Disclosure belangen spreker

Potentiële belangensverstrengeling	Geen / zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk….	• Celgene, Frame Therapeutics. Lead Pharma • Servier, Olympus, Wholomics • NVT • NVT

Pancreatic and EsophagoGastric cAncer: improving Survival and qUality of life through perSonalized medicine

PEGASUS

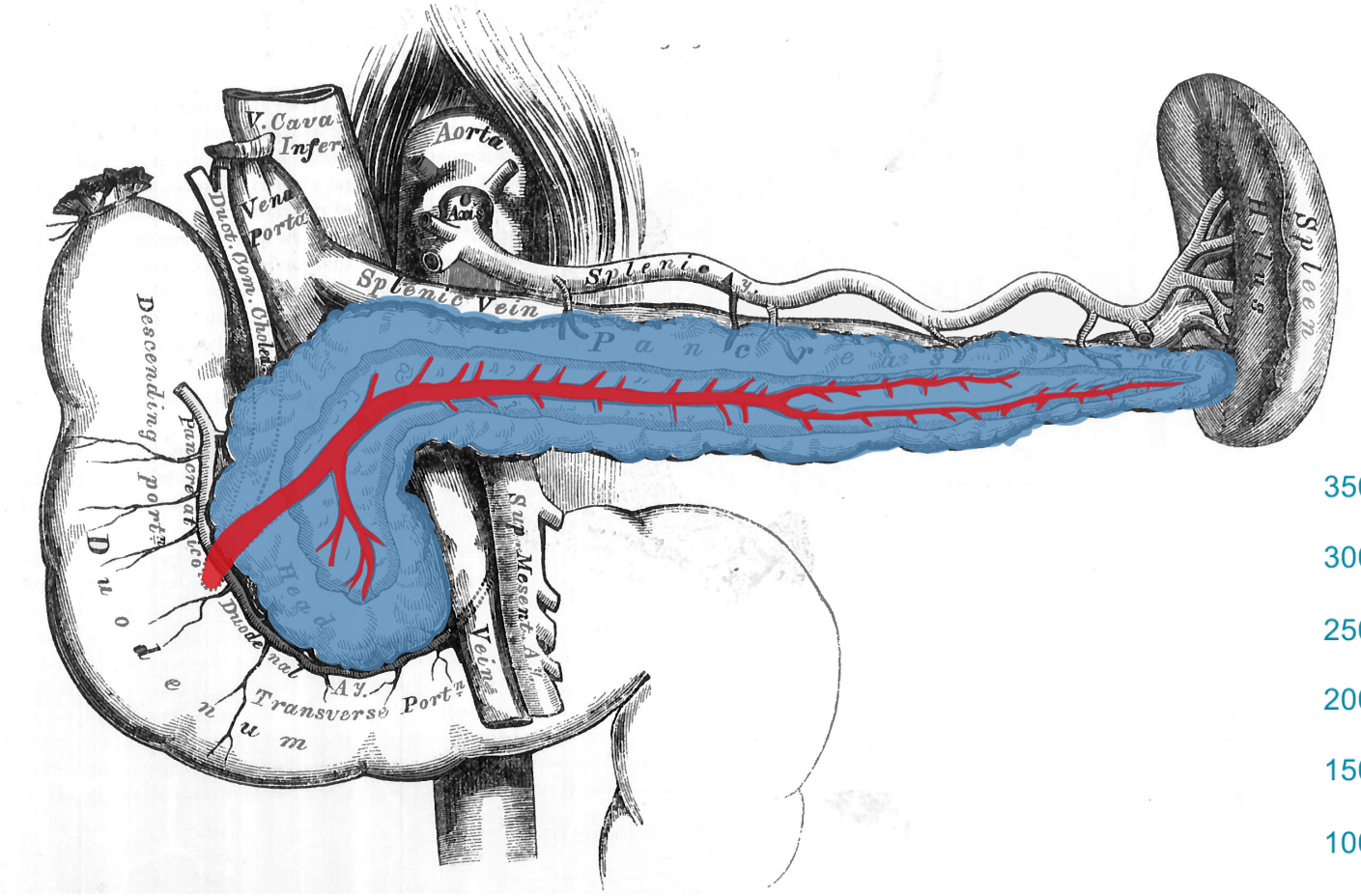
Maarten Bijlsma, Amsterdam UMC

Congres Goed Gebruik Geneesmiddelen 10 April 2025

