Individuelle Therapien durch Bestimmung des „Fingerabdrucks „ ihrer Krebserkrankung

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Koordinator Cancer Center Oldenburg, Pius-Hospital
Sprecher CRISP Register Studie
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PD Dr. Lukas Carl Heukamp, PhD
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Hämatopathologie Hamburg

Große Leute bekommen häufiger Krebs !

Hunterian Museum

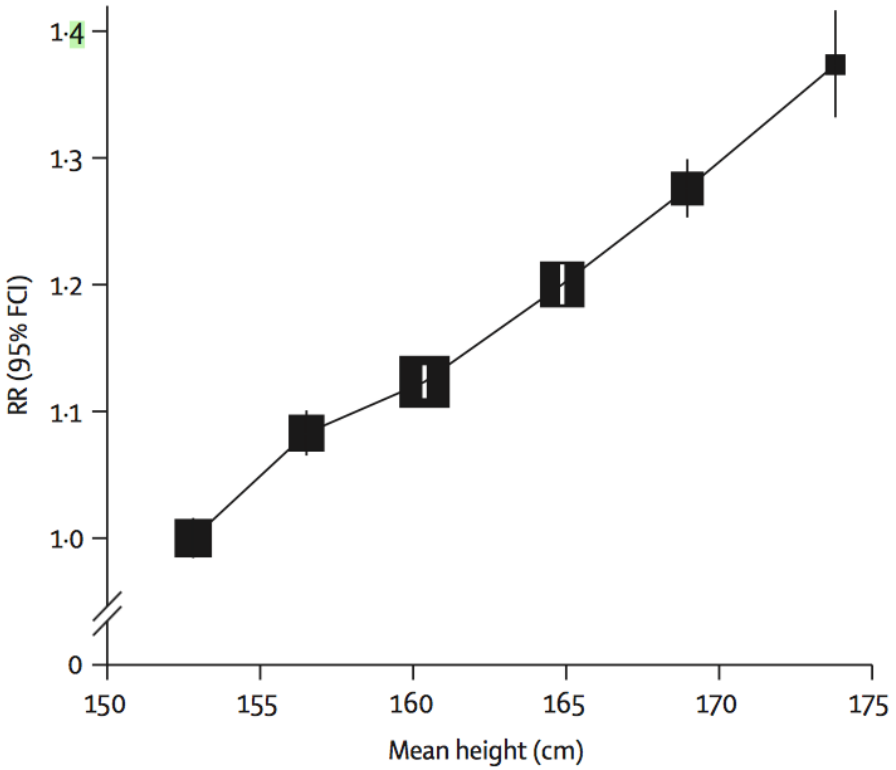
Körpergröße:

Platz 1: Niederlande
Platz 6: Deutschlang

Royal College of Surgeons
ADVANCING SURGICAL CARE

nowel Lungennetzwerk

Große Leute bekommen häufiger Krebs !

