USZ Universitäts Spital Zürich

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
ÖGHO SSMO SSOM SGMO SGHSSH

JAHRESTAGUNG
Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie
www.jahrestagung-haematologie-onkologie.com

2023 13.–16. Okt. Hamburg

Personalisierte Therapie des metastasierten Pankreaskarzinoms mit Fokus auf KRAS-Targeting

Ralph Fritsch

Leiter Medizinische Gastrointestinale Onkologie und Viszeralonkologisches Zentrum

Universitätsspital Zürich, Comprehensive Cancer Center Zürich

DGHO Jahrestagung 2023, Hamburg

Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition

2. Beratungs- bzw. Gutachtertätigkeit
BMS, MSD, Pierre Fabre, Roche, Astra Zeneca

3. Besitz von Geschäftsanteilen, Aktien oder Fonds

4. Patent, Urheberrecht, Verkaufslizenz

5. Honorare
Pierre Fabre, Merck, Servier, MSD, BMS, Roche, Astra Zeneca

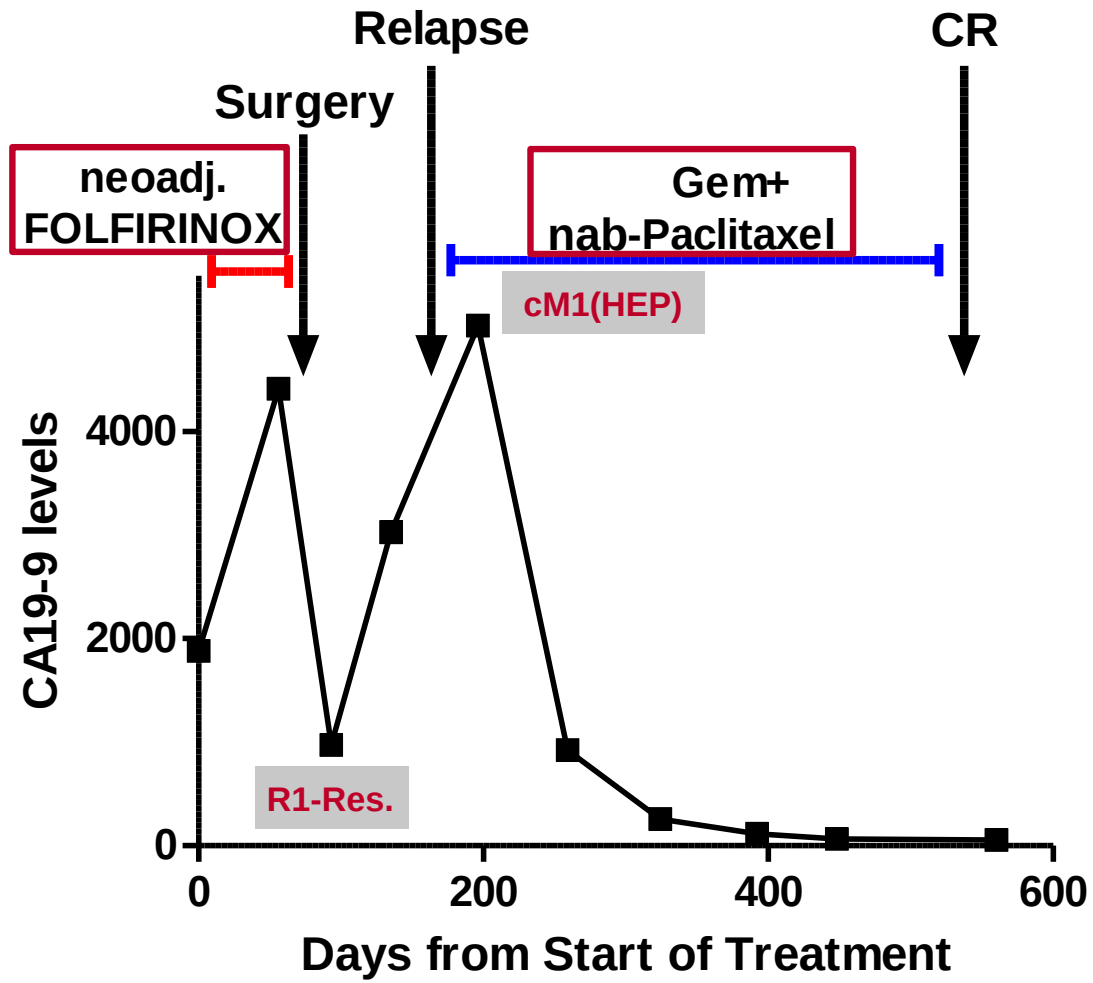
6. Finanzierung wissenschaftlicher Untersuchungen
Pierre Fabre, Novartis

7. Andere finanzielle Beziehungen

8. Immaterielle Interessenkonflikte

Präzisionsbehandlung beim Pankreaskarzinom?

Fallbeispiel



32-jähriger Patient

- leere Familienanamnese, keine Risikofaktoren
- Borderline-resektabler Pankreaskopftumior
- CA19-9 2000 kU/l