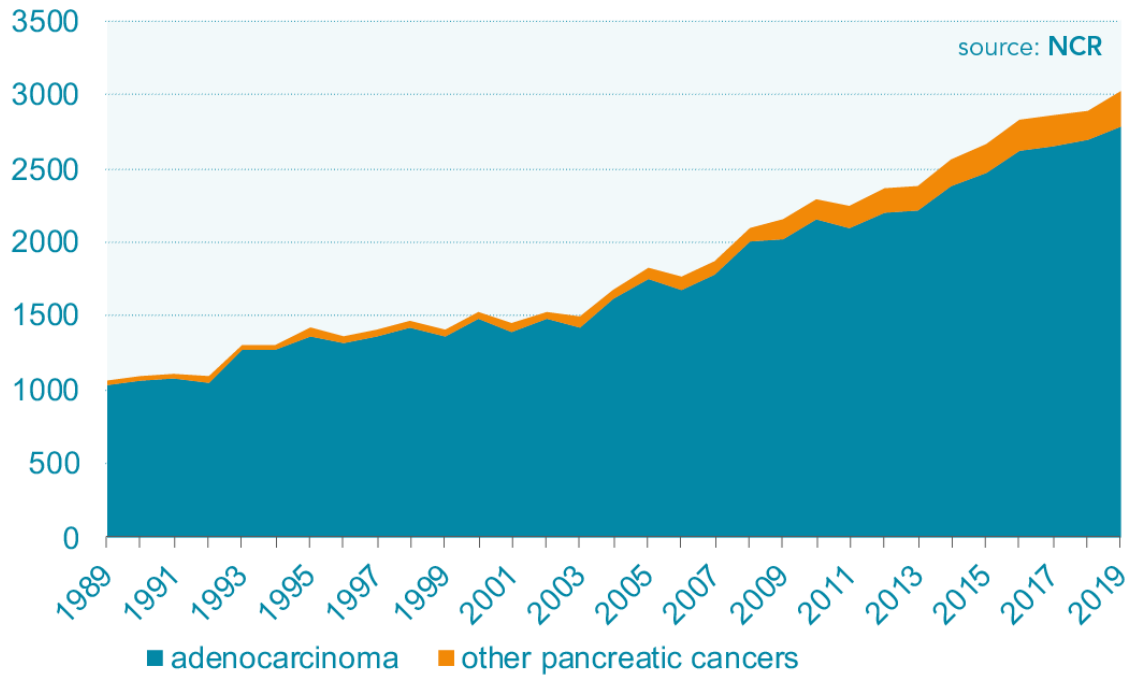
GGG-project 848101012

PANCREASKANKER

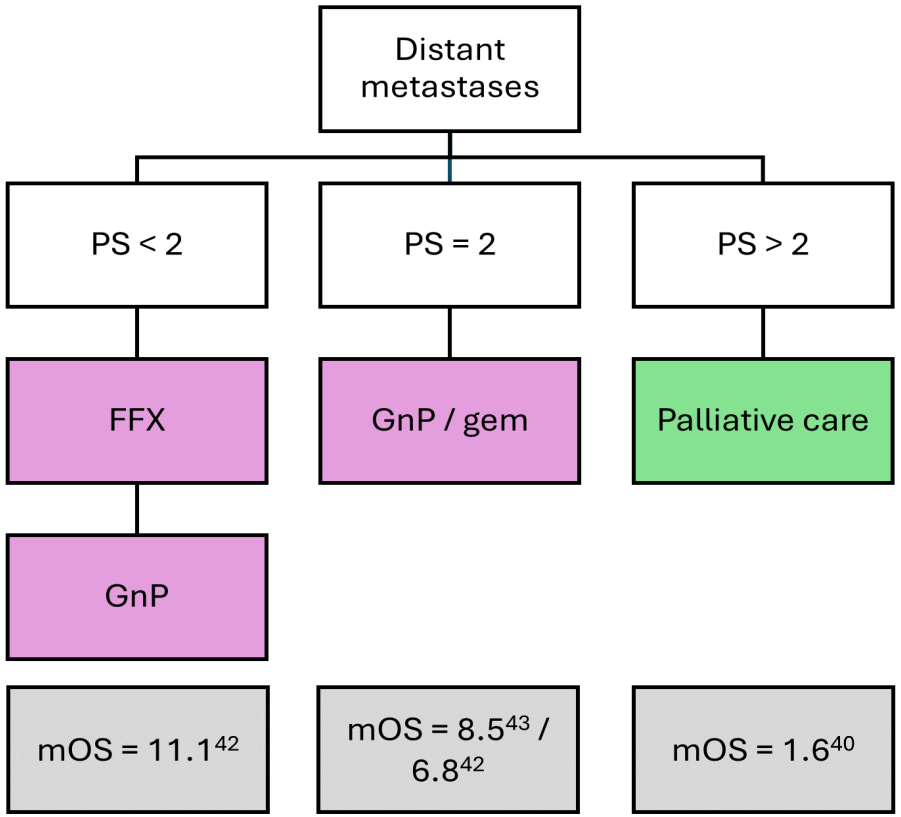
PDAC

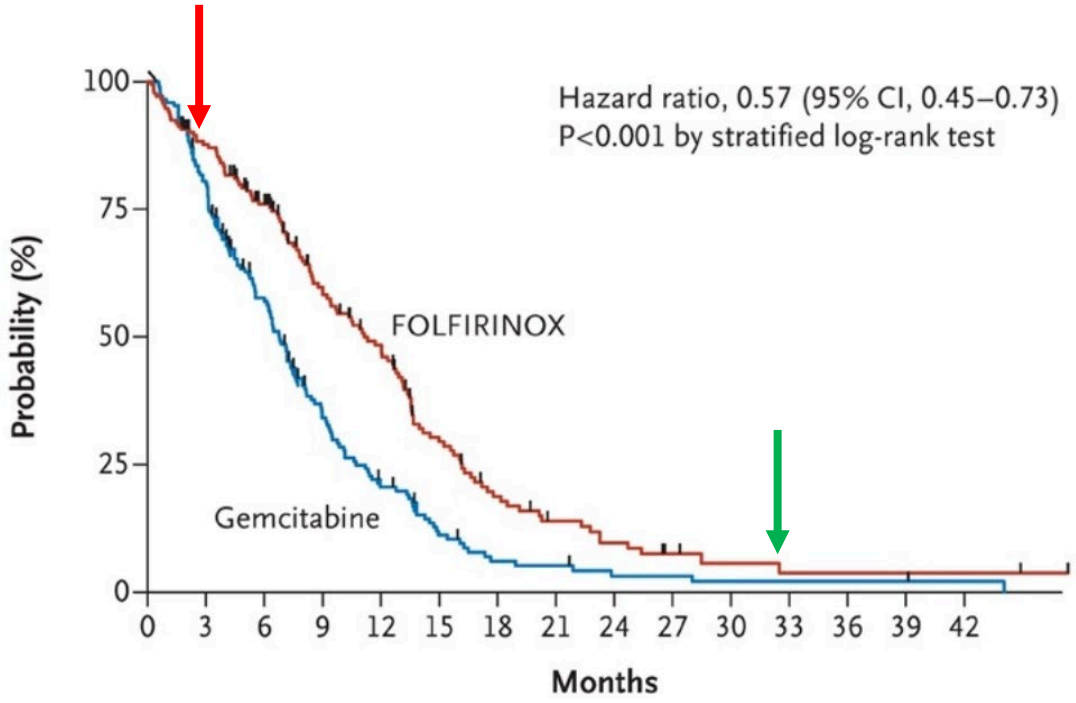


Grey's Anatomy



BEHANDELING
mPDAC

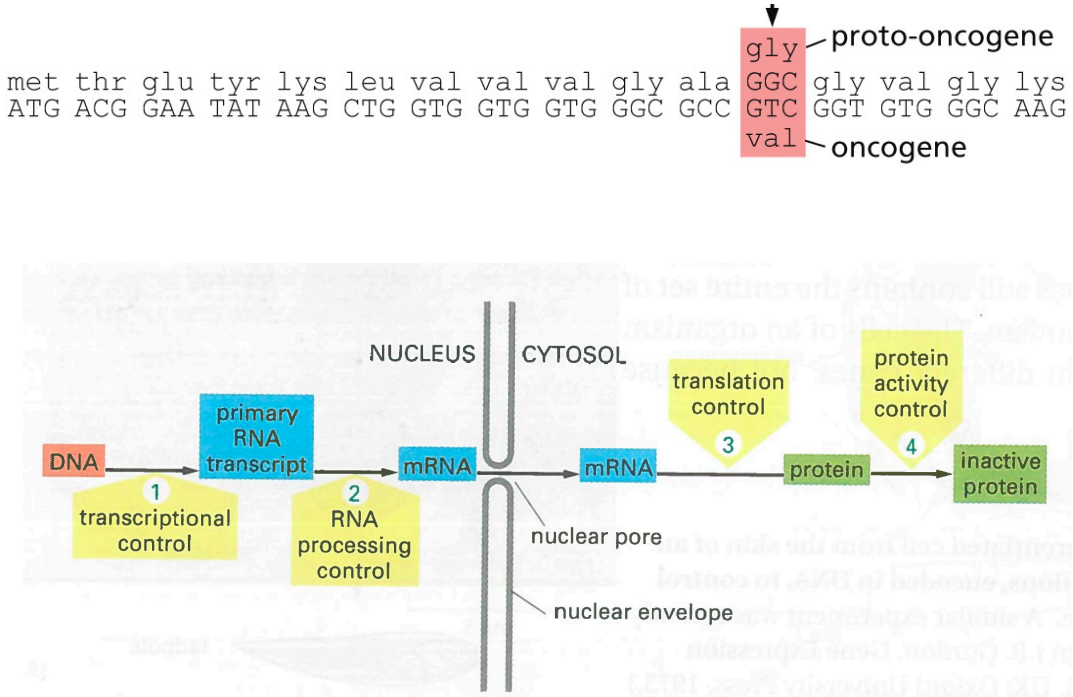


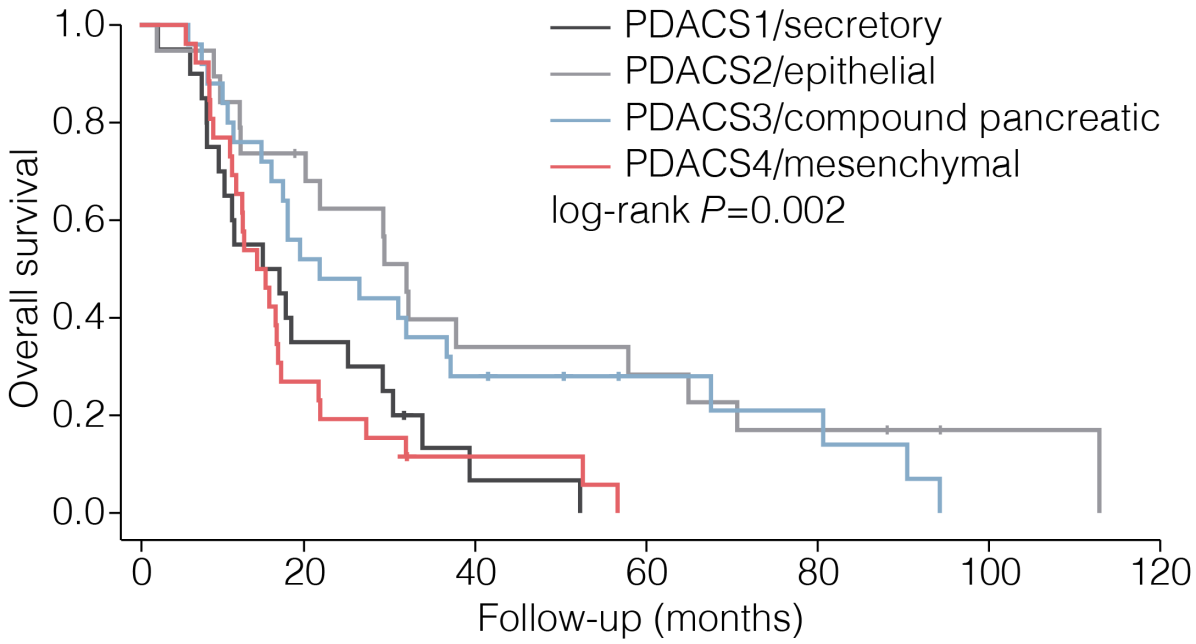


courtesy of Marjolein Lansbergen

Conroy et al. 2011

MOLECULAIRE SUBTYPES





Collisson et al., 2011; Moffitt et al., 2015; Bailey et al., 2016; Puleo et al. 2018; Dijk et al. 2020