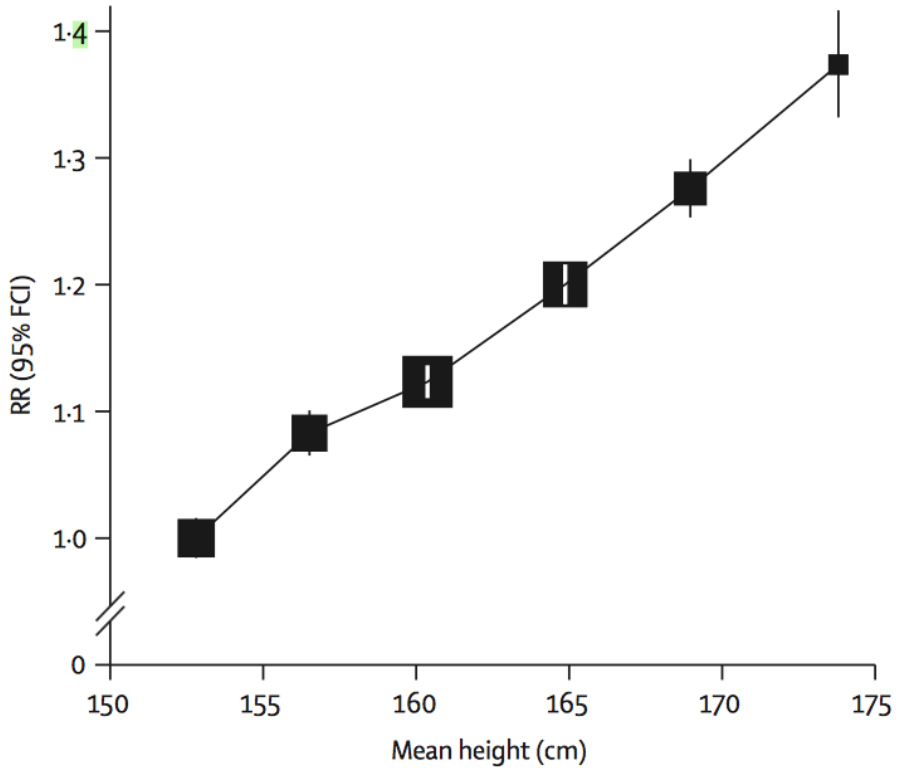


Lancet Oncol 2011; 12: 785–94

nowel Lungennetzwerk

Große Leute bekommen häufiger Krebs !

Krebs ist eine Erkrankung des Genoms



Mehr Zellteilung
Mehr DNA Replikationsfehler
Mehr Mutationen in Krebsgenen
(Protoonkogenen)

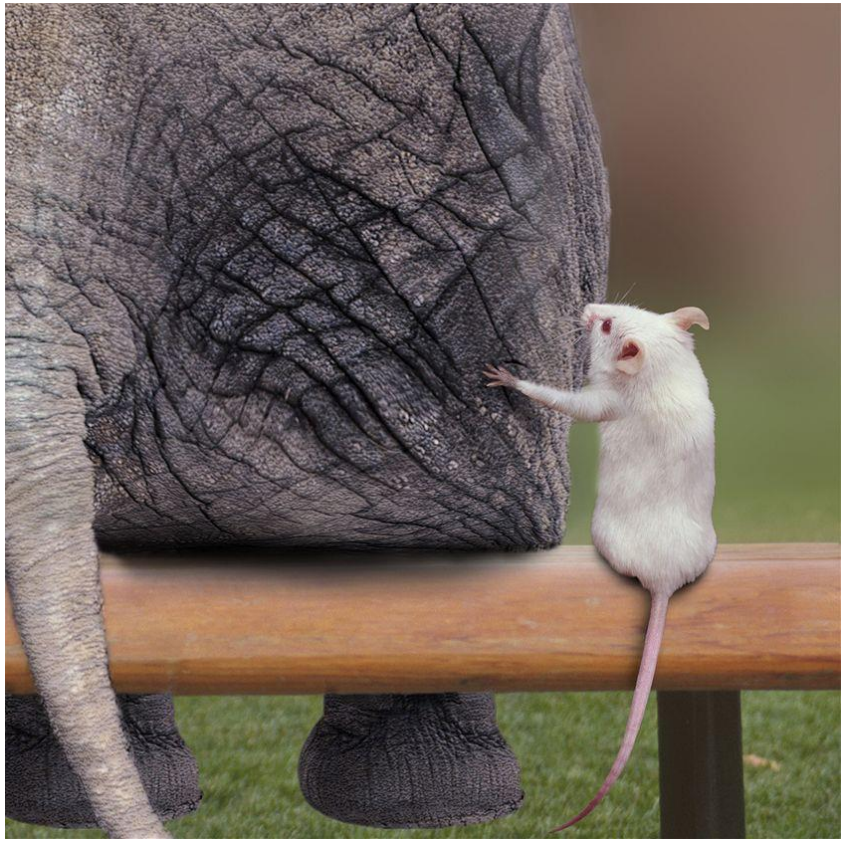
Onkogen

Lancet Oncol **2011; 12: 785–94**

nowel Lungennetzwerk

Peto’s Paradox

Bekommen große Tiere häufiger Krebs als Kleine?

