPFS of gemcitabine and *nab*-paclitaxel

Change in *KRAS-G12D* Variant Allele Frequency in ctDNA



	C2D1 (Week 3) (n = 19*)	C4D1 (Week 9) (n = 18*)
Complete clearance, n (%)	10 (52.6)	16 (88.9)

*20 patients with baseline *KRAS-G12D* ctDNA positivity were evaluable for changes in *KRAS-G12D* variant allele frequency, with 1 patient discontinued treatment prior to week 3 (n = 19) and 1 additional discontinuation by week 9 (n = 18).

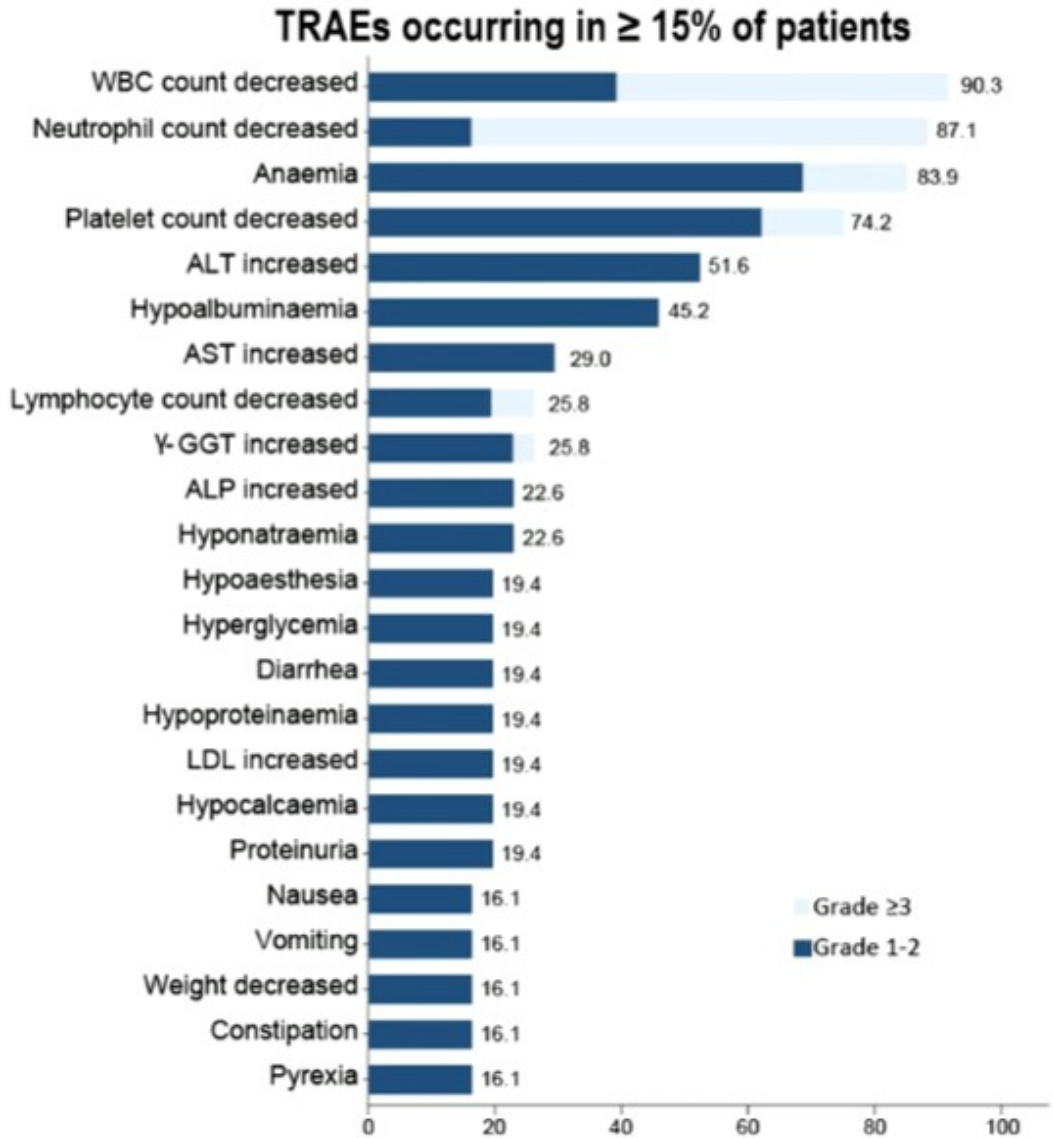
HRS-4642 combined with GA achieved:

- Remarkable and sustained clearance of the *KRAS-G12D* mutant allele;
- A high rate of complete *KRAS-G12D* mutant allele clearance by C4D1.