PEGASUS DOELEN

mPDAC

De overleving en kwaliteit van leven van patiënten met alvleesklierkanker verbeteren.

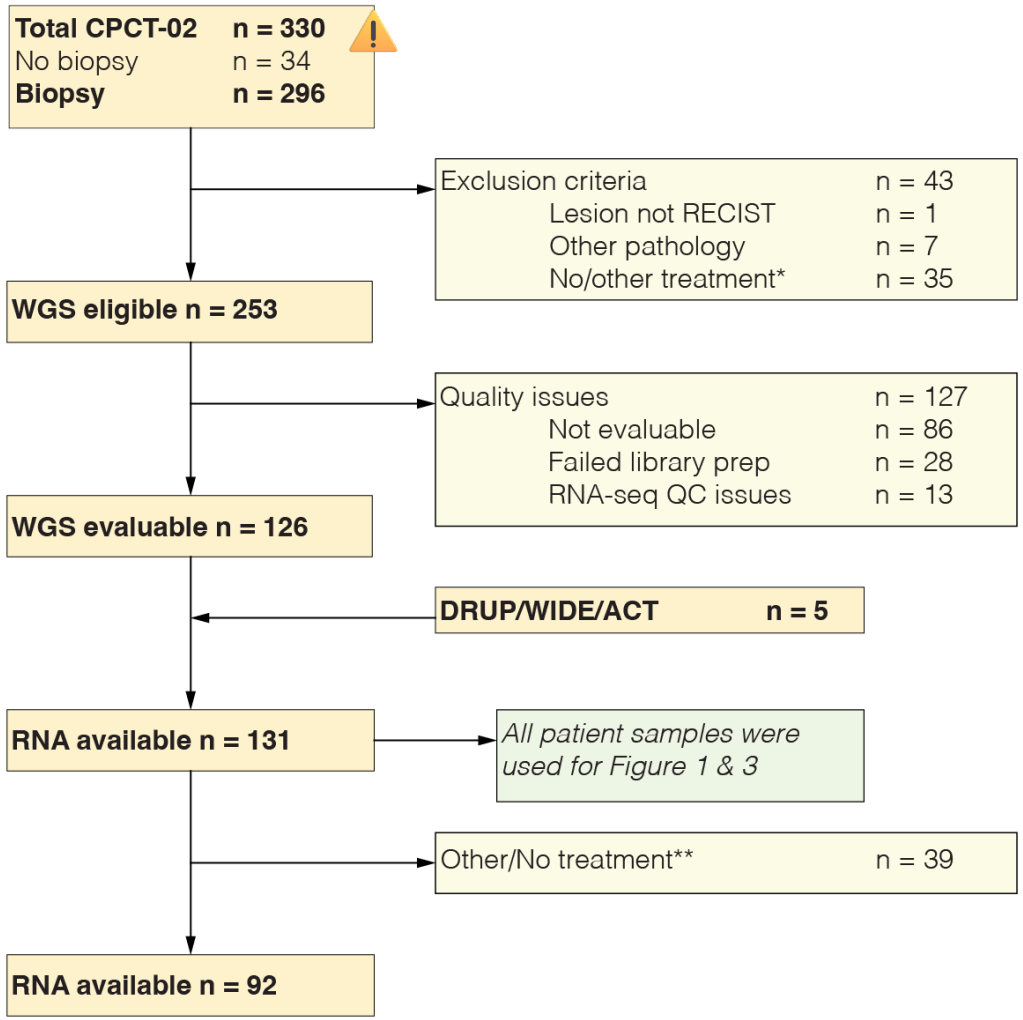
❶ Bepalen of **moleculaire subgroepen** de respons op FOLFIRINOX in uitgezaaide alvleesklierkanker kunnen voorspellen

❷ Het predictieve profiel **versimpelen** tot een eenvoudigere en goedkopere test

❸ Het profiel verbeteren met op **DNA gebaseerde biomarkers**, en mogelijkheden voor targeted interventies identificeren