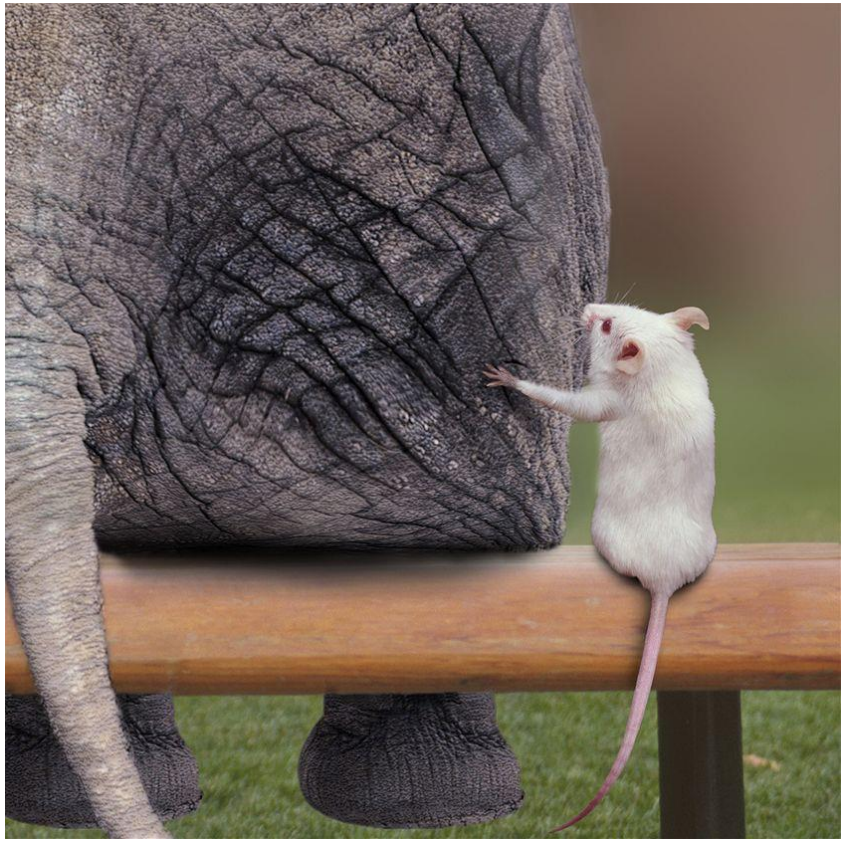


Callaway, E. 2015 *Nature*. **526**.

nowel Lungennetzwerk

Peto’s Paradox

Kleine Tiere bekommen häufiger Krebs als Große....