Liwel Wang, ESMO 2025

Safety

	All patients (N=31)
Any AE, n (%)	31 (100)
Grade ≥ 3	27 (87.1)
Any TRAE, n (%)	31 (100)
Grade ≥ 3	27 (87.1)
Leading to dose reduction	15 (48.4)
Leading to treatment interruption	19 (61.3)
Leading to treatment discontinuation	0
Leading to death	0
Serious	5 (16.1)



AE, adverse event; TRAE, treatment-related adverse event; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALP, Alkaline phosphatase

Pro. Liwei Wang

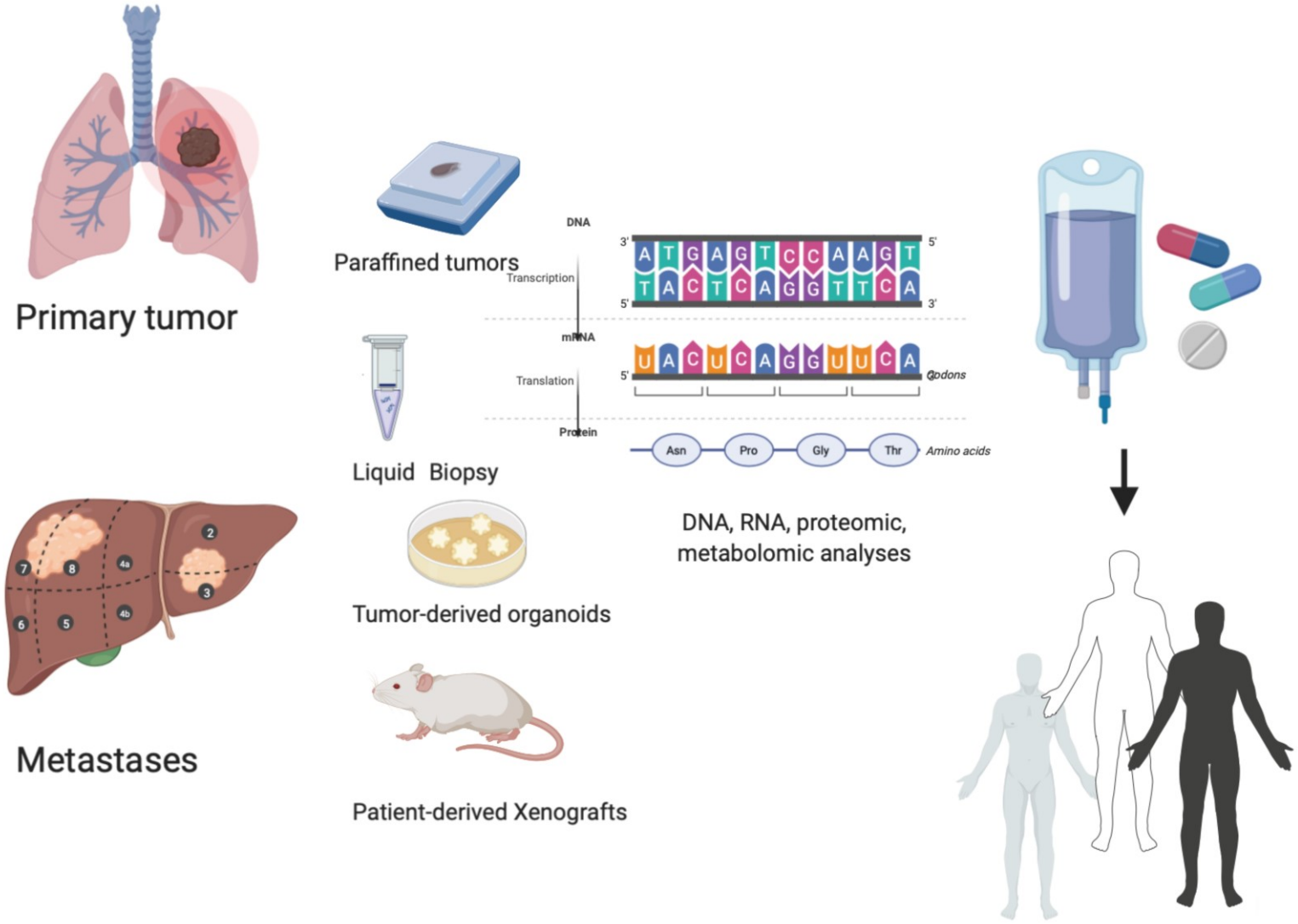
Nye DPCG guidelines for biomarkøranalyse hos patienter med non-resektabel sygdom

Molekylær-genetisk profilering bør foretages hos patienter, der er kandidater til systemisk kræftbehandling, såfremt der er egnet materiale. Undersøgelsen foretages med henblik på valg af førstelinje kemoterapi og senere mulighed for målrettet behandling.