❶ PEGASUS COHORT

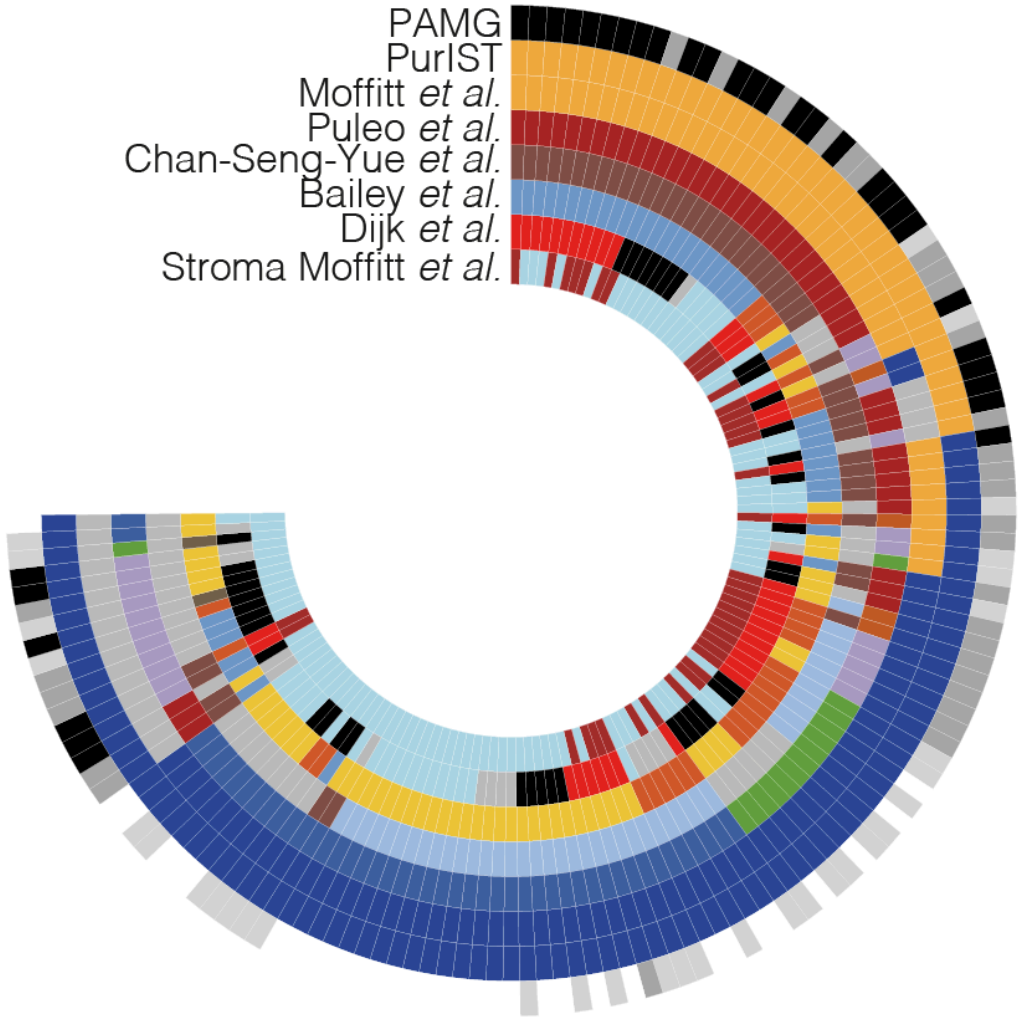
mPDAC



Lansbergen et al. 2024

❶ SUBTYPES IN PEGASUS

mPDAC COHORT



PurIST
- Basal-like
- Classical

Moffitt *et al.*
- Basal–like
- Classical
- Double negative
- Activated Stroma
- Normal Stroma

Puleo *et al.*
- Pure Basal–like
- Desmoplastic
- Stroma Activated
- Immune Classical
- Pure Classical

Bailey *et al.*
- Squamous
- Immunogenic
- ADEX
- Pancreatic Progenitor

Dijk *et al.*
- Mesenchymal
- Secretory
- Compound
- Epithelial

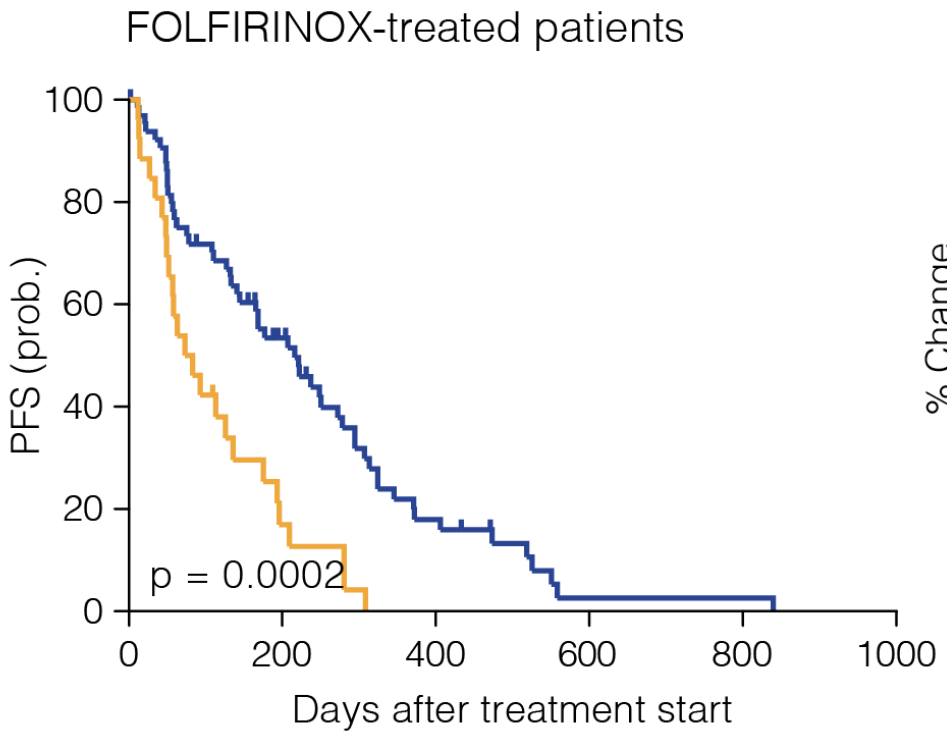
PAMG Quartiles
- 1 - 0.75 (-0.635 — -0.186)
- 0.75 - 0.5 (-0.182 — -0.031)
- 0.5 - 0.25 (-0.026 — 0.171)
- 0.25 - 0 (0.175 — 0.810)