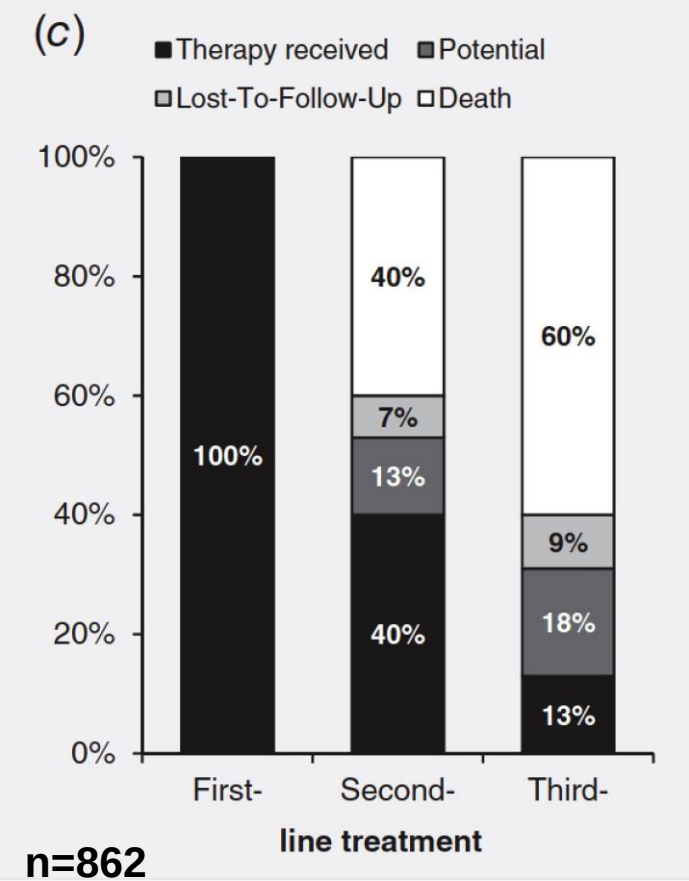
(1) Fehlen prädiktiver Biomarker

(2) Limitierte Behandlungsmöglichkeiten

USZ Universitäts Spital Zürich

Therapiewirklichkeit mPDAC

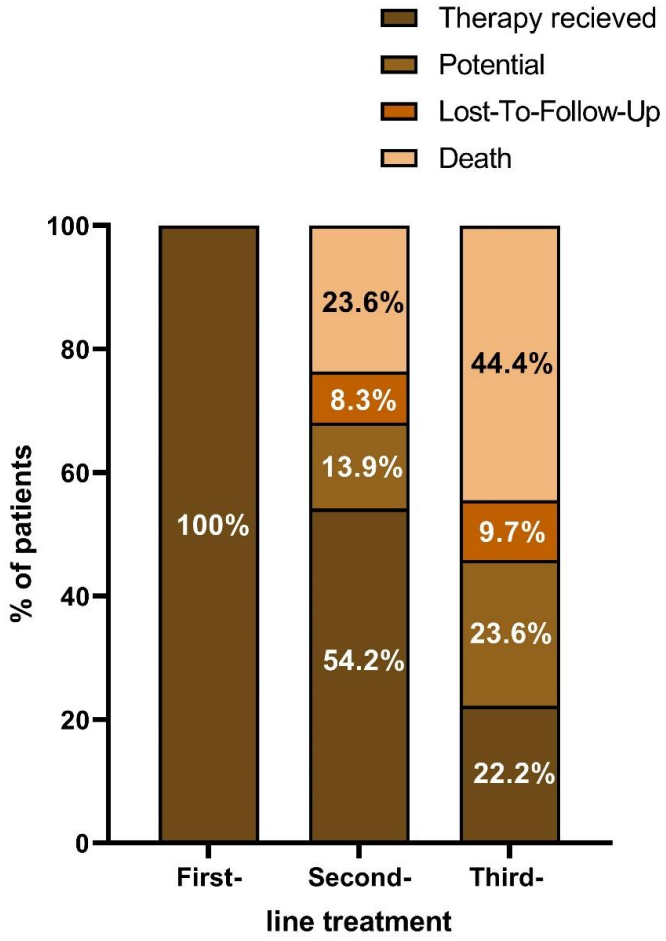
Real-world Daten



International Journal of Cancer 2019; 144 (5), 981-990

Real-World

- nur ca. 40-60% Zweitlinientherapie
- Präzisionsmedizin 1st line

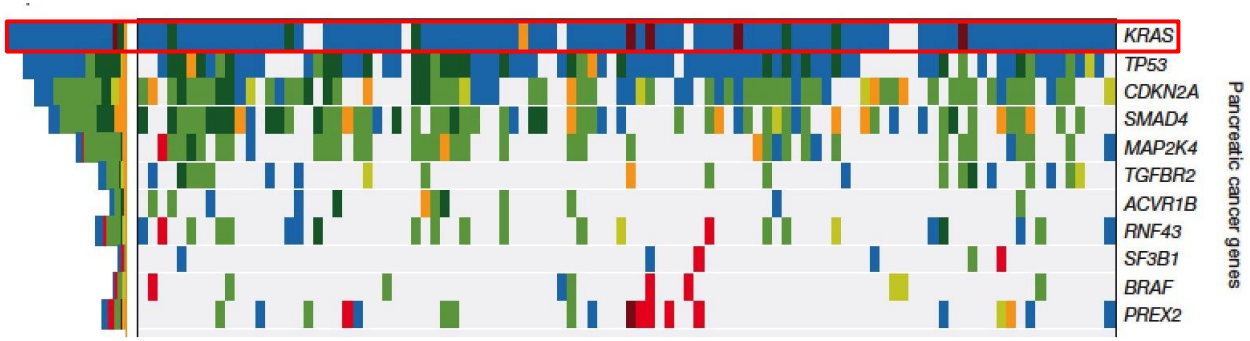


USZ cohort

Hussung et al. unpublished

USZ Universitäts Spital Zürich

Molekularpathologie Pankreaskarzinom



93-95% *KRAS* mutations

3% KRAS G12C

5-7% *KRAS*–WT

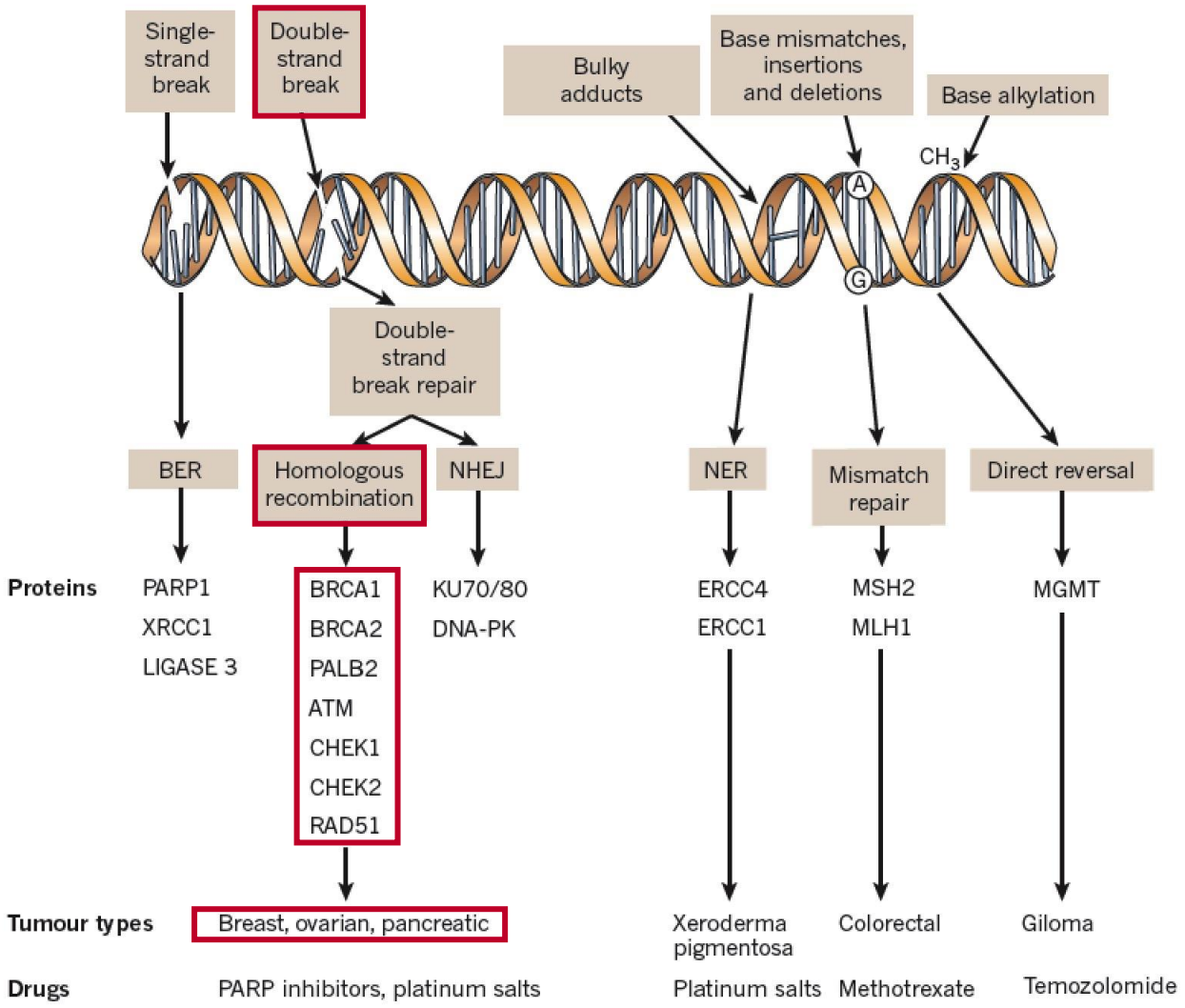
Molecular heterogeneity

20% homologous recombination deficiency (HRD)

<1% dMMR/ MSI-H

Nature. 2015 Feb 26; 518(7540): 495–501.

Homologous Recombination Repair Deficiency (HRD)

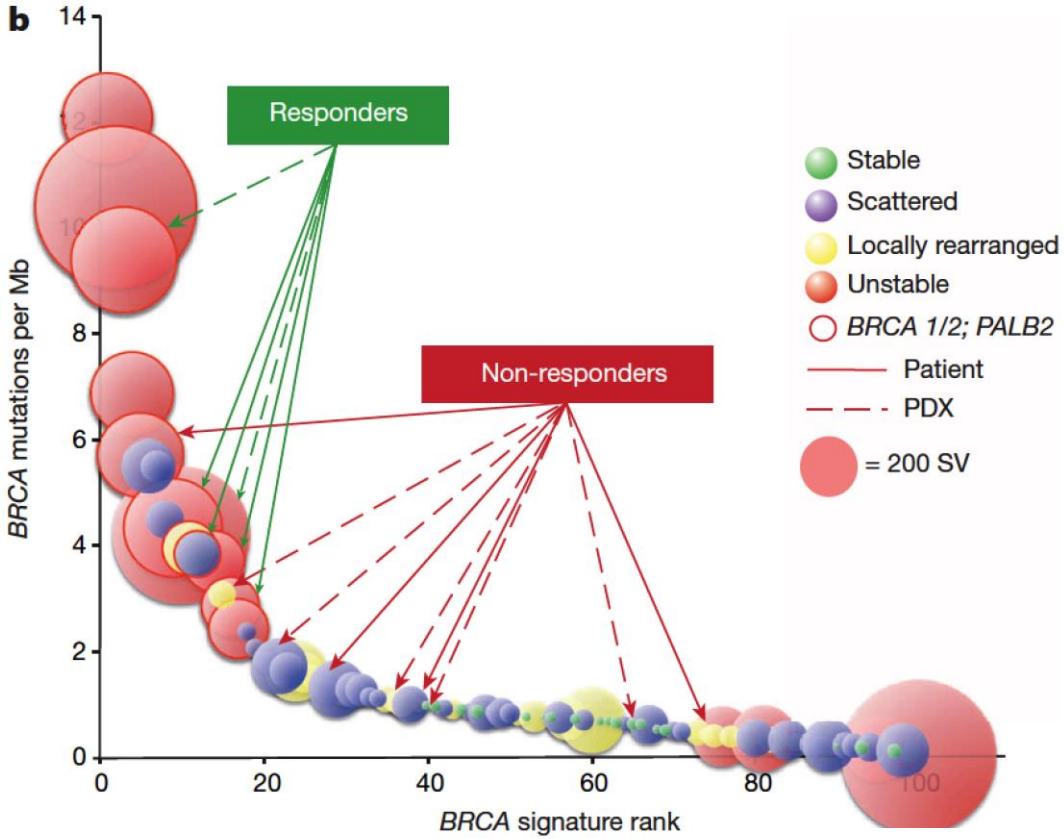


Lord, Nature Reviews 2012

HRD/BRCAness (20%)

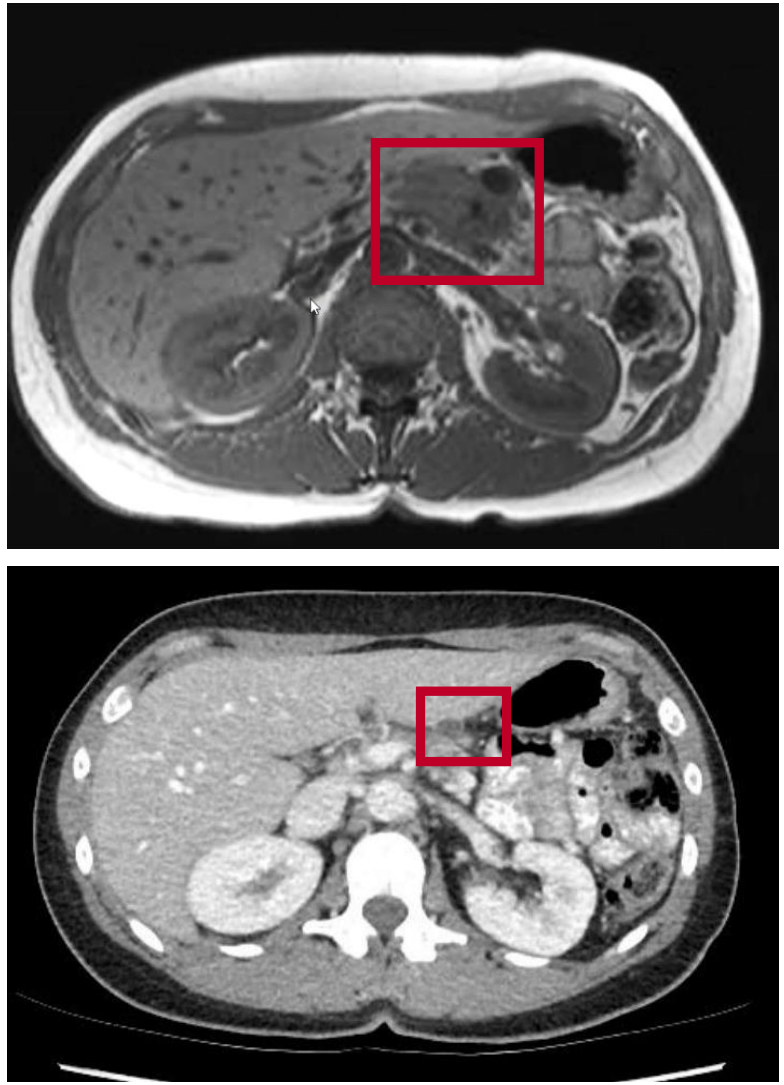
- **"Core":** BRCA1, BRCA2, PALB2,
- **"Non-core":** ATM, ATR, ATRX, BAP1, BARD1, BRIP1, CHEK1, CHEK2, RAD50, RAD51, RAD51B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, or FANCL
- **HRD-positive:** Large Scale Transitions (LST), Loss of Heterozygosity (LOH), Telomeric Allelic Imbalances (TAI) → **Genomic Instability Score (GIS)**

Platinsensitivität HRD Pankreaskarzinome



Nature **518**, 495–501 (26 February 2015) | doi:10.1038/nature14169

gBRCA2-mut. PDAC



pCR nach 12 Zyklen FOLFIRINOX

Platinsensitivität HRD Pankreaskarzinome

Randomized Phase II Cisplatin, Gemcitabine +/- Veliparib; Germline *BRCA/PALB2*

Untreated Stage III- IV
ECOG 0-1
g*BRCA1/2, PALB2*
N= 50

RANDOMIZE

Arm A:
Cisplatin 25 mg/m^2,Gemcitabine 600mg/m^2 day 3,10
+ Veliparib 80 mg BID day 1-12
All q3 weeks
Option for maintenance Veliparib