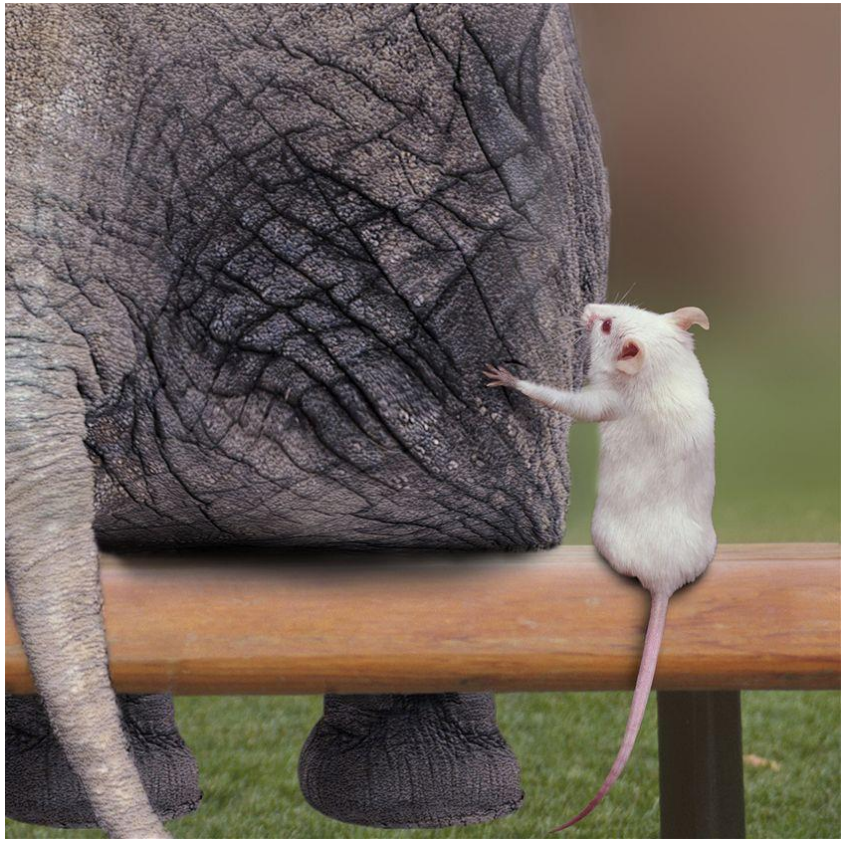


Callaway, E. 2015 *Nature*. **526**.

nowel Lungennetzwerk

Peto’s Paradox

Kleine Tiere bekommen häufiger Krebs als Große....



Organismen mit größeren und langlebigen Körpern müssen Krebs besser unterdrücken.

→ **Tumorsupressorgene**

Callaway, E. 2015 *Nature*. **526**.

Alte Leute bekommen mehr Krebs

Multi-mutation theory on cancer, Carl O. Nordling in 1953 BMJ

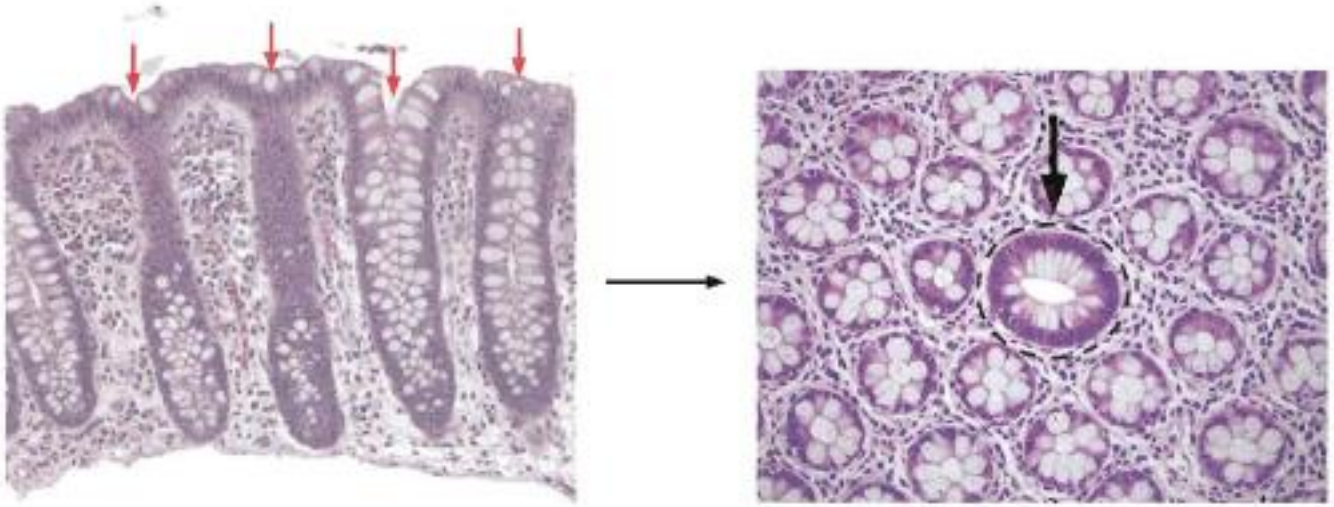
In Industrieländern: Krebsinzidenz = Alter^{6}