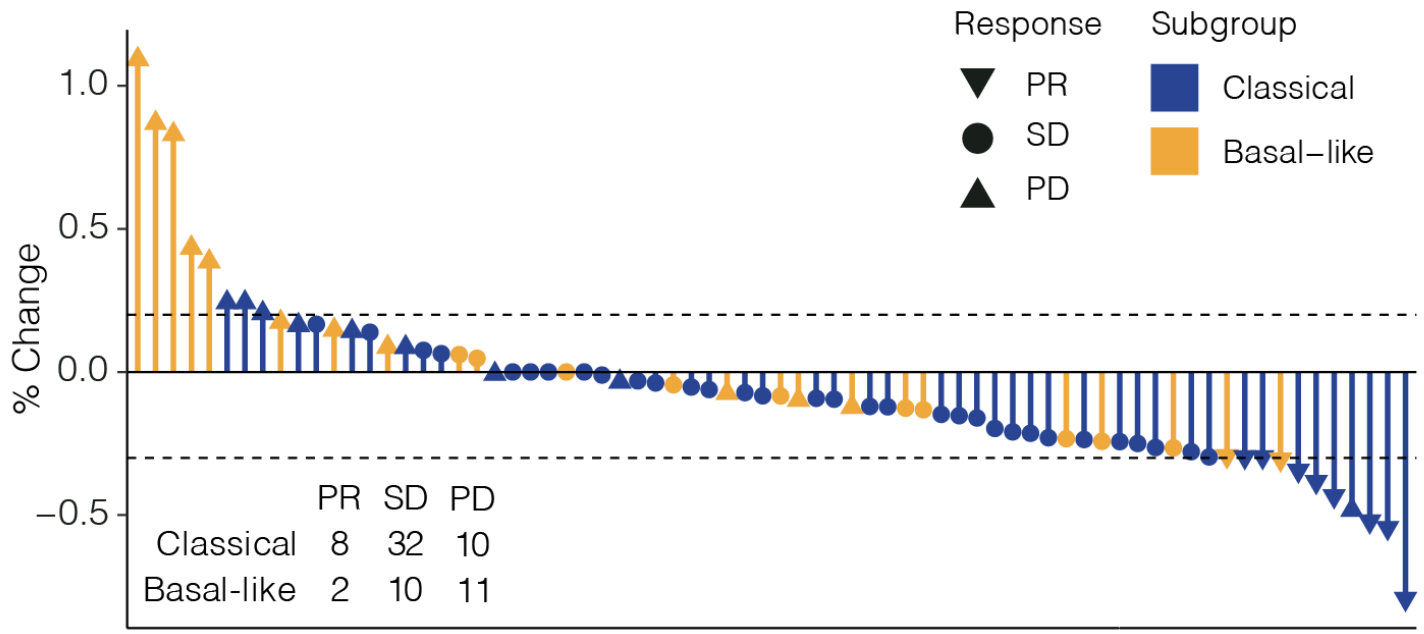
Chan-Seng-Yue *et al.*
- Basal–AB
- Hybrid
- Classical–AB