Arm B:
Cisplatin 25 mg/m^2,Gemcitabine 600mg/m^2 day 1,8 q3 weeks

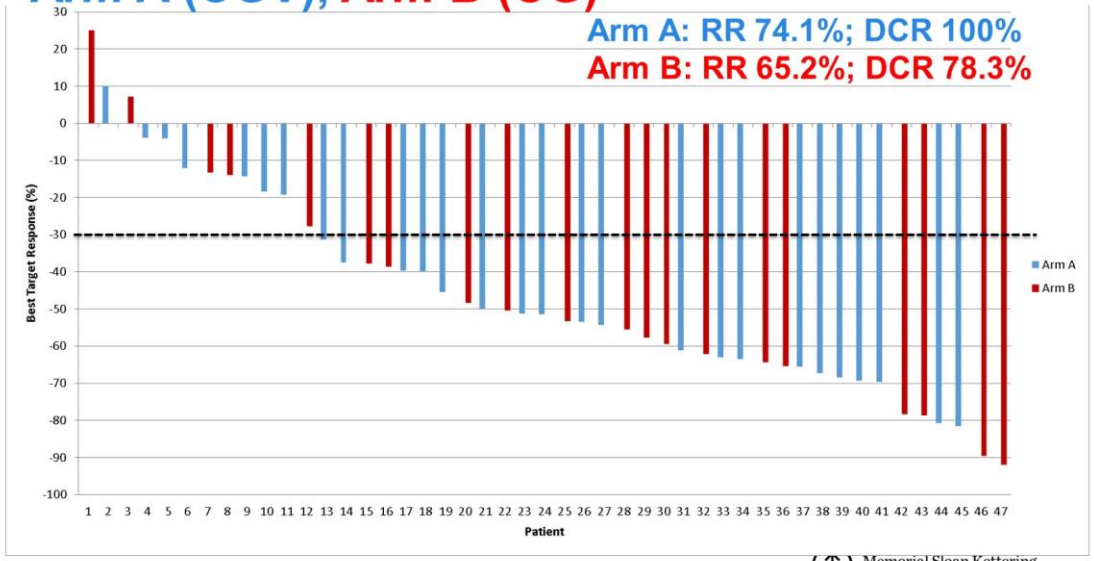
Primary Endpoint: Response Rate
Secondary: PFS, DCR, OS, exploratory
Simon 2-stage design: 16-25/arm
Unacceptable RR 10%; Promising 20%; Type 1, II errors 10%

NCT01585805; O'Reilly, et al. Cancer, 2018

Memorial Sloan Kettering Cancer Center

Primary Endpoint: RECIST Response

Arm A (CGV), Arm B (CG)



RR: Response Rate; DCR: Disease Control Rate

Memorial Sloan Kettering Cancer Center

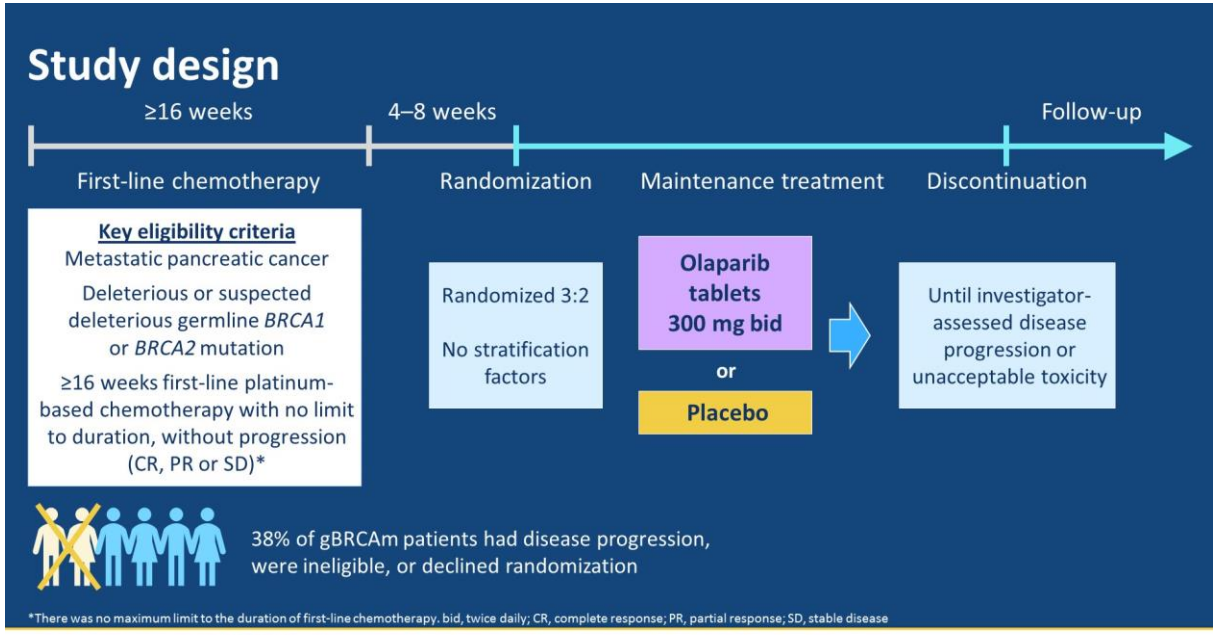
O'Reilly et al. *Journal of Clinical Oncology* (2020)

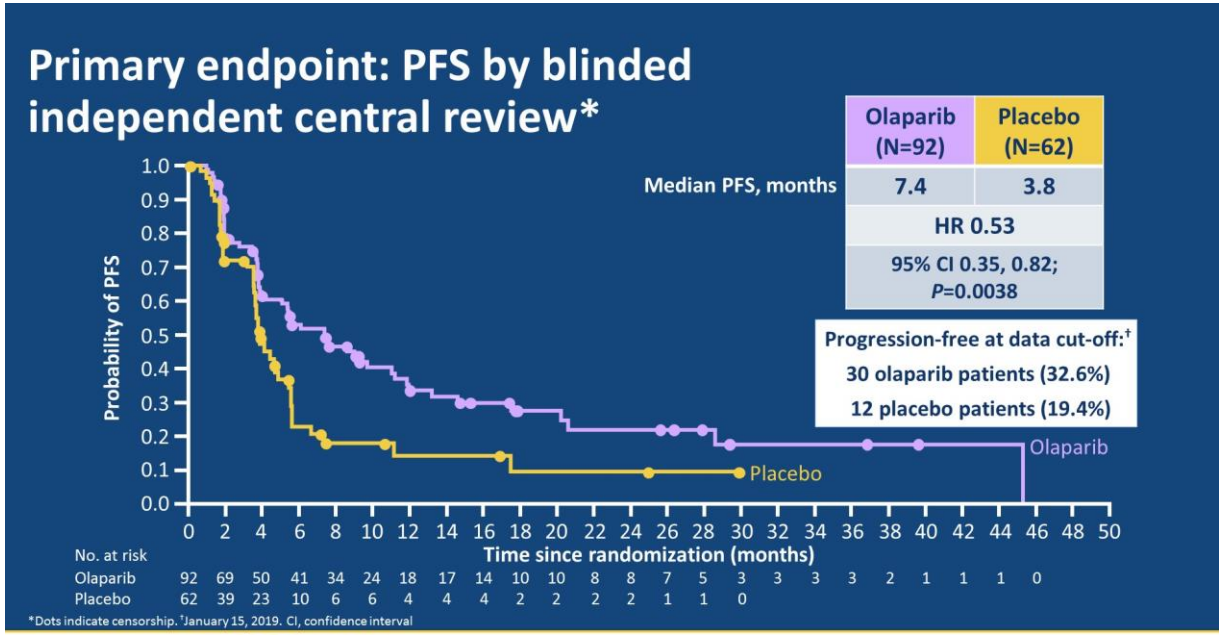
OS 15.5 months (95%CI, 12.2 to 24.3 months)
OS 16.4 months (95%CI, 11.7 to 23.4 months)

Platinhaltige Chemotherapie!

PARP-Inhibition gBRCA^{MUT} Pankreaskarzinom

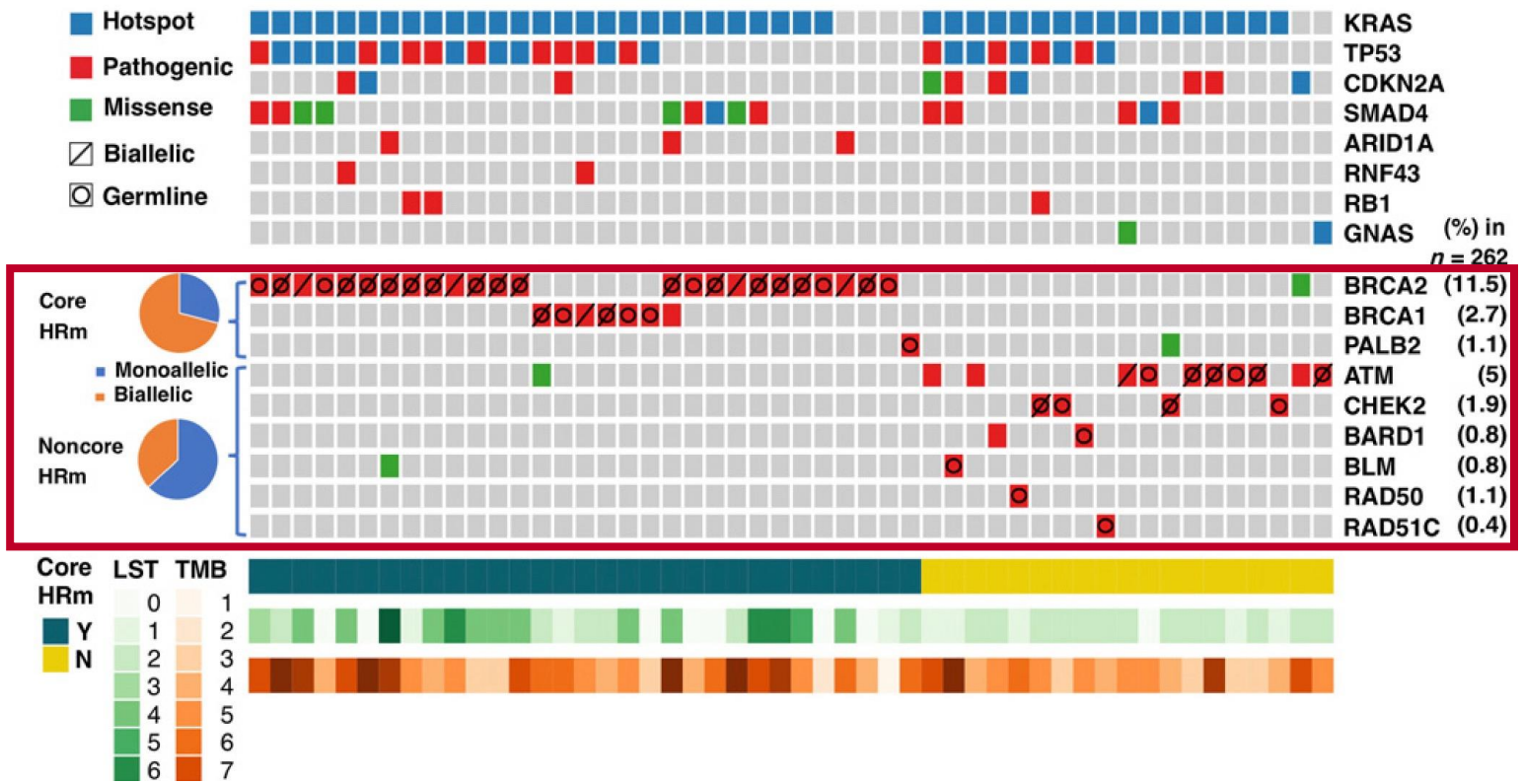
POLO trial – BRCA1/2 germline alterations only