nowel
Lungennetzwerk

Tumormerkmale

Multistep-Karzinogenese und Tumorprogression

Akkumulation von Alterationen am Beispiel des Kolonkarzinoms: Histologie



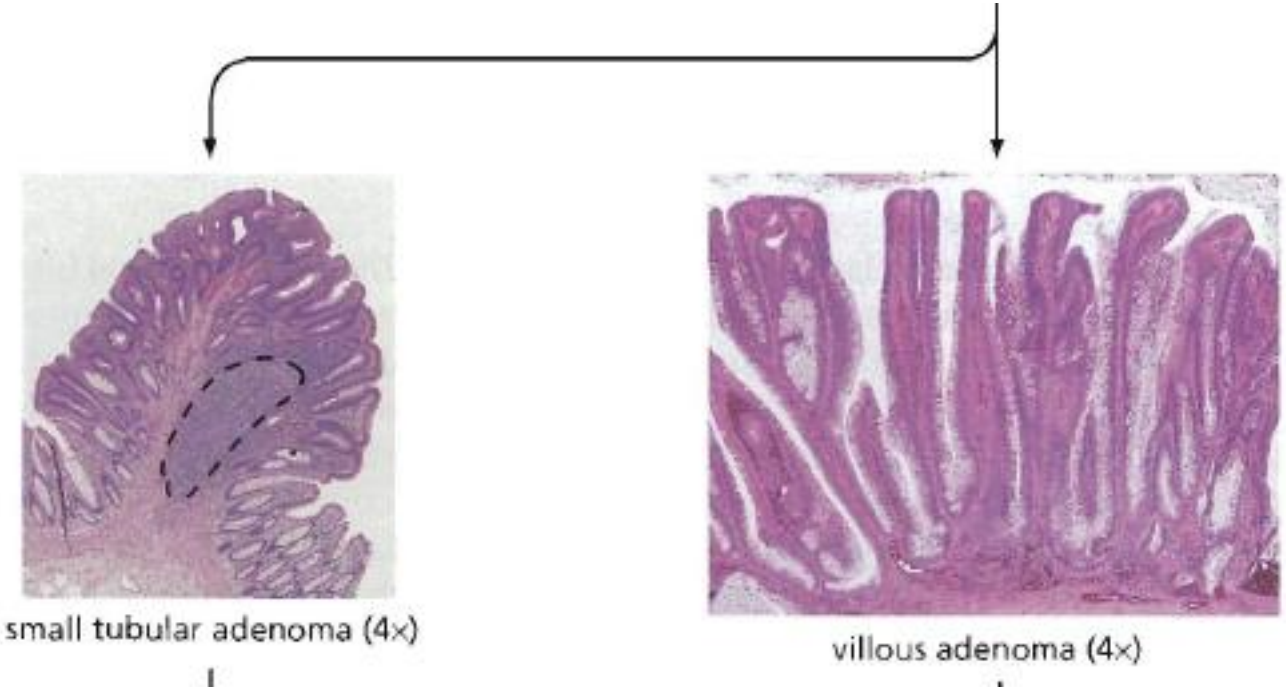
normal colonic crypts (20×)

early adenomatous crypt (20×)

Tumormerkmale

Multistep-Karzinogenese und Tumorprogression

Akkumulation von Alterationen am Beispiel des Kolonkarzinoms:



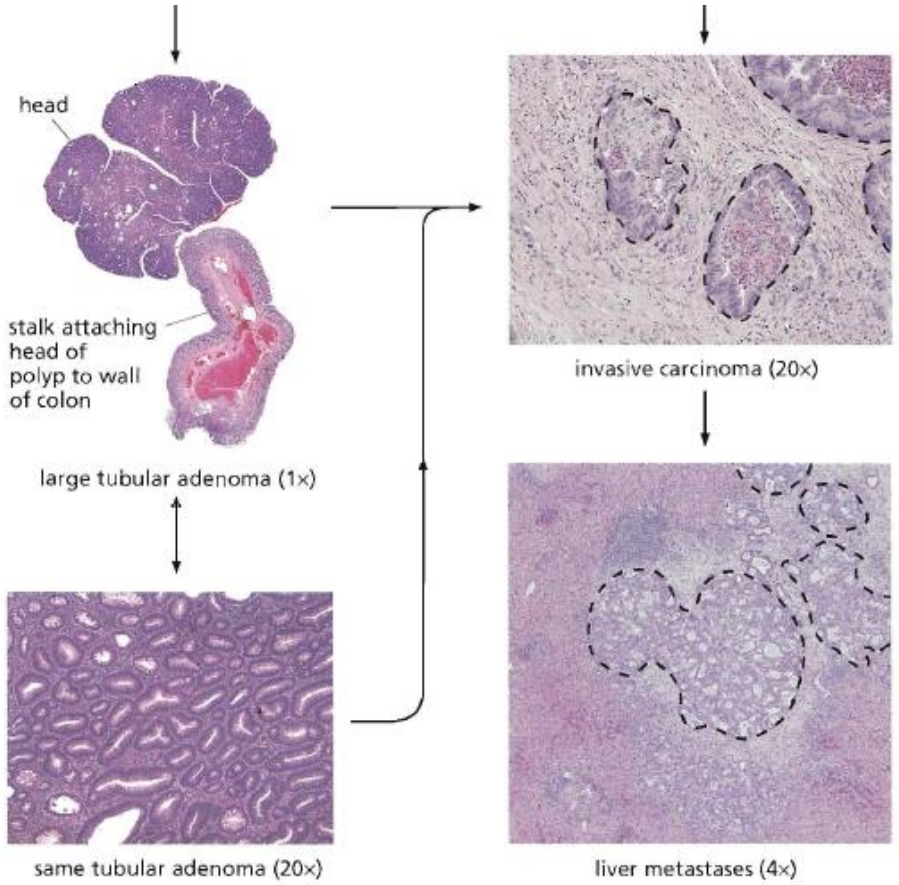
small tubular adenoma (4×)

villous adenoma (4×)

Tumormerkmale

Multistep-Karzinogenese und Tumorprogression

Akkumulation von Alterationen am Beispiel des Kolonkarzinoms:



nowel Lungennetzwerk

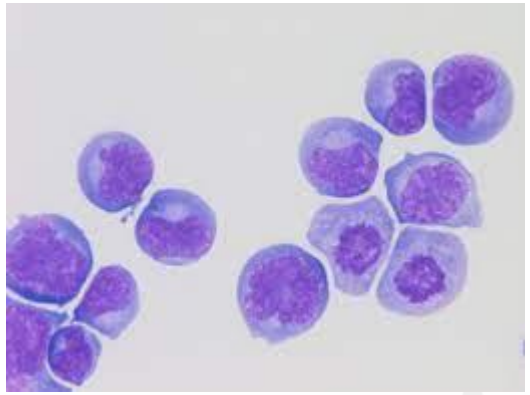
Krebs (Karzinom): Eigenschaften

Krebszellen

wachsen ungehemmt (Proliferation)
können nicht absterben (Apoptose)
wachsen infiltrativ in andere Organe
siedeln sich in anderen Organen an (Tochtergeschwulst, Metastase)
tricksen das Immunsystem aus