Lansbergen et al. 2024

❶ SUBTYPES

FOLFIRINOX RESPONS



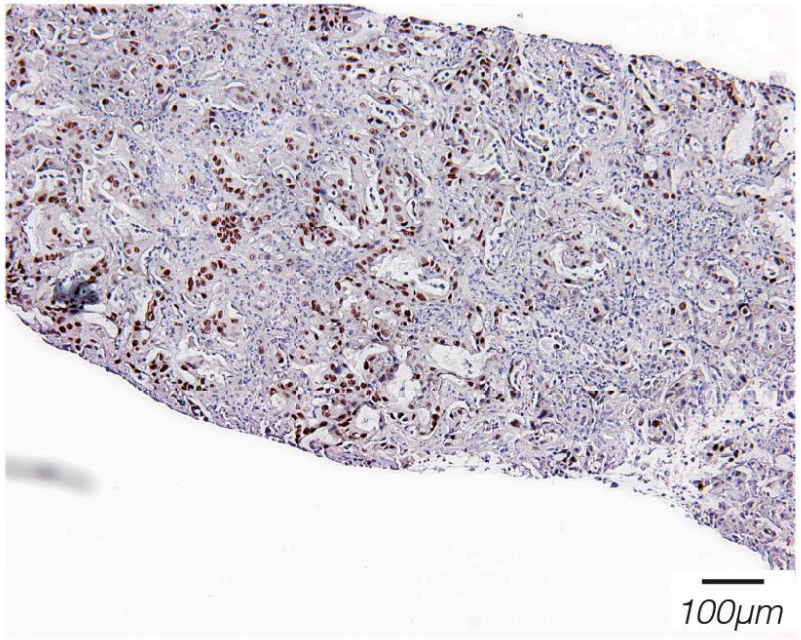


Lansbergen et al. 2024

❷ VERSIMPELEN PROFIEL

SURROGAAT IHC MARKER

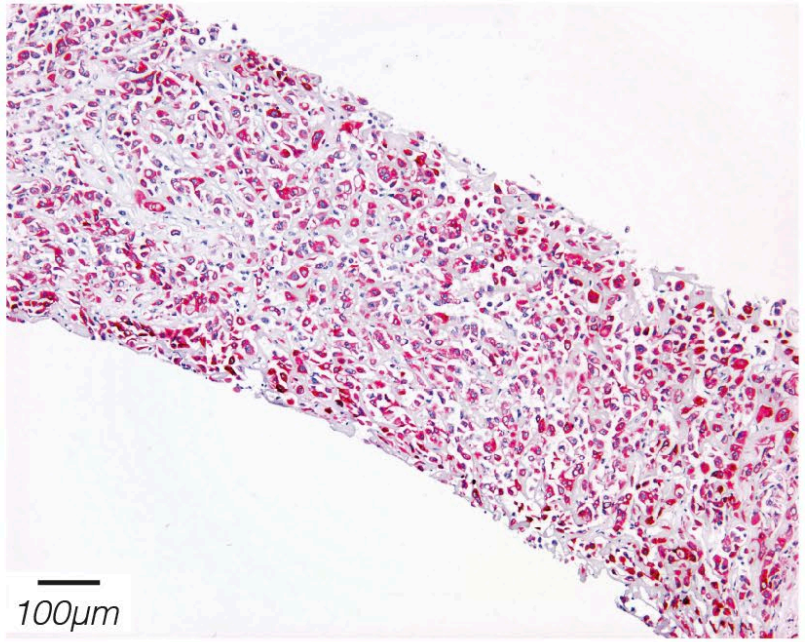
AMC3



IHC: Classical
RNA: Classical

95% GATA6⁺
0% KRT17⁺

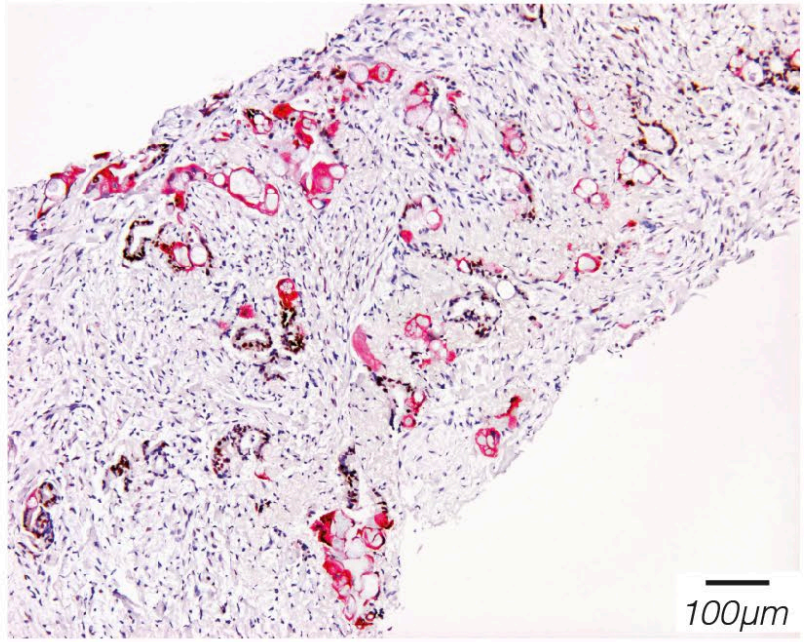
AMC5



IHC: Basal-like
RNA: Basal-like

1% GATA6⁺
80% KRT17⁺

AMC2



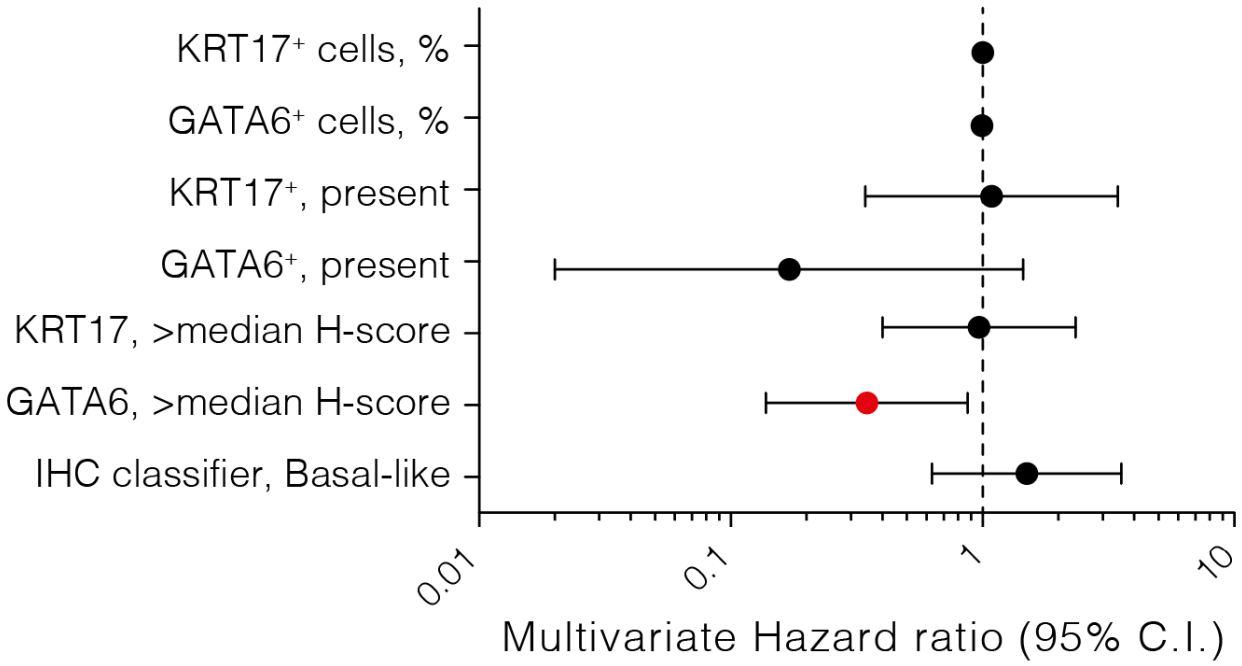
IHC: Classical
RNA: Classical