Som minimum bør analyserne omfatte BRCA-mutationer, dMMR/MSI og KRAS-mutationer. Hvis tumor er KRAS-vildtype, bør omfattende molekylær profilering overvejes for at afdække sjældne, men potentielt targeterbare varianter

Ny forskning i biomarkører

Omics biomarkører og funktionelle assays

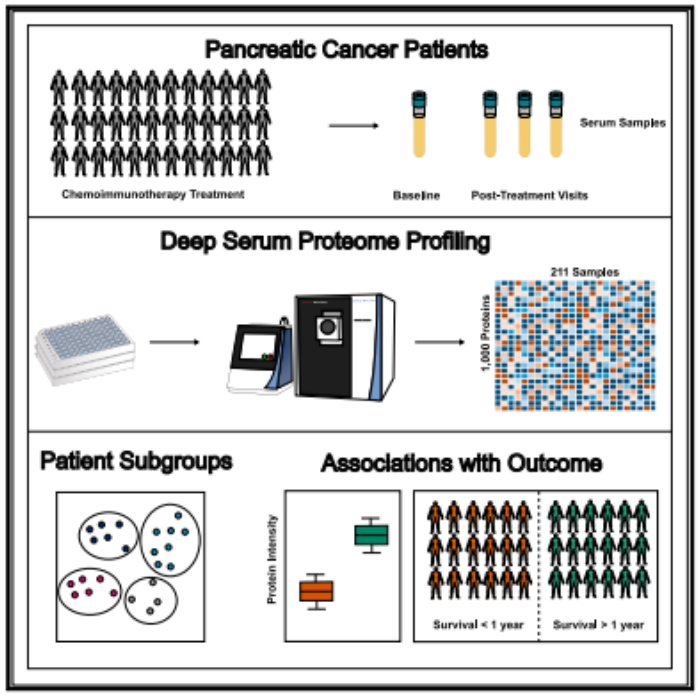


iScience

Article

Serum proteomics reveals survival-associated biomarkers in pancreatic cancer patients treated with chemoimmunotherapy

Graphical abstract



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Marco Tognetti, Lopamudra Chatterjee, Nigel Beaton, Kamil Sklodowski, Roland Bruderer, Lukas Reiter, Christoph B. Messner

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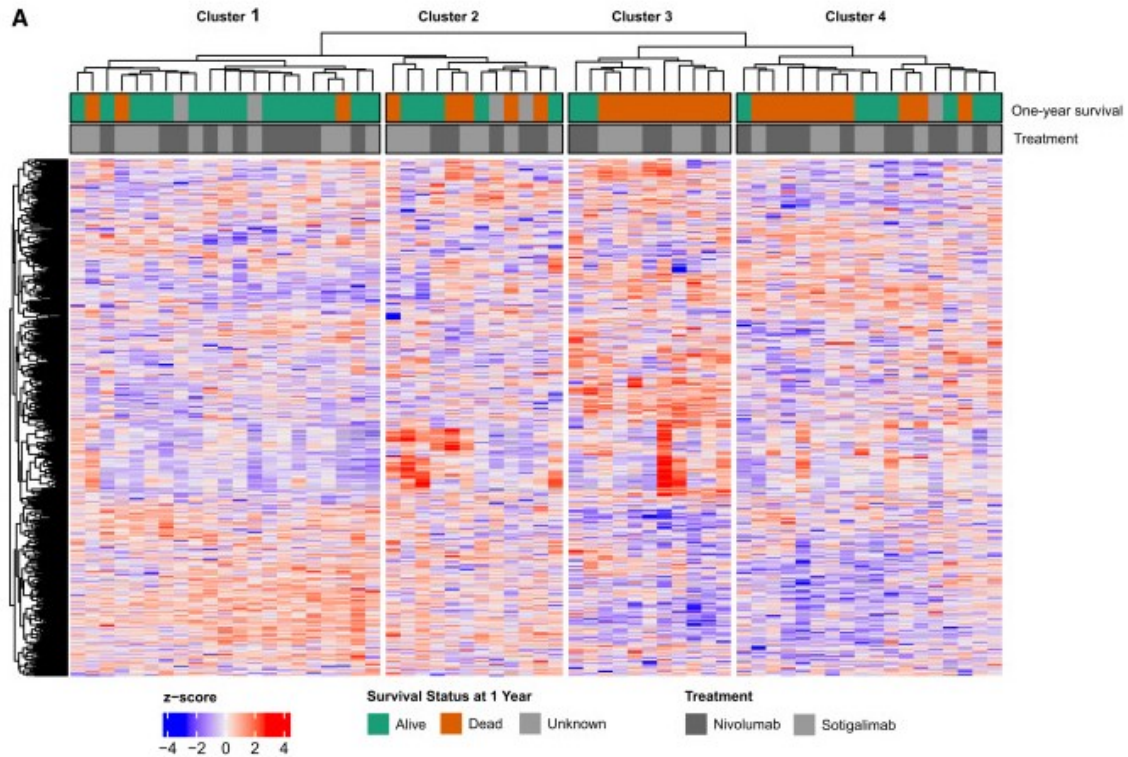
In brief