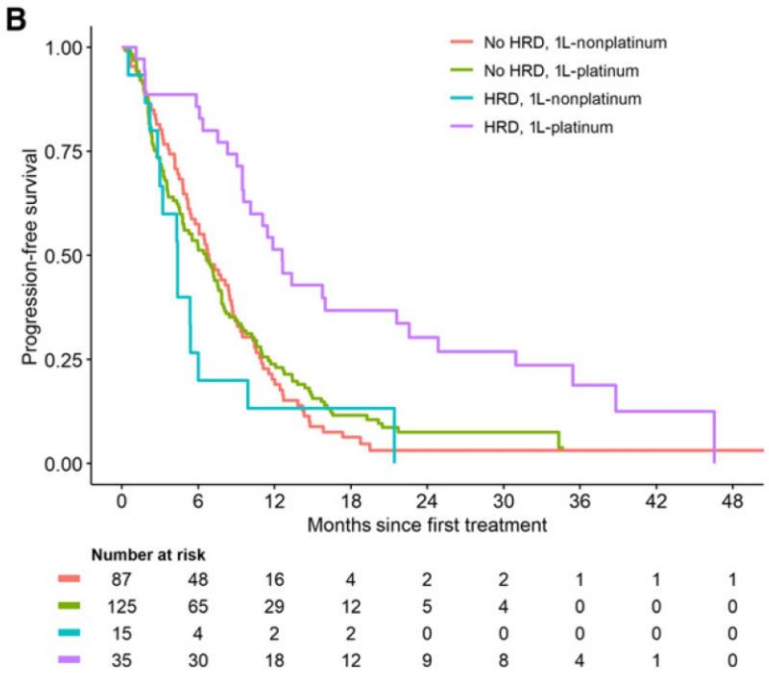




Olaparib-Erhaltung für BRCA^{MUT} PDACs

HRD jenseits von gBRCA1/2





Clin Cancer Res; 26(13) July 1, 2020

HRD PDACs

- Platin-Benefit auch bei somatischen HRD-Alterationen
- mögliche Relevanz einiger Non-Core-HRD Gene

Präzisionsbehandlung 1st line

Erstlinientherapie

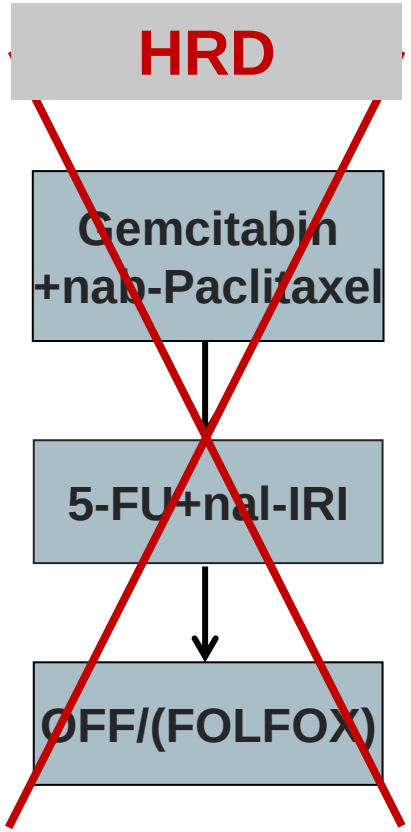
HRD Pankreaskarzinom

→ platinhaltige Erstlinientherapie

→ Olaparib-Erhaltung bei $BRCA^{MUT}$ und Platinsensitivität

→ Keimbahntestung nicht vergessen

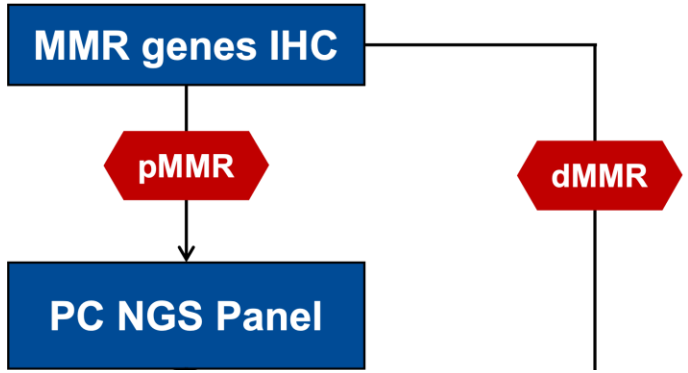
Upront molekulare Testung im Stadium IV oder bei Rezidiv !



Stratifizierte Molekulare Testung – USZ Algorithmus

Teststrategie

Stage 1

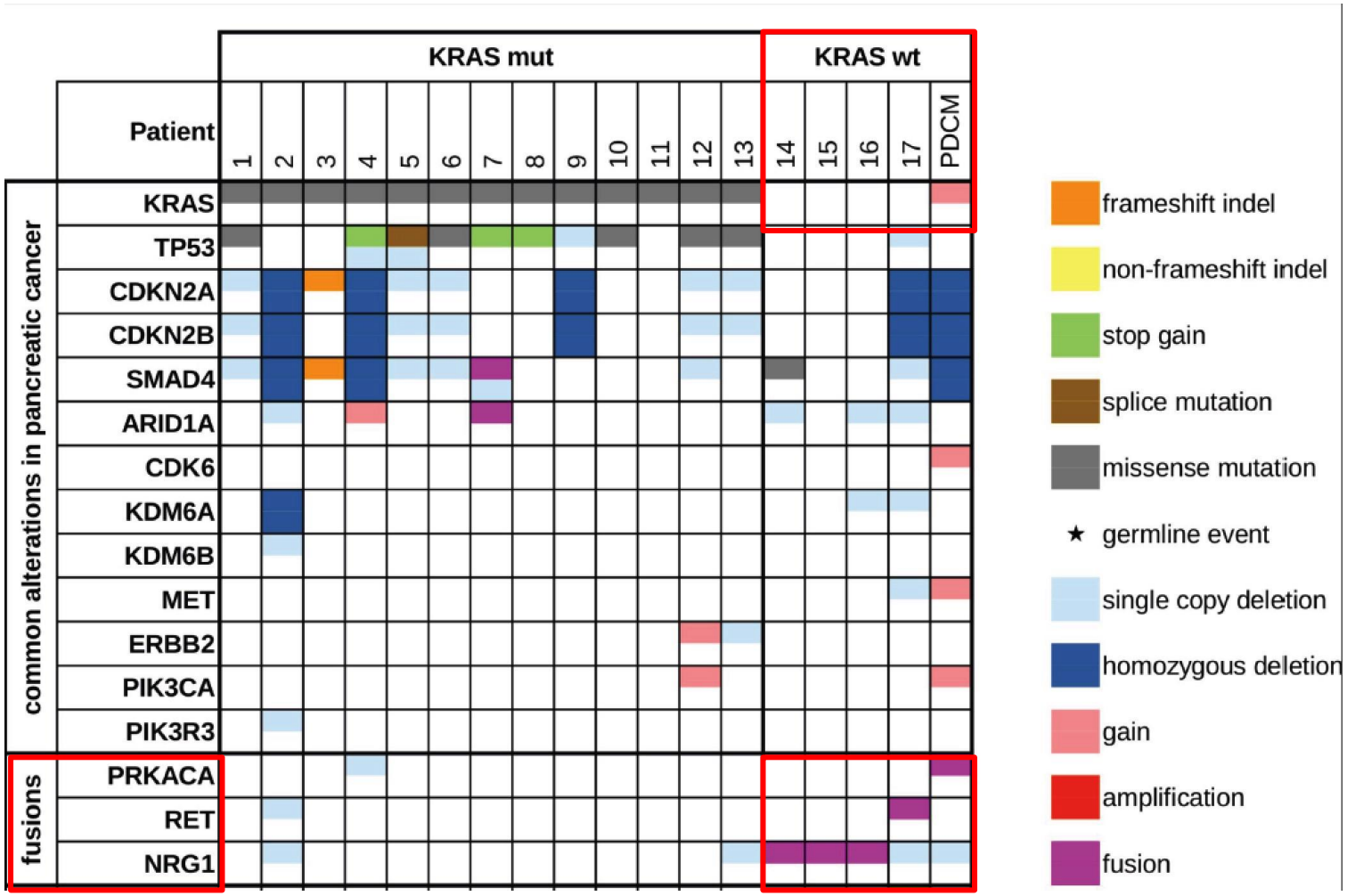


PC DDR Panel

KRAS	*CHEK2*
TP53	*RAD50*
CDKN2A/B	*RAD51*
SMAD4	*RAD51B*
BRAF	*RAD51C*
GNAS	*RAD51D*
ERBB2	*FANCA*
MYC	*FANCD2*
PIK3CA	*FANCI*
RB1	*BAP1*
STK11	*BARD1*
	ATRX
BRCA1	*ARID1A*
BRCA2	*BRIP1*
PALB2	*ATR*
ATM	*CDK12*
CHEK1	*POLE*

R. Fritsch und A. Weber, USZ)

Rare drivers in KRAS wild type tumors



5-7% KRAS–WT

- harbor distinct oncogenic drivers
- oncogenic fusions (RET, ROS, ALK, NTRK, NRG1, BRAF)
- Class I-III BRAF alterations
- RTK alterations