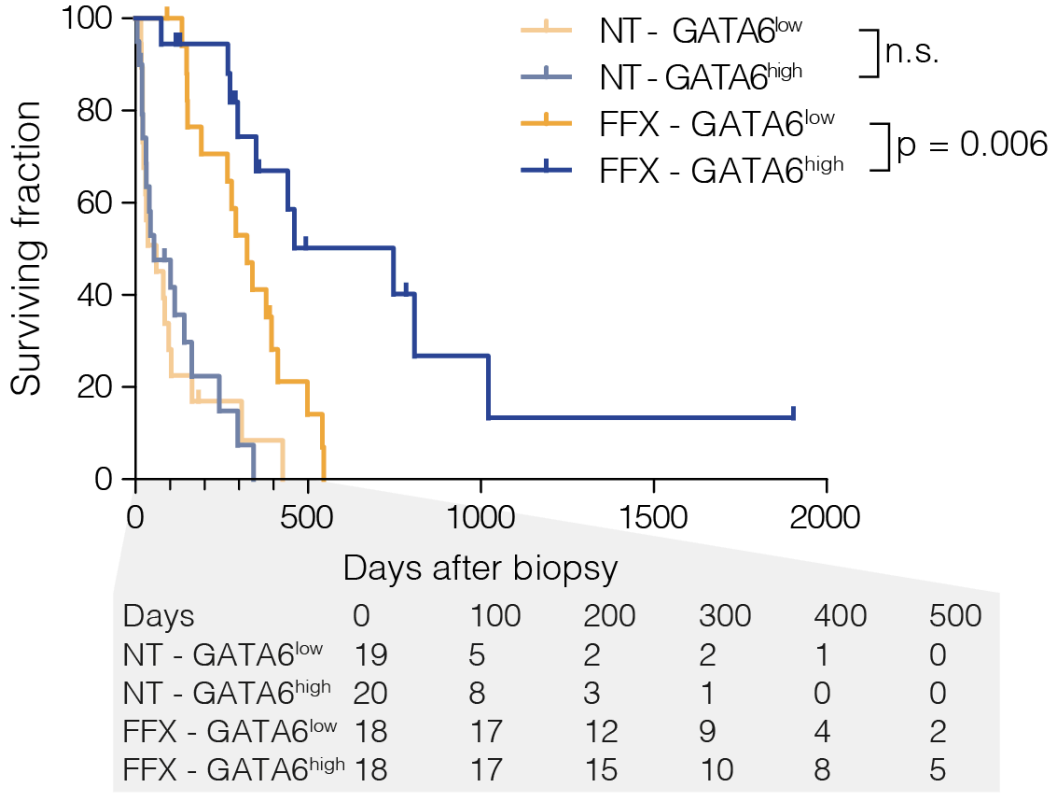
90% GATA6⁺
40% KRT17⁺

Lansbergen et al. 2024

❷ VERSIMPELEN PROFIEL

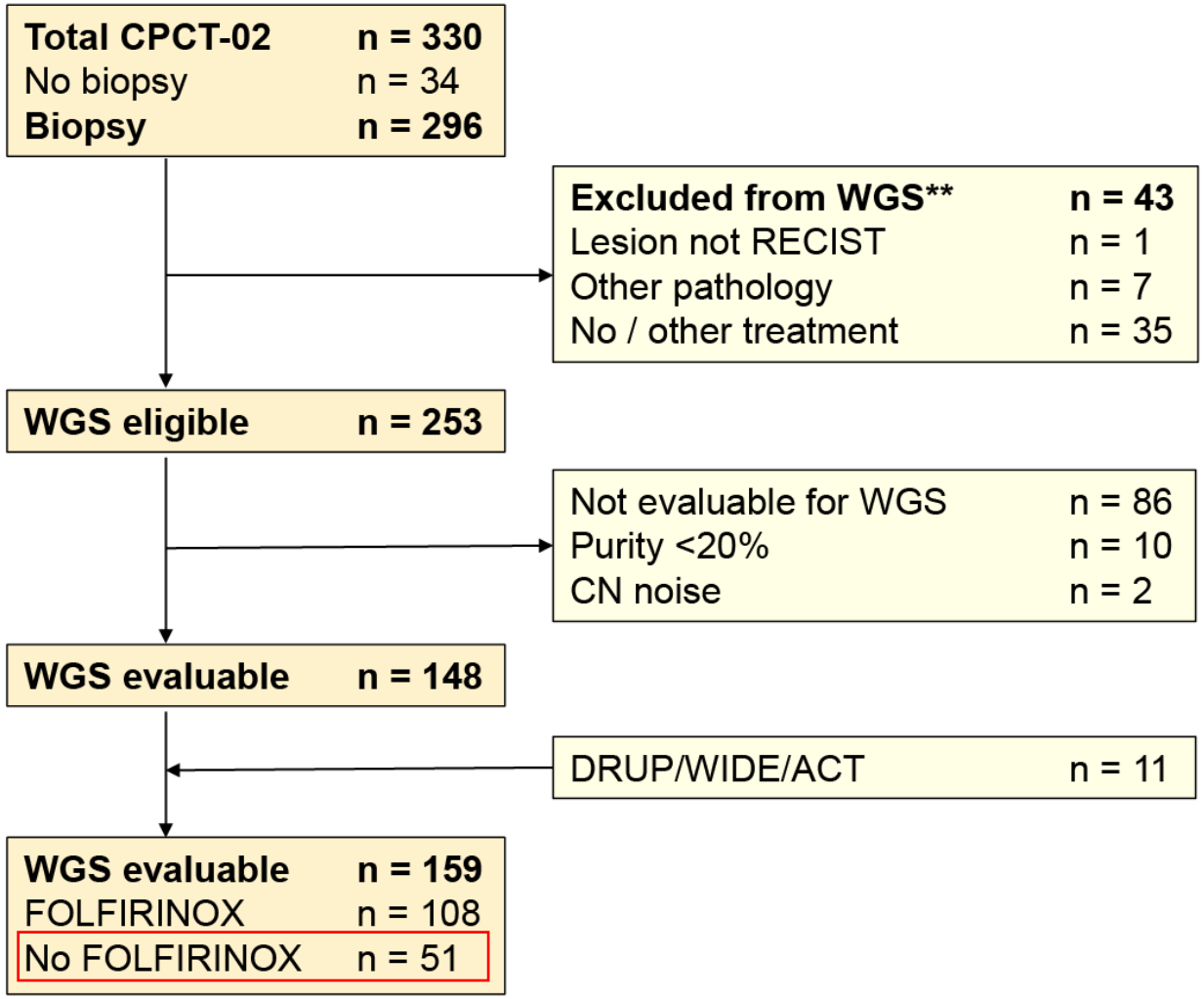
SURROGAAT IHC MARKER





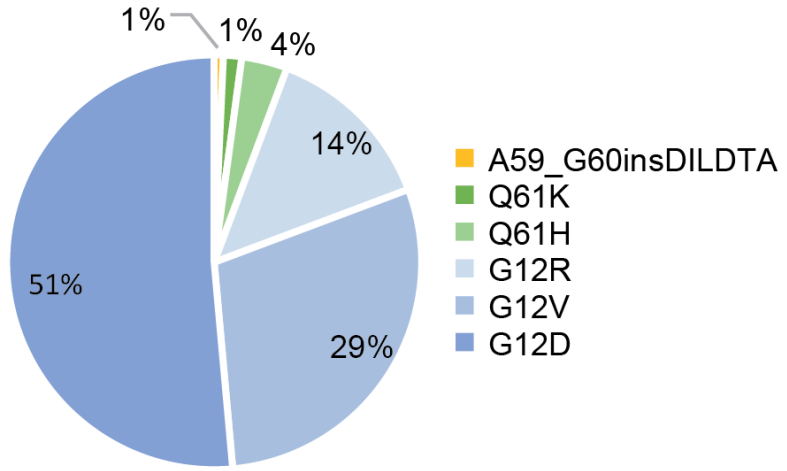
Lansbergen et al. 2024

❸ PROFIEL VERBETEREN MET WGS



Lansbergen et al. 2025

3



Alterations
- Mutation
- Amplification
- Fusion
- Loss

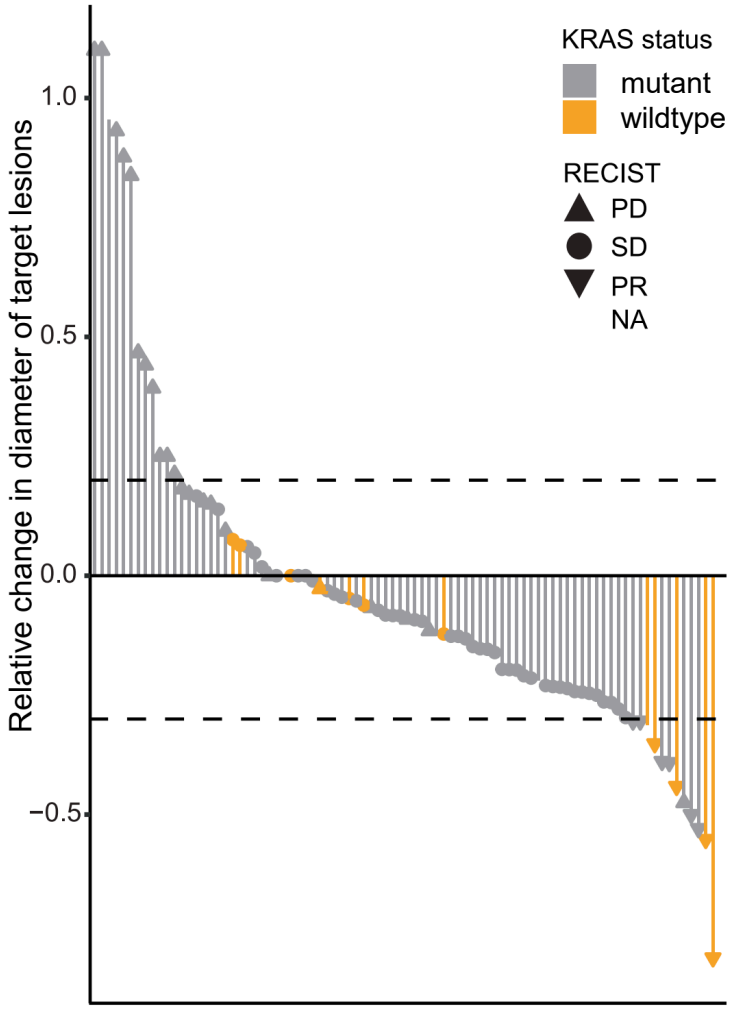
Moffitt subtype
- Negative
- Classical
- Basal−like
- Missing