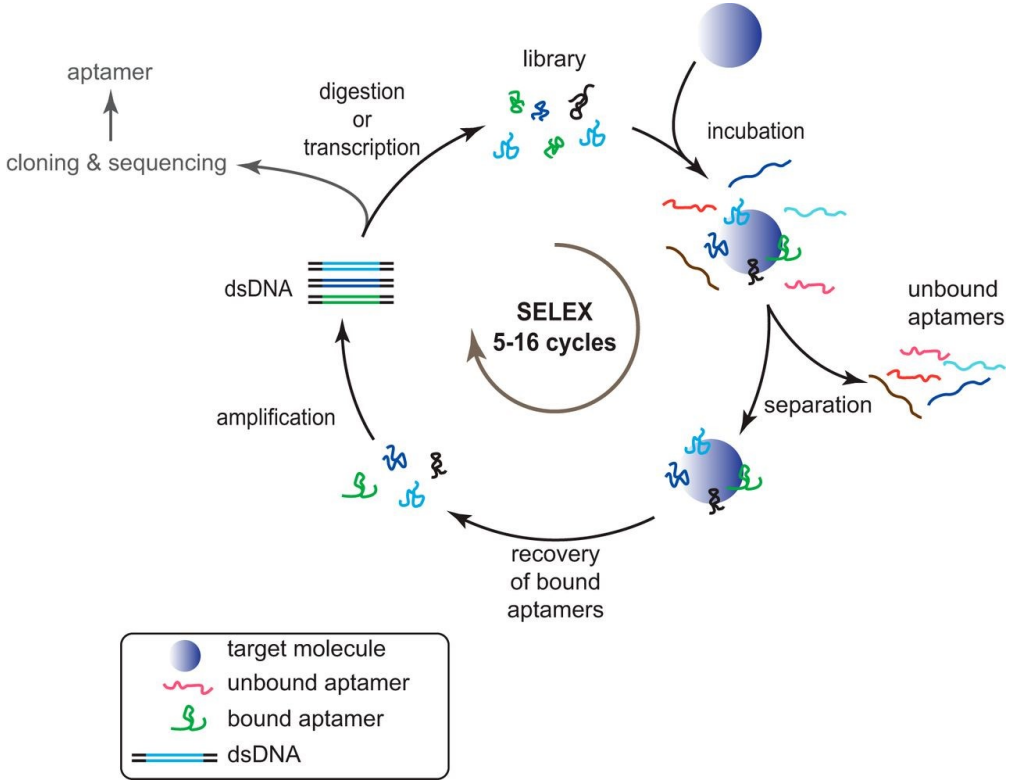
Treatment; Body substance sample; Cancer; Proteomics