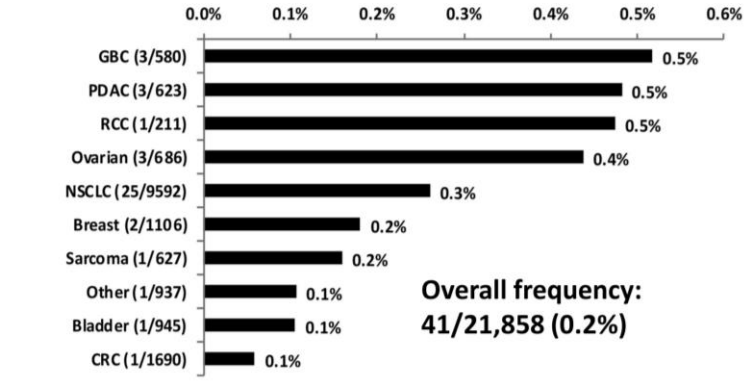
KRAS-WT

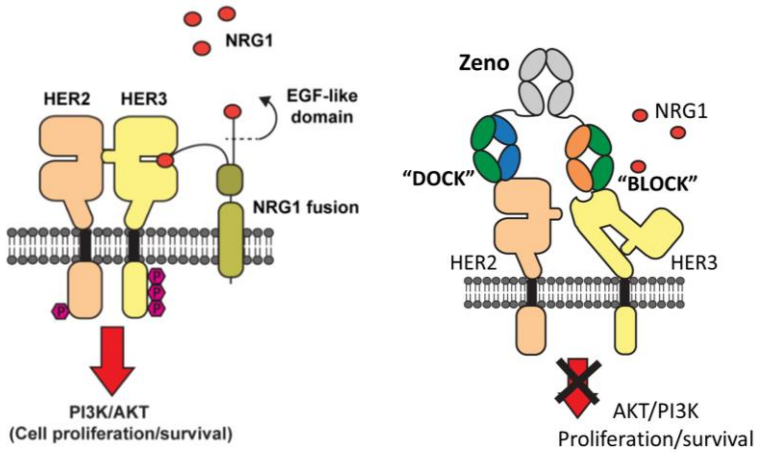
USZ Universitäts Spital Zürich

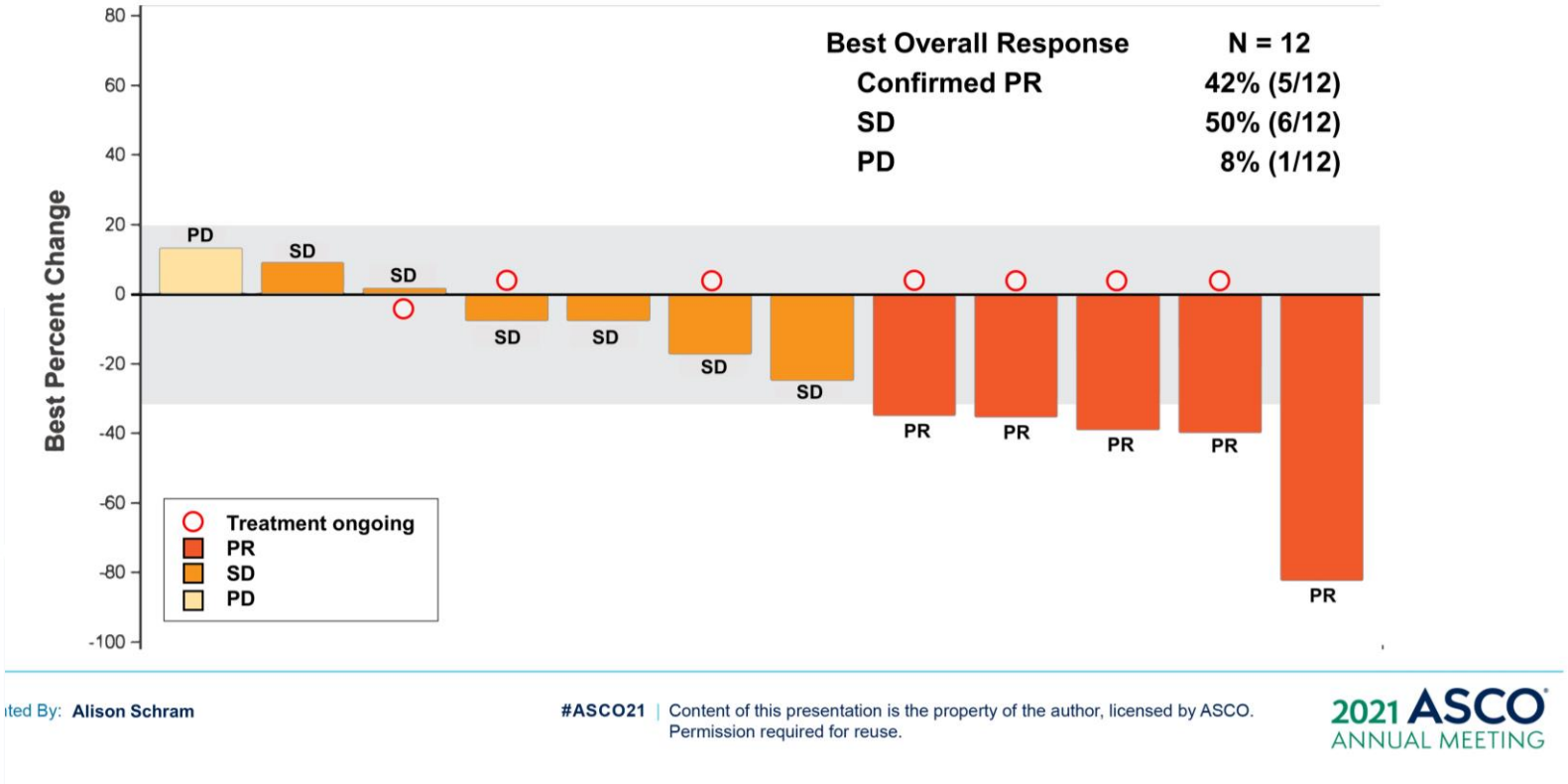
DKTK/NCT-MASTER Programm Heining et al., Cancer Discovery (2018), online 25 May 2018

KRAS wild type

NRG-1 (Neuregulin 1) fusions in pancreatic cancer







Cancer Discov 2022

Zenocutuzumab for NRG1-fusions in pancreatic cancer

Fallbeispiel – *KRAS* WT Pankreaskarzinom

Seltene Treiber

Genomic Signatures

Microsatellite status - MS-Stable

Tumor Mutational Burden - TMB-Low (4 Muts/Mb)

Gene Alterations

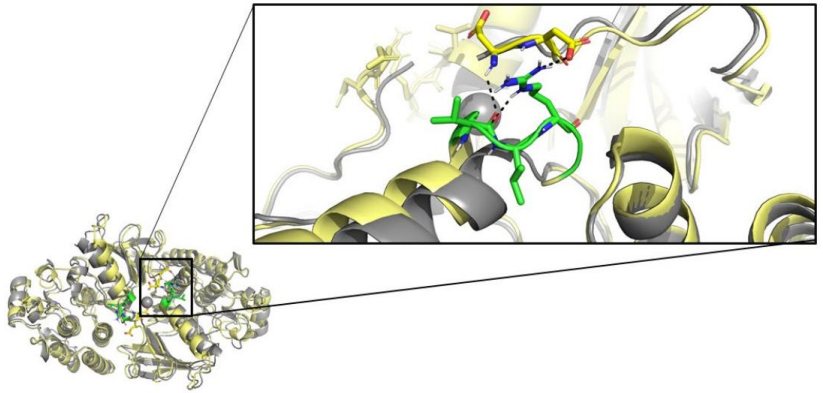
For a complete list of the genes assayed, please refer to the Appendix.