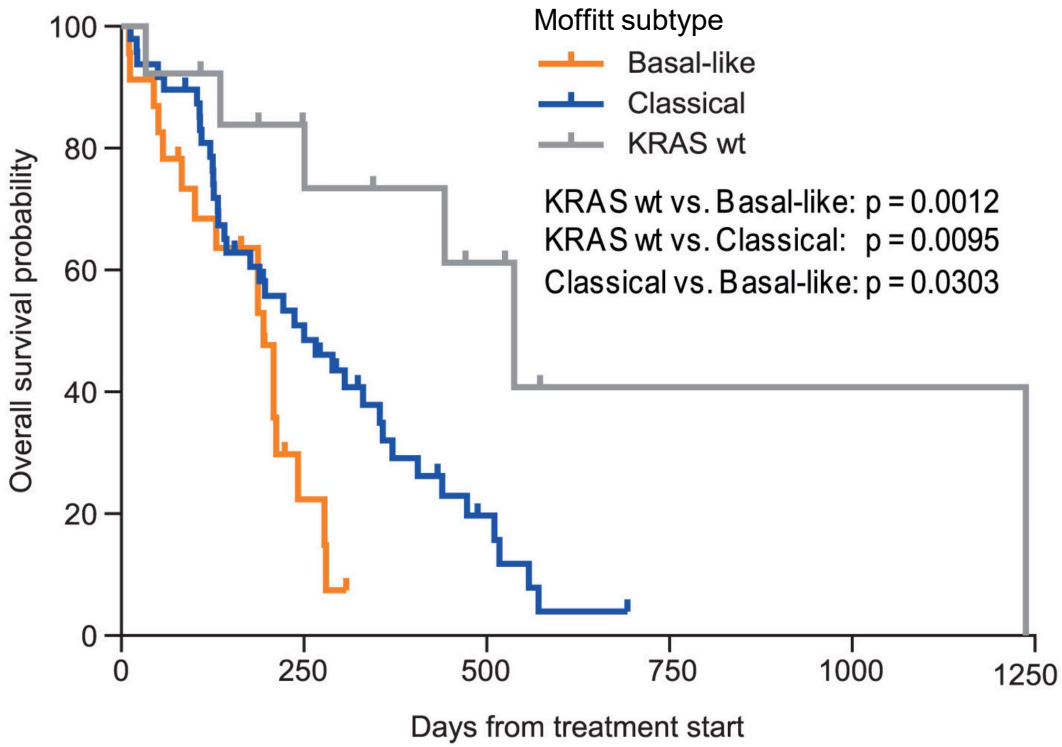
DNA repair status
- HR proficient
- HR deficient
- MSI
- Missing

TML
- Low
- High
- Missing

Lansbergen et al. 2025

❸ PROFIEL VERBETEREN MET WGS





Actionable alterations in
42% [8/19] of *KRAS* wild-type vs.
17% [24/140] of *KRAS* mutant tumors

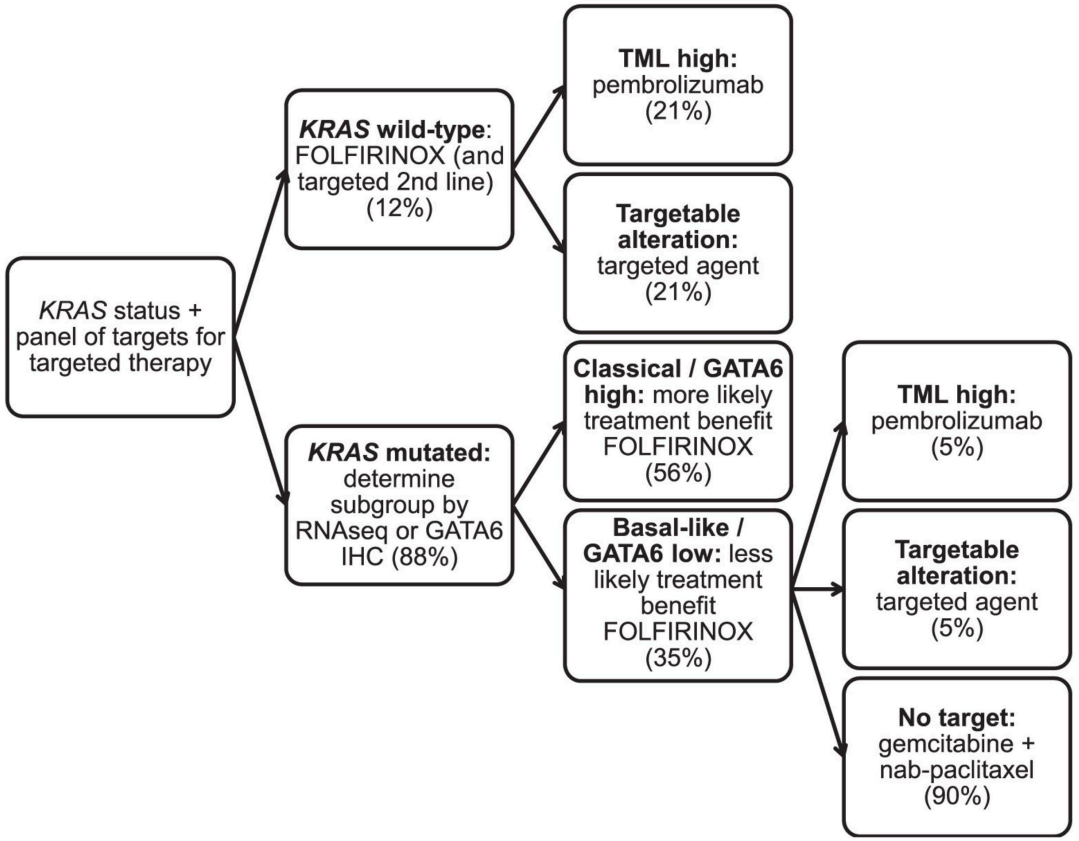
Lansbergen et al. 2025

CONCLUSIES

❶ Moleculaire subgroepen voorspellen respons op FOLFIRINOX in mPDAC (predictief? haalbaar?)

❷ Subtypes kunnen nauwkeurig worden bepaald met behulp van IHC

❸ *KRAS* mutatie status is sterk bepalend voor de uitkomst en evt. stratificatie



HORDES EN UITDAGINGEN
VOOR IMPLEMENTATIE

- Moleculaire analyse niet praktisch

Ondanks goedkope, eenvoudig te implementeren IHC:

- Niet duidelijk predictief
- Verschuivend mechanistisch inzicht
- *Use case?*

DANKWOORD

Hartwig MEDICAL FOUNDATION

stichting CPCT Center for Personalized Cancer Treatment

PACAP Dutch Pancreatic Cancer Group

ZonMw

PEGASUS

PancreasParel DPCG Dutch Pancreatic Cancer Group Dutch Pancreatitis Study Group

A: OncoKB level 1, 2 and 3 targetable alterations for pancreatic cancer.

Level OncoKB	Gene	Alteration	Drug	Prevalence
1	NTRK1	fusion	entrectinib	1
1	NTRK3	fusion	larotrectinib	1
1	other	MSI-H	pembrolizumab	1
1	other	TMB-H	pembrolizumab	10
2	BRCA1	oncogenic mutation	rucaparib	1
2	BRCA2	oncogenic mutation	rucaparib	2
3	NRG1	fusion	zenocutuzumab	2
3	NTRK1	fusion	repotrectinib	1
3	NTRK3	fusion	repotrectinib	1
3	TP53	Y220C	PC14586	2

B: OncoKB level 1 and CIVIC level A alterations for other tumor types than pancreatic cancer.

Level OncoKB	Gene	Alteration	Drug	Prevalence	Cancer type
1	MET	D1010, 963_1010del, 963_1010splice, exon 14 deletion	capmatinib	1	NSCLC
1	ATM	oncogenic mutation	talazoparib + enzalutamide	4	prostate cancer
1	PIK3CA	C420R and other alterations	alpelisib	4	breast cancer
1	SMARCB1	deletion	tazemetostat	1	epithelioid sarcoma
1	ALK	amplification	crizotinib and other drugs	1	NSCLC
1	ERBB2	amplification	trastuzumab (+ chemotherapy)	6	breast cancer