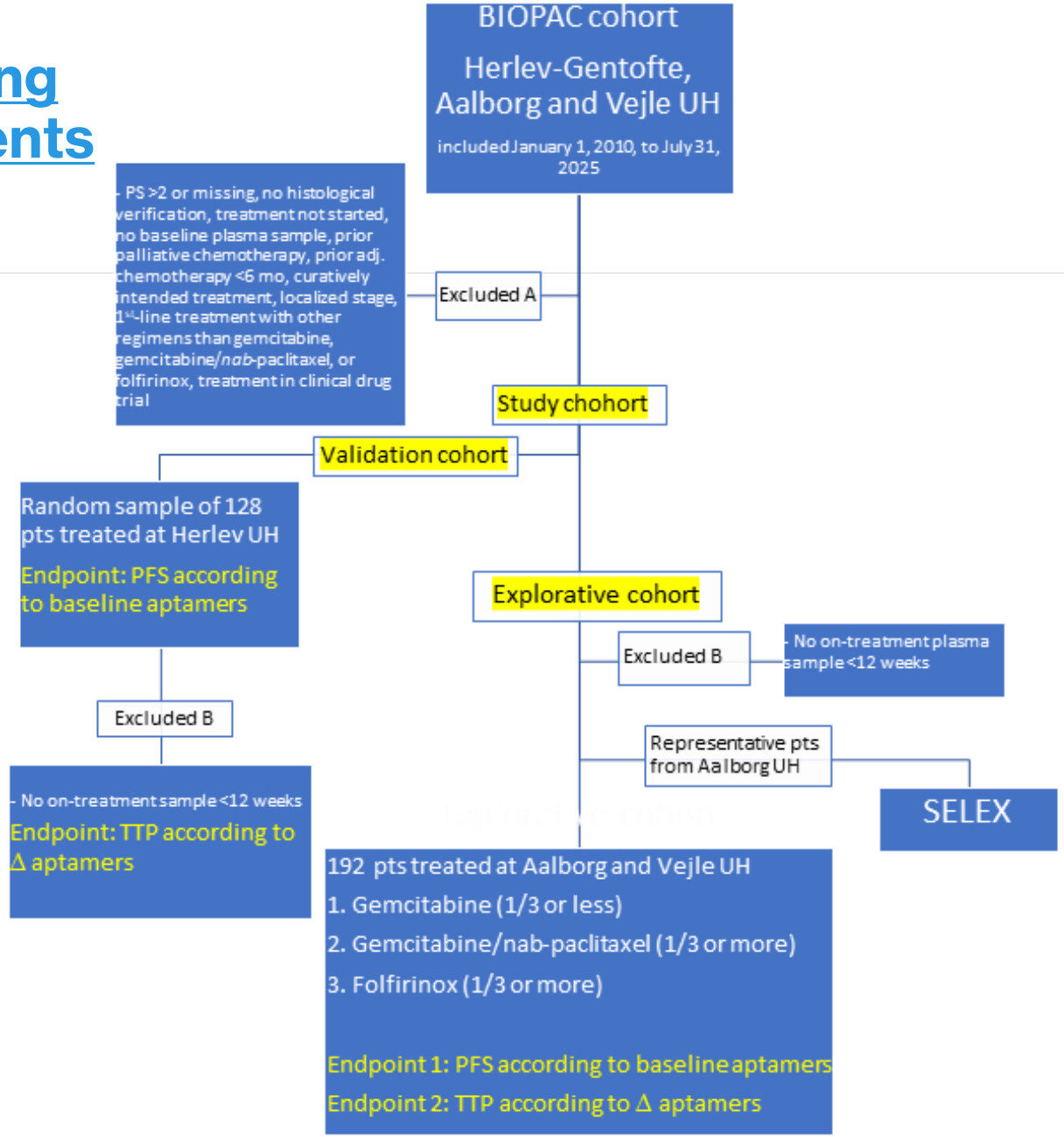
Highlights

- Serum proteomics reveals molecular subgroups of PDAC patients with prognostic value
- Glycolysis is associated with survival in nivolumab-treated patients
- Protein biomarkers predict one-year survival in patients receiving nivolumab treatment



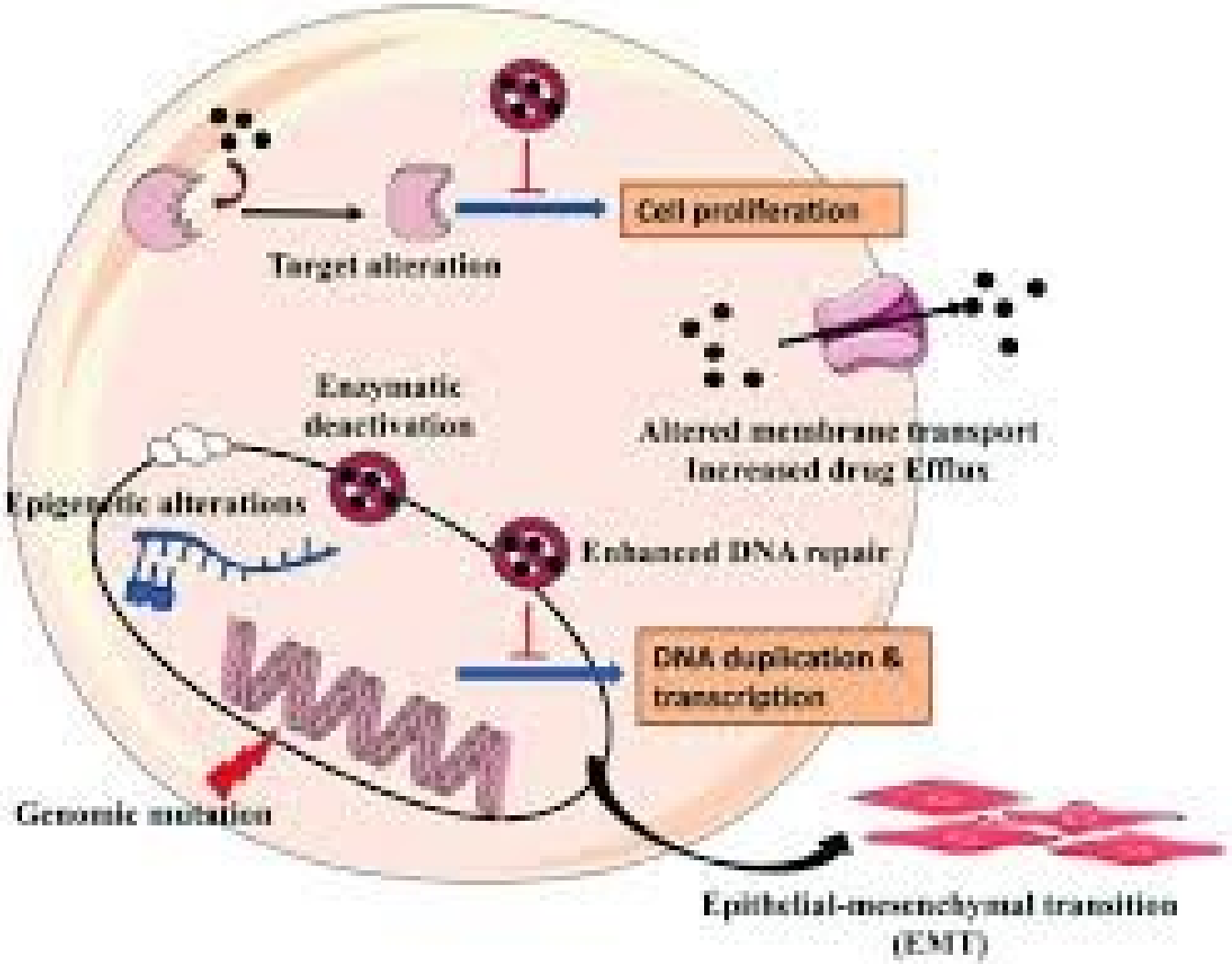
Study protocol: Aptamers for discovery of proteins predicting chemotherapy benefit in patients with pancreatic cancer