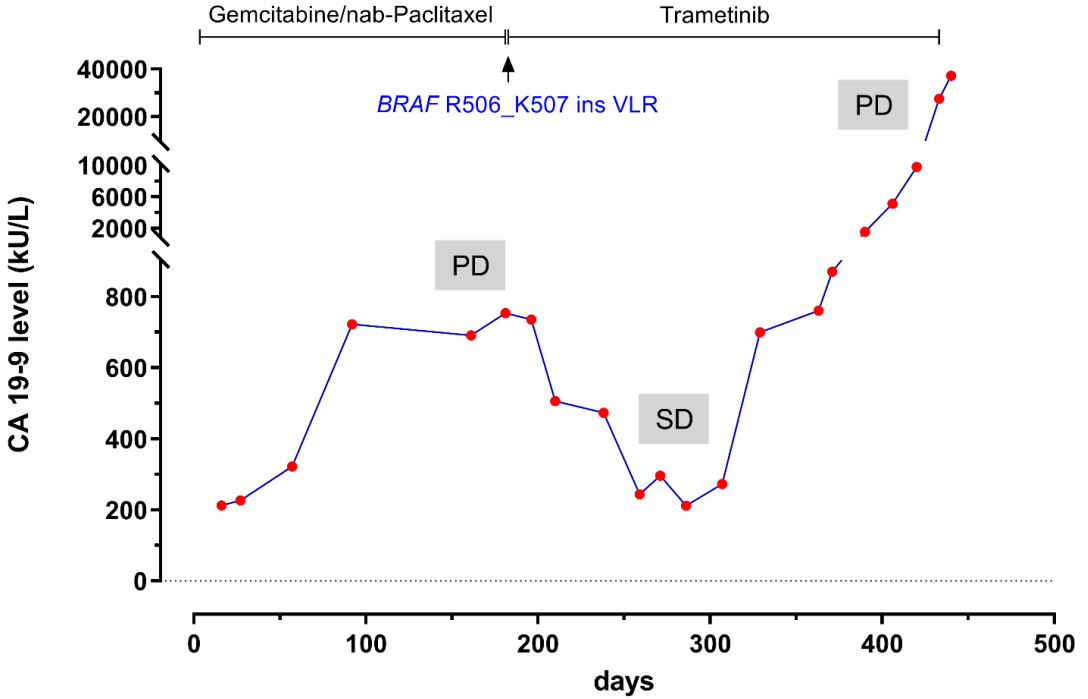
BRAF R506_K507insVLR

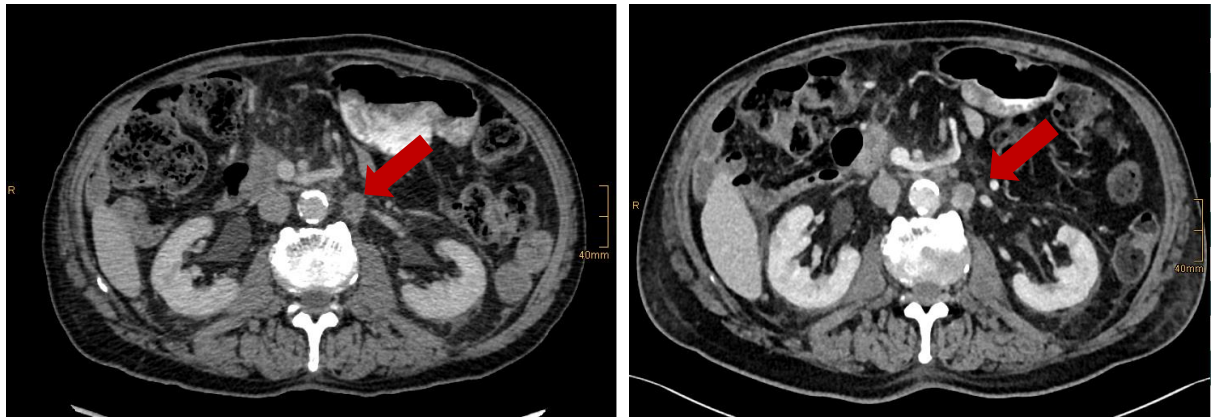
BARD1 C304fs*9

CDKN2A/B p16INK4a R58* and p14ARF P72L

TP53 M246V







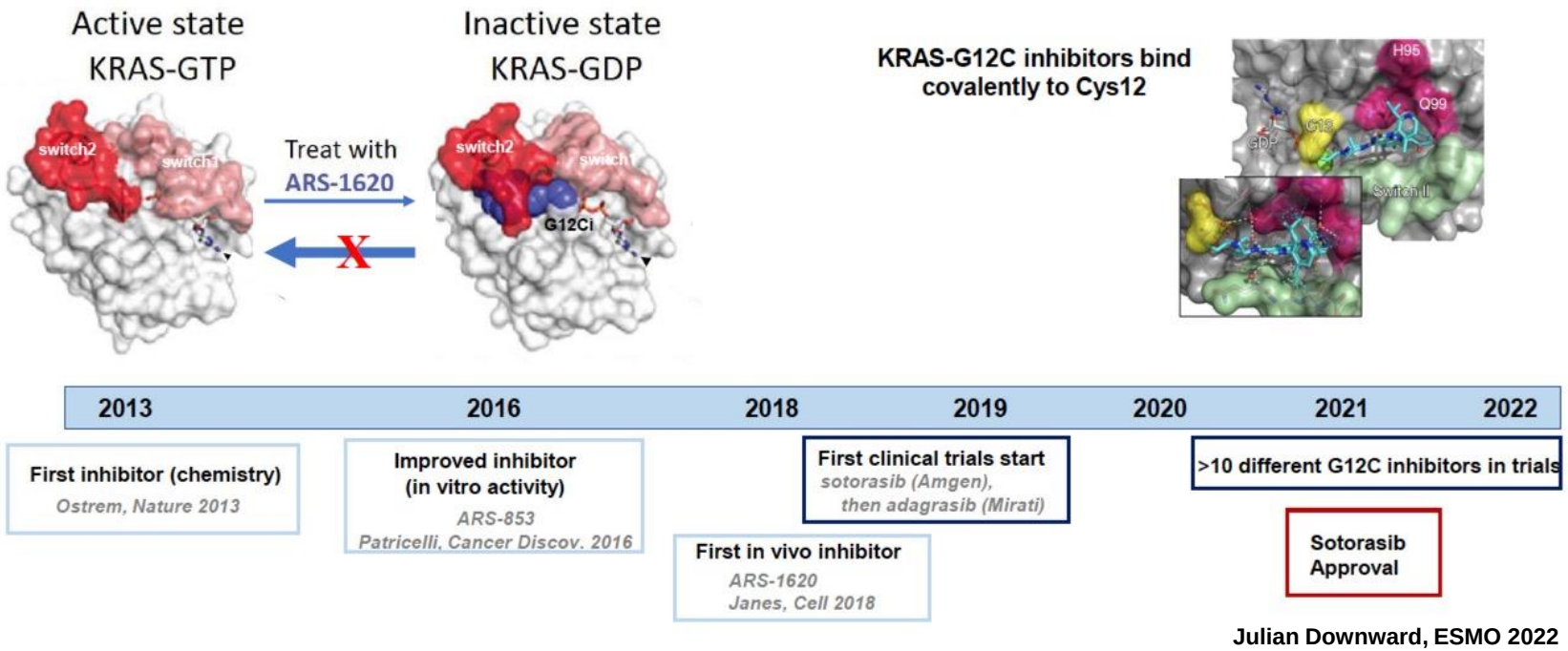
Seltene Klasse II *BRAF* Mutation

Behandlung mit Trametinib

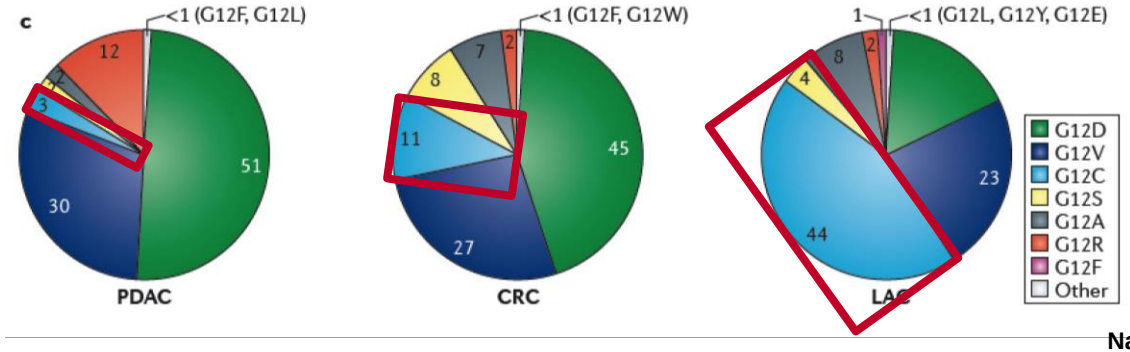
6 Monate stabile Erkrankung

USZ Universitäts Spital Zürich

KRAS G12C Inhibitoren



Julian Downward, ESMO 2022



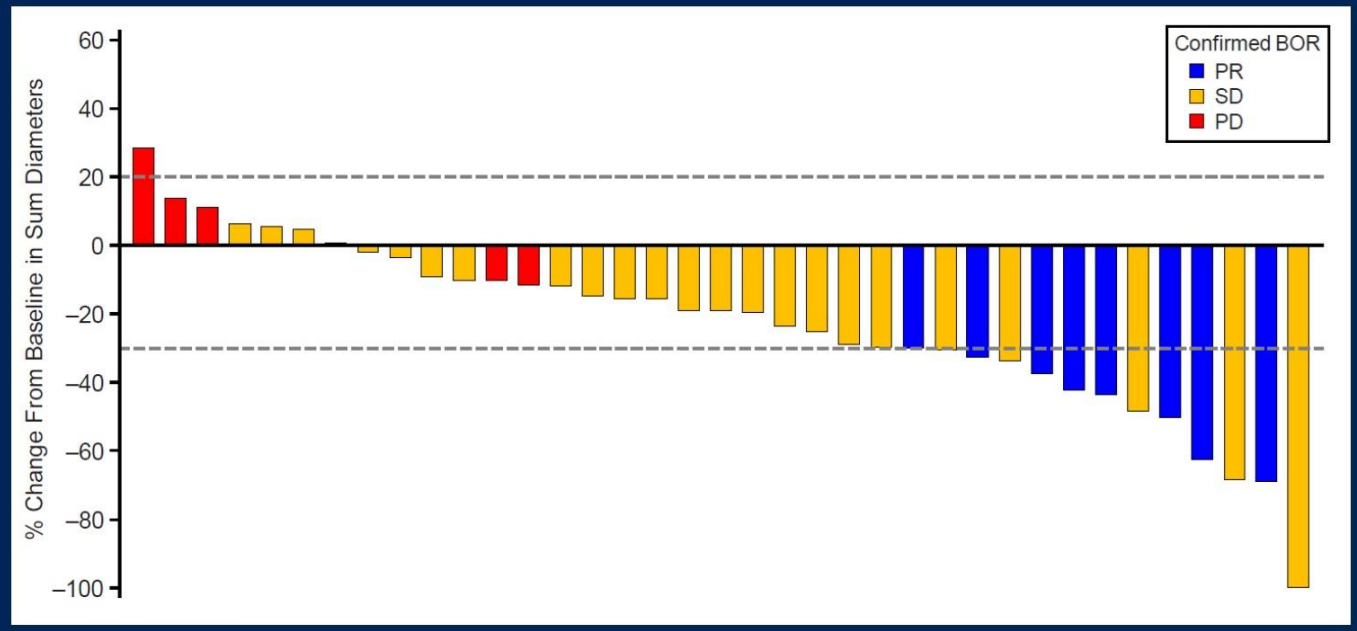
Nat. Rev. Cancer

2-3% KRAS-G12C im Pankreaskarzinom

Sotorasib mPDAC

KRAS G12C

Best Tumor Shrinkage by Central Review



Data cut-off date 01NOV2021
Percent change from baseline in sum of diameters only considers tumor assessments prior to and include the 1st assessment where timepoint response is progressive disease, and prior to start of next anti-cancer therapy.
1 Patient with unknown tumor shrinkage % is not shown

ASCO Plenary Series #ASCOPlenarySeries

PRESENTED BY: John H Strickler, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

ASCO-GI 2022
NEJM 2023

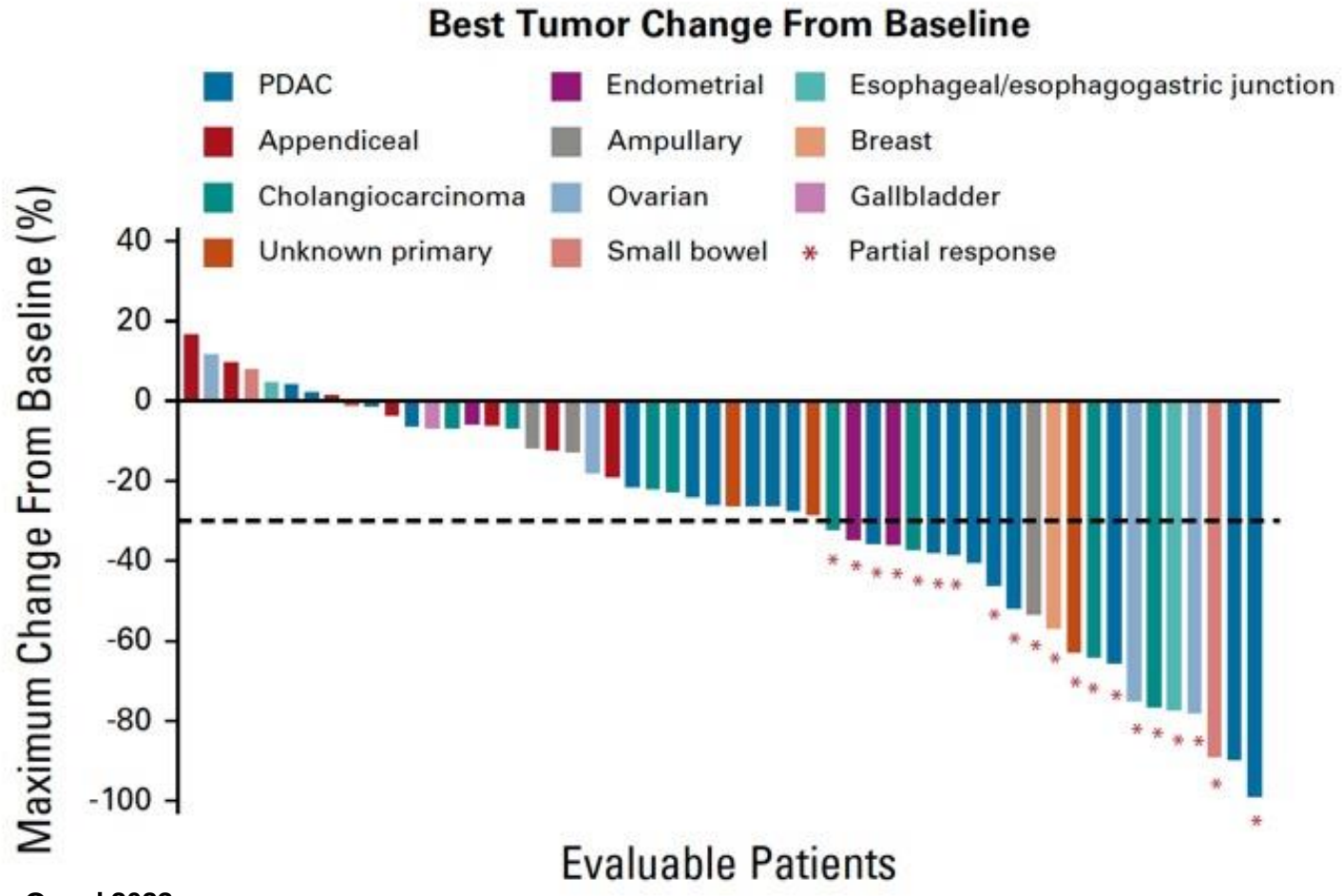
CodeBreaK100:

n=38; ORR= 21%; 84% DCR; mOS 6.9 Monate

USZ Universitäts Spital Zürich

Adagrasib mPDAC

KRAS G12C



J Clin Oncol 2023

KRAS Inhibition PDAC

(1) Pankreaskarzinome sind «KRAS-addicted»

(2) Potential für Kombinationen (anti-EGFR, -HER2, Chemo-therapie, neue Substanzen?)

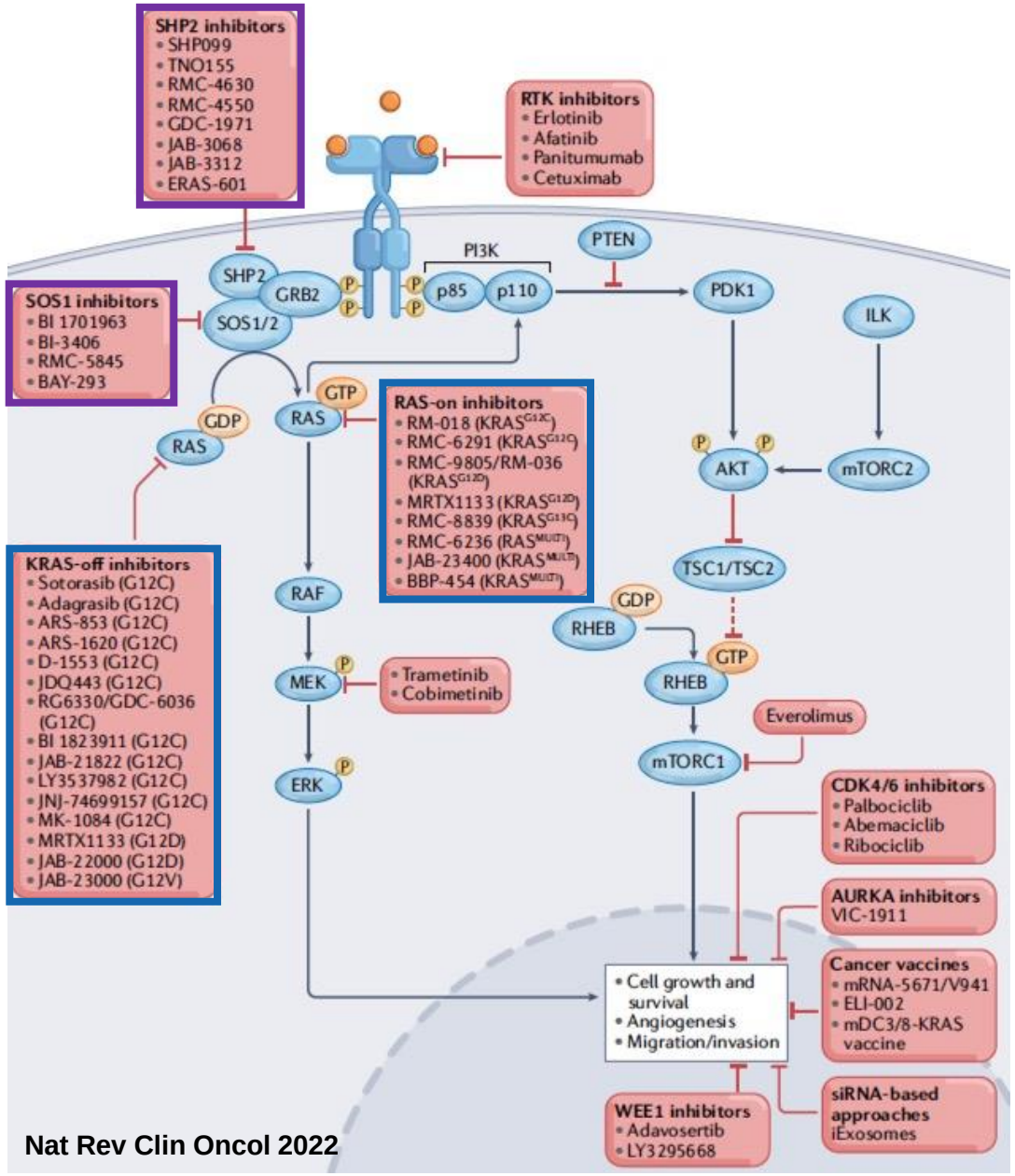
(3) Mechanismen primärer und erworbener Resistenz

KRYSTAL-1 mPDAC:

n=21; ORR: 33%; mPFS: 5.4 months, mOS: 8.0 months

KRAS Inhibition

KRAS Inhibitoren in Entwicklung



Nat Rev Clin Oncol 2022

Neue KRAS- und Signalweginhibitoren

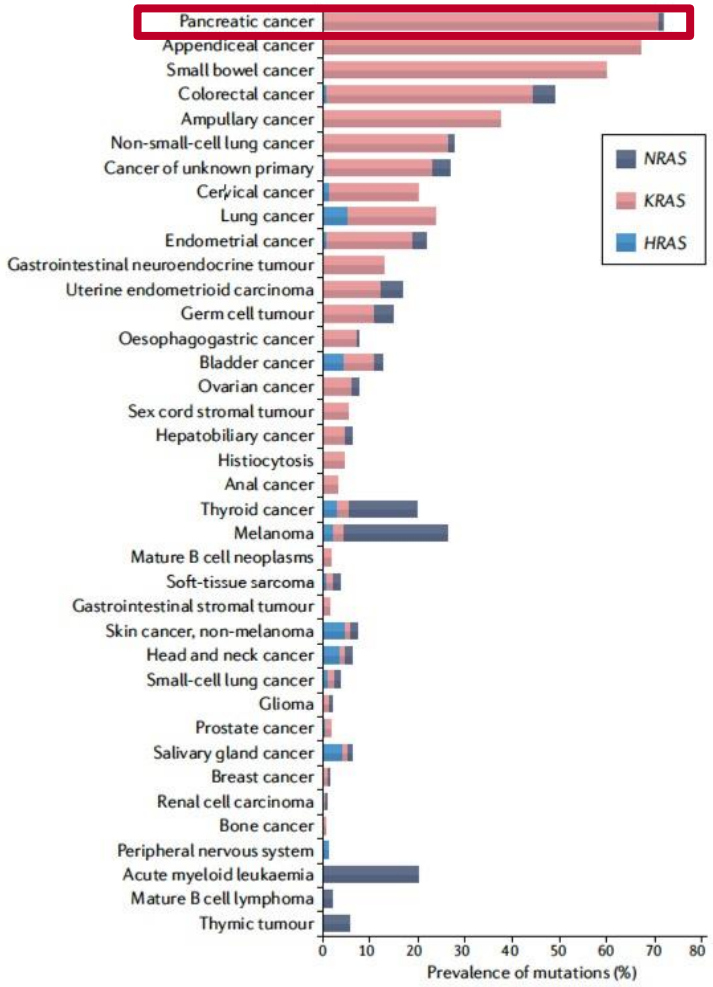
(1) Erste Inhibitoren für KRAS G12D

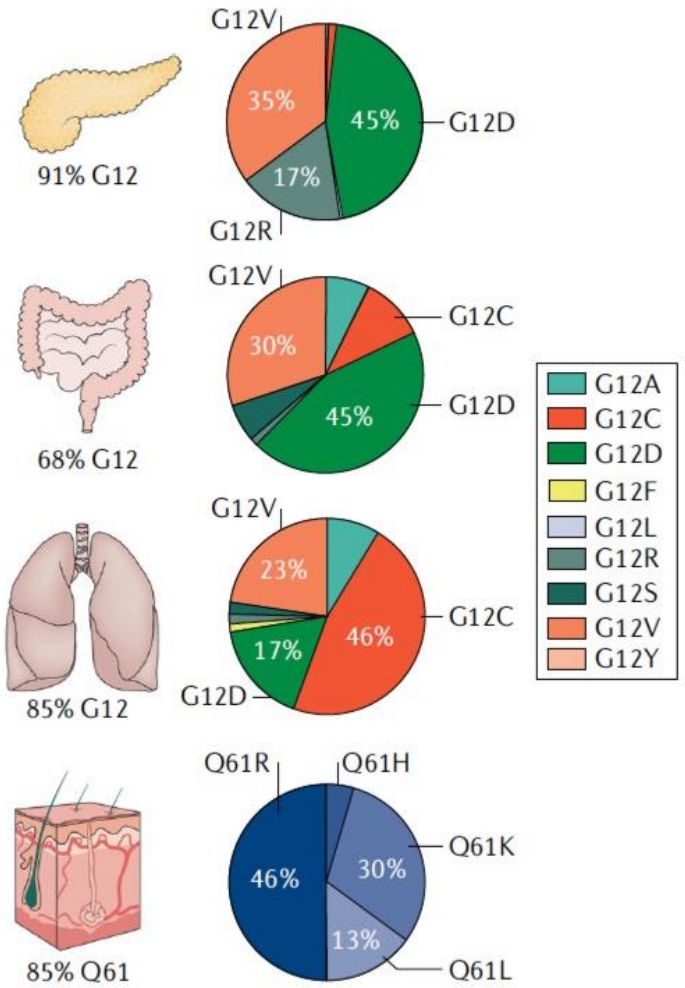
(2) Pan-KRAS-Inhibitoren

(3) SHP2- und SOS-Inhibitoren

(4) Kombinationen

KRAS G12D mutations in cancer





KRAS G12D

Häufigste SNV im Pankreaskarzinom

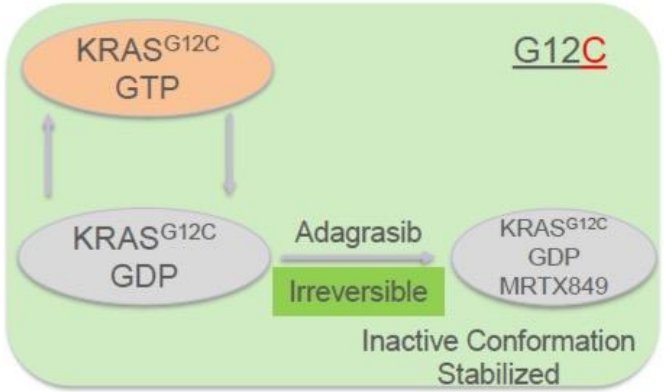
Bisher keine Inhibitoren

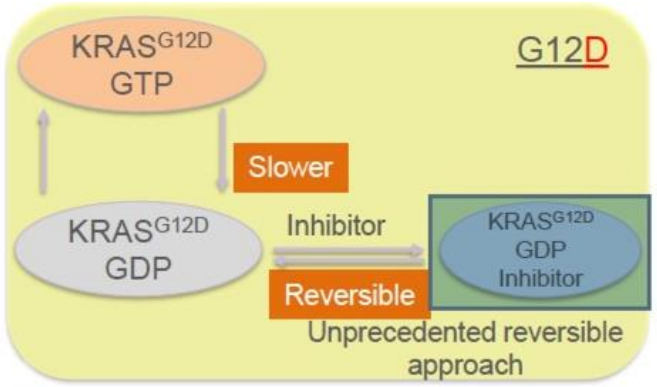
KRAS-G12D Protein schwierig zu targeten

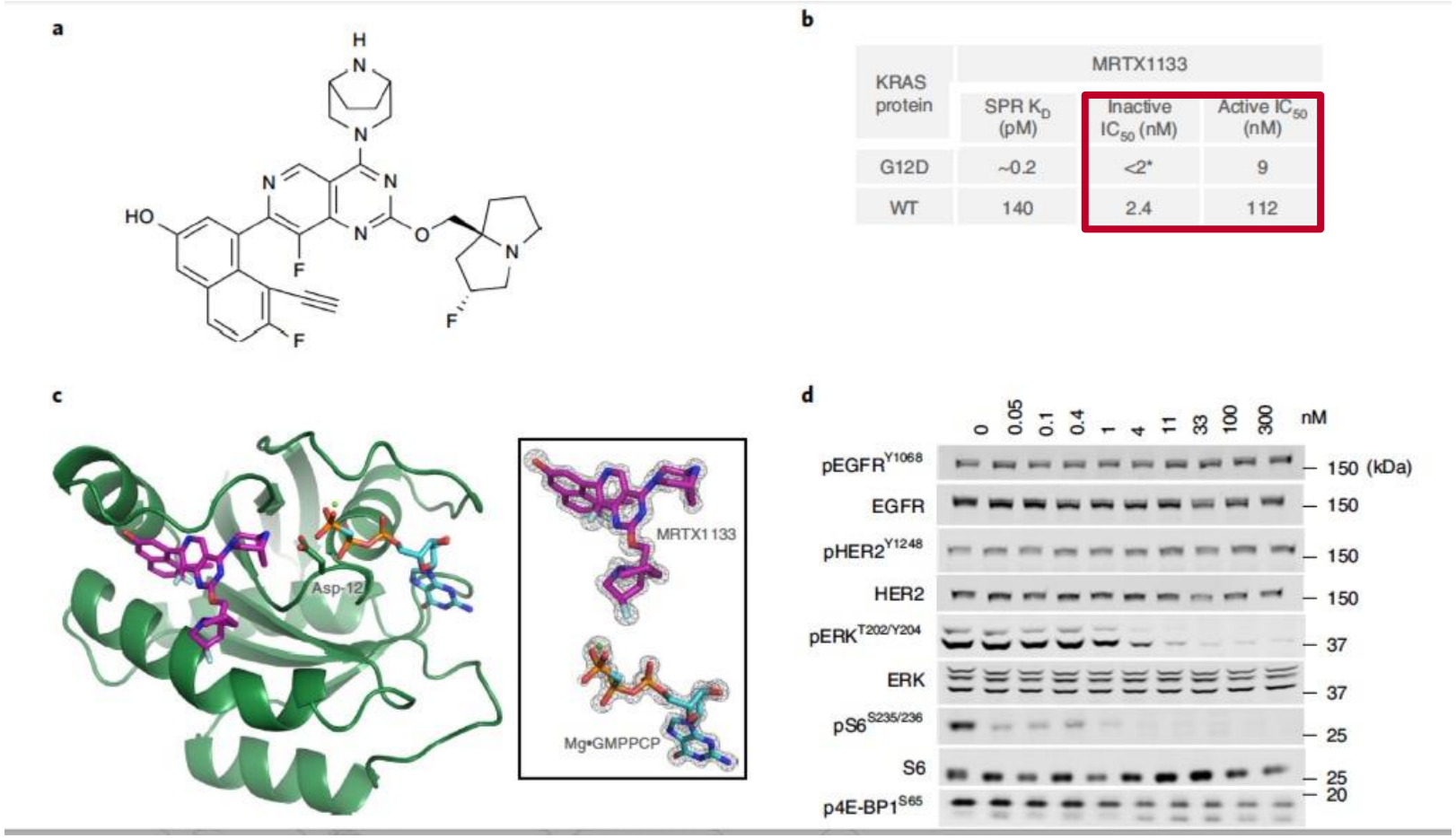
Nat Rev Clin Oncol 2022

MRTX1133 - nicht-kovalenter KRAS G12D Inhibitor

KRAS G12D







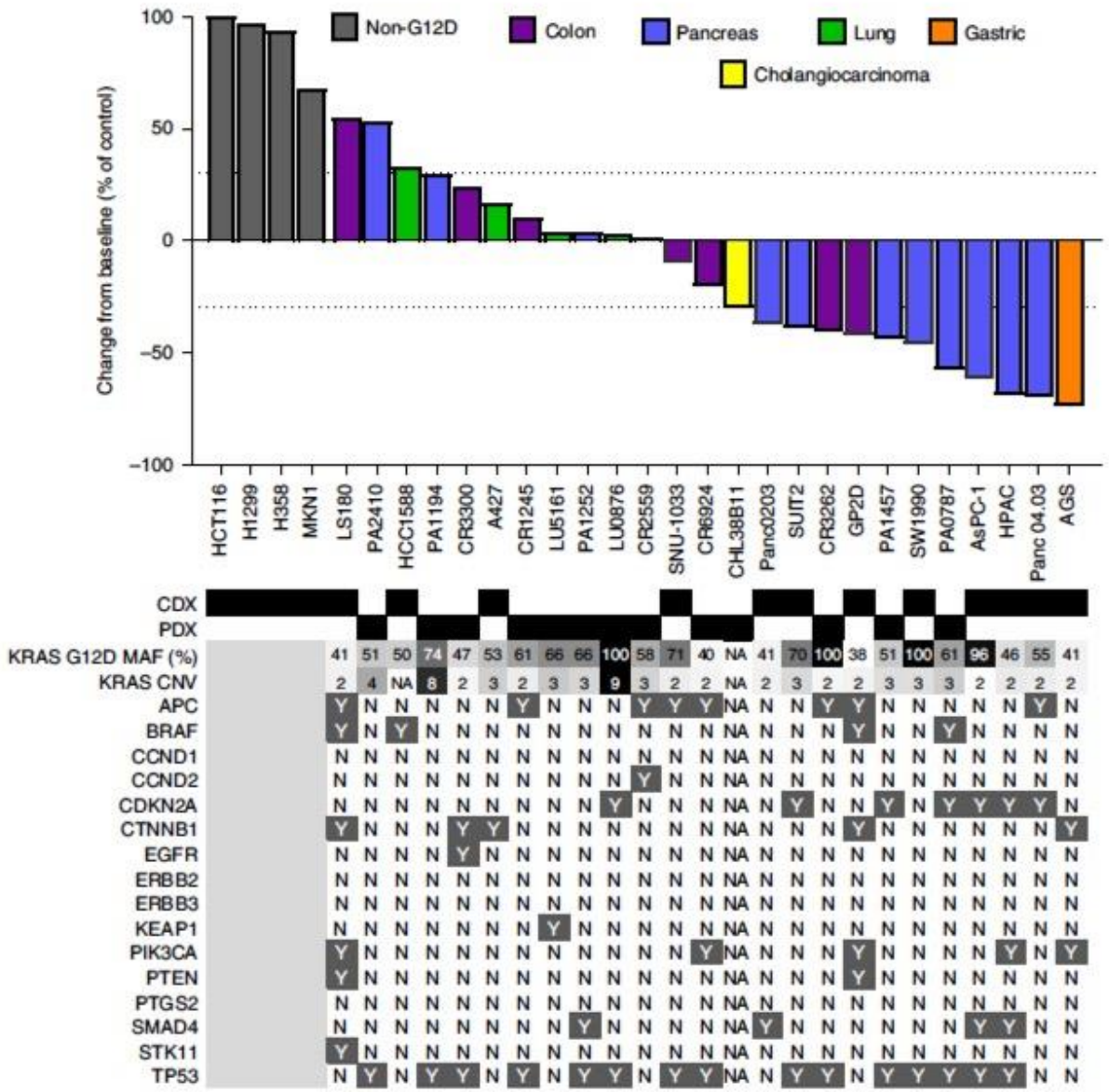
KRAS protein	MRTX1133		
	SPR K_D (pM)	Inactive IC_{50} (nM)	Active IC_{50} (nM)
G12D	~0.2	<2*	9
WT	140	2.4	112

Hallin et al., Nat Med 2022

Strukturell aus Adagrasib entwickelt

KRAS G12D

MRTX1133 - PDX und Xenografts



Hallin et al., Nat Med 2022

Patient-derived Xenografts und Zelllinien

Effekt nur in KRAS G12D mutierten Tumoren

Phase I Studie gestartet (USA)

Frontrunner für die Klinik

Neue KRAS Inhibitoren

Table 1 | New KRAS frontiers

Drug	Sponsor	Properties	Status
New variant-specific agents			
ASP3082	Astellas	KRAS-G12D targeted degrader	Phase I
HRS-4642	Jiangsu Hengrui Medicine	KRAS-G12D inhibitor	Phase I in China
MRTX1133	Mirati	Non-covalent KRAS-G12D inhibitor	Phase I/II to start
RMC-9805	Revolution Medicines	KRAS-G12D molecular glue inhibitor[a]	IND-enabling
RMC-8839	Revolution Medicines	KRAS-G13C molecular glue inhibitor[a]	IND-enabling
BI-KRASG12D	Boehringer Ingelheim	Non-covalent KRAS-G12D inhibitor	Preclinical
JAB-22000	Jacobio	KRAS-G12D inhibitor	Preclinical
ERAS-4	Erasca	KRAS-G12D inhibitor	Preclinical
Pan-KRAS inhibitors			
RMC-6236	Revolution Medicines	RAS^{MULTI} molecular glue inhibitor[a]	Phase I
NA	Astellas	Pan-KRAS degrader	IND in 2023
NA	Boehringer Ingelheim	Pan-KRAS degrader	Preclinical
BI-2865	Boehringer Ingelheim	Pan-KRAS inhibitor	Preclinical
New on-state inhibitors			
FMC-376	Frontier Medicines	KRAS-G12C inhibitor	IND-enabling
BBO-8520	BridgeBio	KRAS-G12C inhibitor	IND-enabling

[a]Revolution Medicines' KRAS-targeted agents act on the on-state protein. IND, investigational new drug; NA, not available.

Wirkprinzipien

(1) Selektive Inhibitoren (kovalent und non-kovalent)

(2) Protein degraders

(3) Molecular glues

Nat Rev Drug Discov 2023

Erste klinische Daten ESMO 2023

Neue KRAS Inhibitoren

652O - Preliminary clinical activity of RMC-6236, a first-in-class, RAS-selective, tri-complex RAS-MULTI(ON) inhibitor in patients with KRAS mutant pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC)

Presentation Number 652O
Speakers Kathryn C. Arbour (New York, United States of America)
Lecture Time 08:30 - 08:40

RMC-6236

RAS^{MULTI} molecular glue inhibitor

LBA33 - A first-in-human phase 1 study of a novel KRAS G12D inhibitor HRS-4642 in patients with advanced solid tumors harboring KRAS G12D mutation

Presentation Number LBA33
Speakers Caicun Zhou (Shanghai, China)
Lecture Time 08:50 - 09:00

HRS-4642

Covalent KRAS G12D inhibitor

653O - Glecirasib (KRAS G12C inhibitor) in combination with JAB-3312 (SHP2 inhibitor) in Patients with KRAS p.G12C mutated solid tumors.

Presentation Number 653O
Speakers Jie Wang (Beijing, China)
Lecture Time 08:40 - 08:50

JAB-3312

SHP2 inhibitor plus KRAS G12C

Zusammenfassung

1. Die personalisierte Therapie metastasierter Pankreaskarzinome nimmt Fahrt auf
2. Rationale für platinhaltige Erstlinienchemotherapie für HRD Pankreaskarzinome
3. Olaparib mögliche Erhaltungstherapie für $BRCA^{MUT}$ Tumoren mit Platinresponse
4. KRAS WT PDACs brauchen umfassendes Profiling zum Aufspüren seltener Treiberonkogene
5. KRAS G12C Inhibitoren sind klinisch wirksam und sollten eingesetzt werden
6. Vielversprechende KRAS G12D- und panKRAS-Inhibitoren sind in frühen Studien

Vielen Dank!