PhD-projekt i Aalborg

Kemoterapi - resistensmarkører



Resistensmarkører – ABC drug transporter

ABCG2 protein expression in tumors of patients with non-resectable pancreatic cancer treated with gemcitabine and *nab*-paclitaxel

Susy Shim[1,2*], Mette Bak Nielsen[3], Mikkel Eld[4], Jan Stenvang[5,6], Rasmus Froberg Brøndum[2,7], Britta Weber[8], Anne Krejbjerg Motavaf[1] and Morten Ladekarl[1,2]

Progression-free survival

Variable		N	Hazard ratio (95%CI)	P-value
ABCG2 expression	Negative	94	Reference	
	Positive	45	0.64 (0.43, 0.94)	0.02
ECOG PS	0	22	Reference	
	1	91	0.98 (0.59, 1.65)	0.95
	2	26	1.59 (0.86, 2.95)	0.14
Age		139	0.99 (0.97, 1.01)	0.29
Gender	Female	52	Reference	
	Male	87	0.80 (0.56, 1.15)	0.23
Clinical stage	Locally advanced	24	Reference	
	Distant metastatic	115	1.28 (0.80, 2.06)	0.30
Prior pallitative CTx	No	84	Reference	
	Yes	55	1.55 (1.05, 2.30)	0.03
Prior (neo)adj. CTx	No	104	Reference	
	Yes	35	1.64 (1.06, 2.53)	0.03

10.3389/fonc.2025.1558184

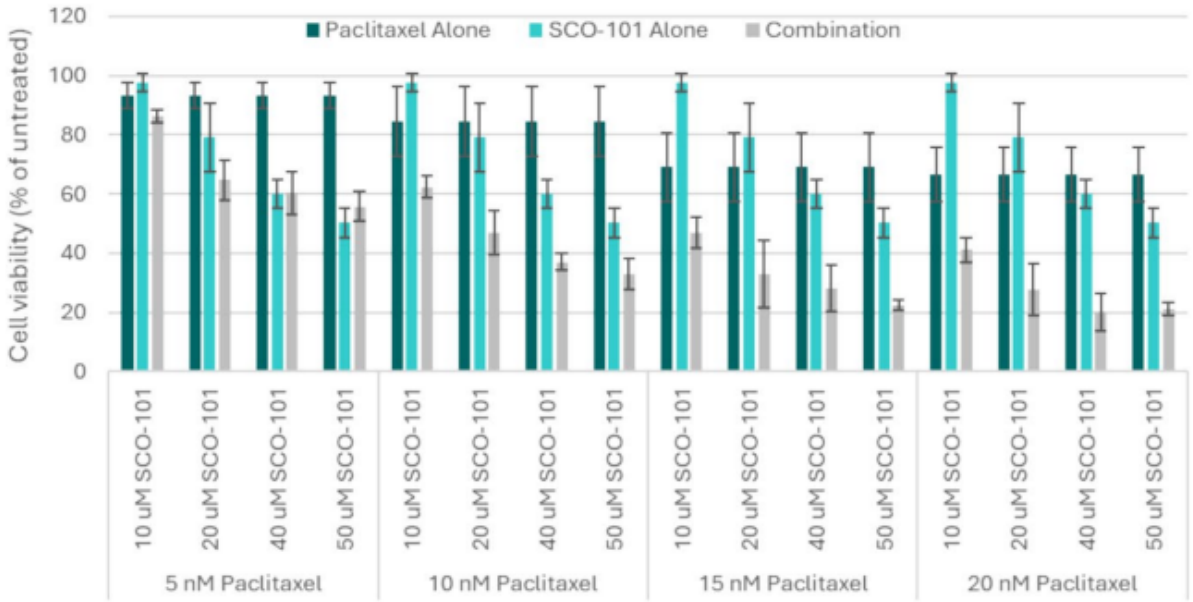
Resistens-inhibitorer

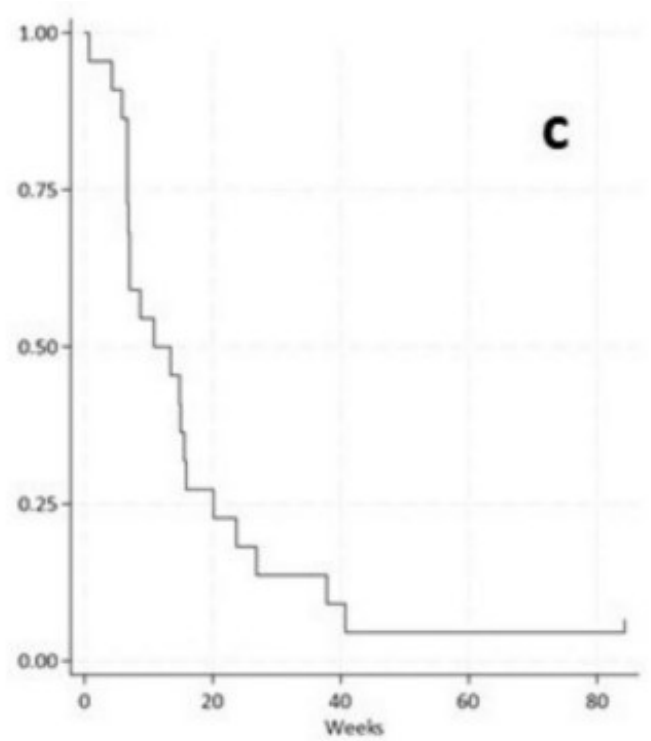
Investigational New Drugs
https://doi.org/10.1007/s10637-025-01526-7

RESEARCH

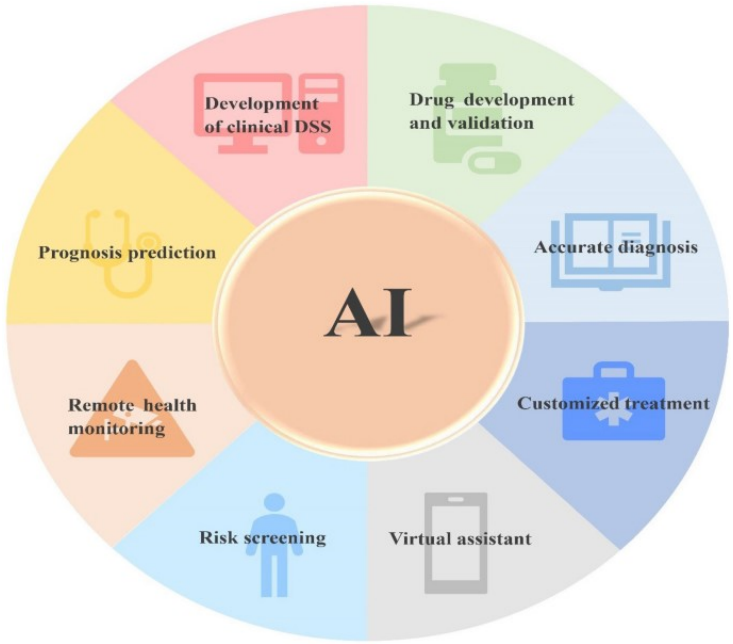
PANTAX: a phase Ib clinical trial of the efflux pump inhibitor SCO-101 in combination with gemcitabine and *nab*-paclitaxel in non-resectable or metastatic pancreatic cancer

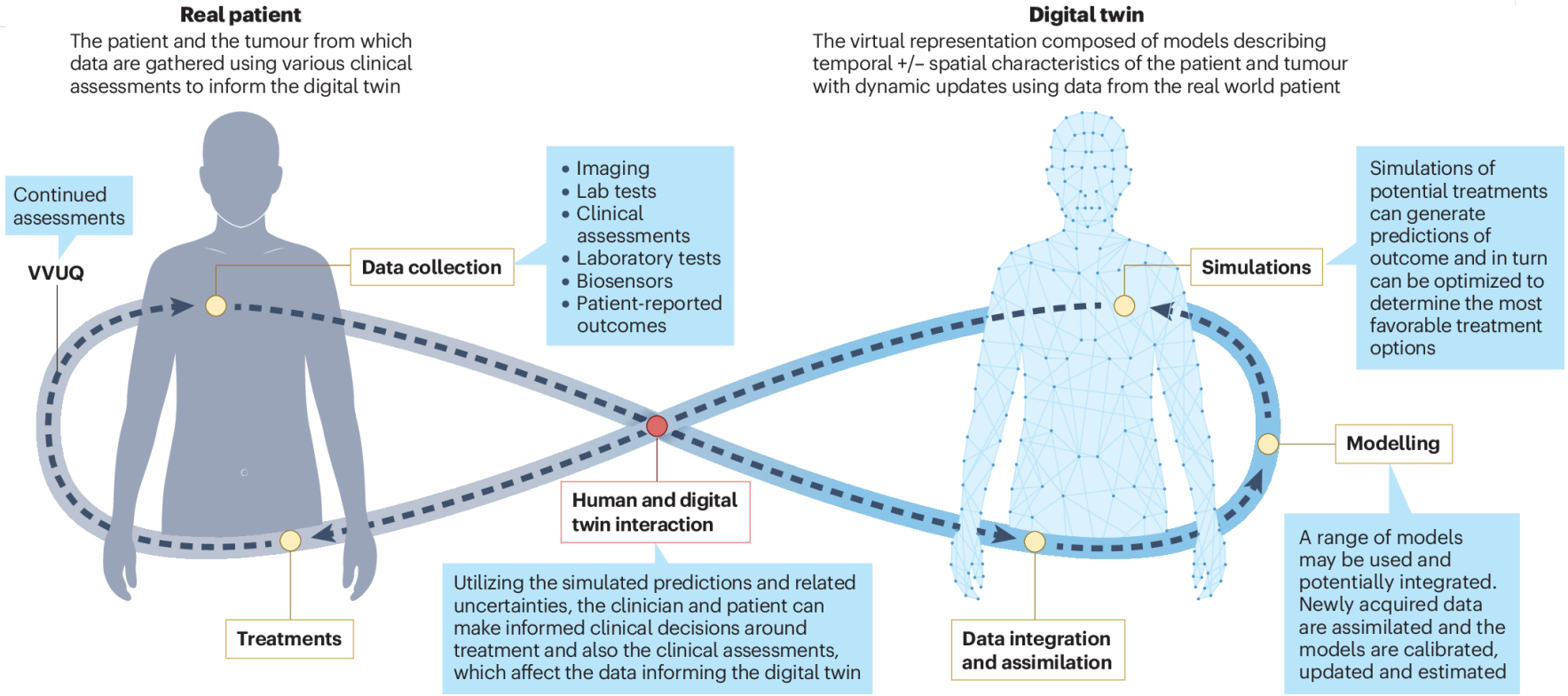
Susy Shim[1,2] · Anke Reinacher-Schick[3] · Anna-Lena Kraeft[3] · Per Pfeiffer[4,5] · Line Schmidt Tarpgaard[4,5] · Thomas Jens Ettrich[6] · Angelika Kestler[6] · Signe Christensen[1] · Haatisha Jandu[7] · Mubeen Nawabi[7] · Nicklas Lindland Roest[7] · Lars Damstrup[7] · Peter Michael Vestlev[7] · Nils Brünner[7] · Jan Stenvang[7] · Morten Ladekarl[1,2]





Valg af behandling vha. kunstig intelligens





The future treatment of pancreatic cancer?

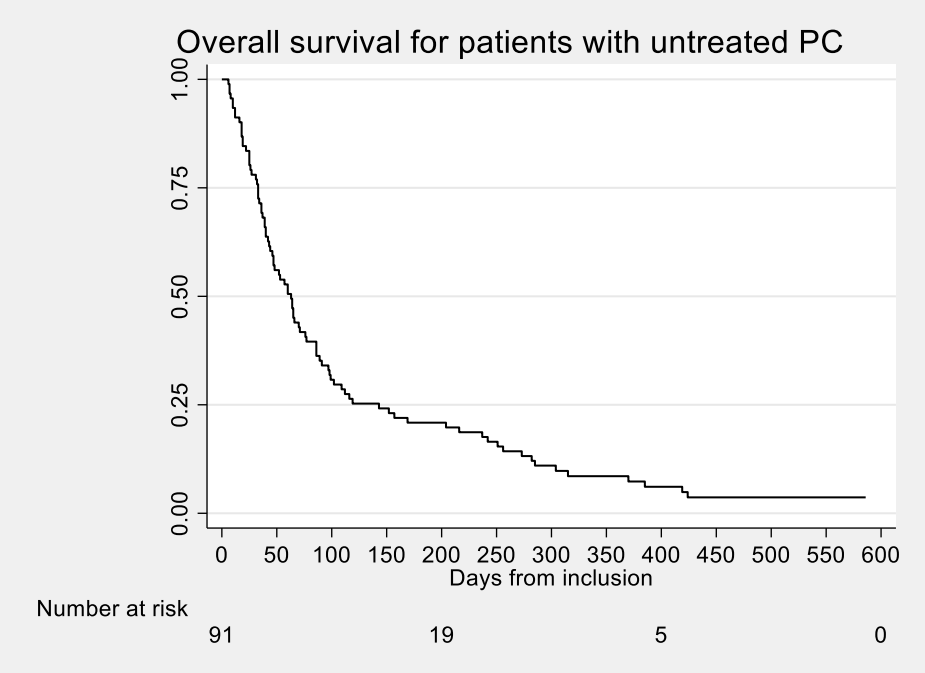
10-15%	gBRCA1/2	Platinum-CTx +/- maintenance PARPi
1-2%	MSI/dMMR	Immunotherapy
2-3%	rare mutations	Targeted treatment
40%	$KRAS^{G12D}$	$KRAS^{G12D}$ inhibitor
1-2%	$KRAS^{G12C}$	$KRAS^{G12C}$ inhibitor
Rest	$KRAS^{G12V/R/+}$	Pan-KRAS inhibitor

+/- chemotherapy, other druggable variants, ADC's, ATMPs, RNA-vaccines, etc.

Morten Ladekarl, Post-ESMO 2025

Den største fremtidige udfordring

40% af danske PC-patienter er ikke egnede til eller fravælger (10%) behandling ved diagnosen (mOS = 2 mdr.)



Characteristics, prognosis and reasons for opting-out

treatment in patients with untreated pancreatic cancer

Ladekarl M, Stender M

Submitted 2025