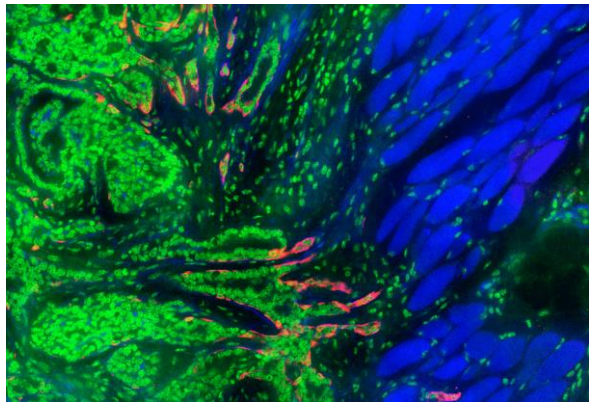
Merkmale von Krebszellen

ungehemmtes Wachstum von einer Patientin aus den 50 iger Jahren mit Zervixkarzinom



Apoptose: aus einer Handplatte wird eine Hand mit Fingern

Invasion/Infiltration in ein anderes Organ

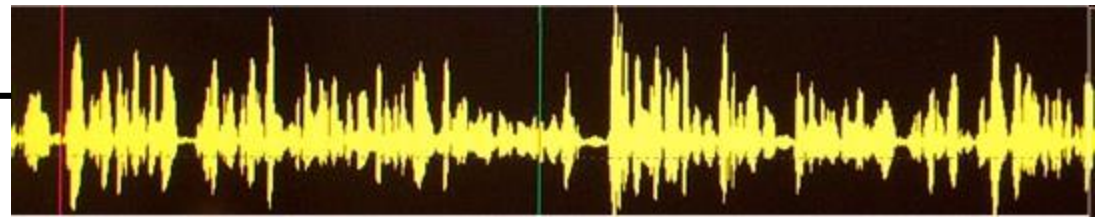


Metastasierung

Genetische Schalter = onkogene Treiber

Normale Zelle

Radiowellen



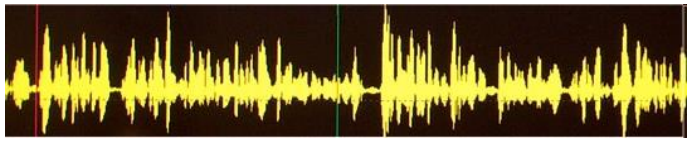
Antenne

Schalter

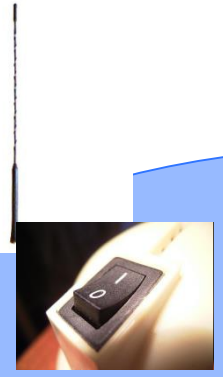
Töne aus dem Lautsprecher

Normale Zelle

Radiowellen = Botenstoffe



Antenne =
Rezeptor



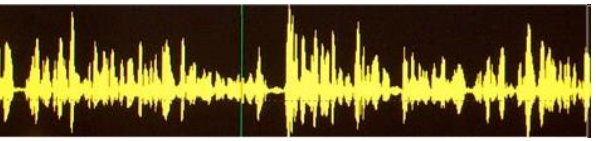
Schalter =
Tyrosinkinase

Töne aus dem Lautsprecher =
Zellteilung, programmierter Zelltod

Krebszelle: zu viele Schalter/ onkogene Treiber unabhängig von den Botenstoffen Amplifikation/Translokation

„Antennen-Wald“
Überexpression von Rezeptoren

Radiowellen=Botenstoffe



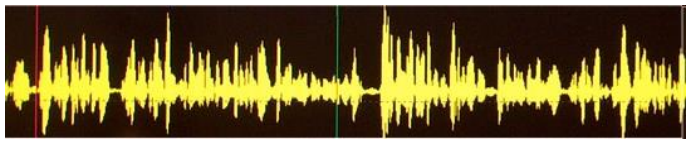
Viele Schalter
Viele Tyrosinkinasen

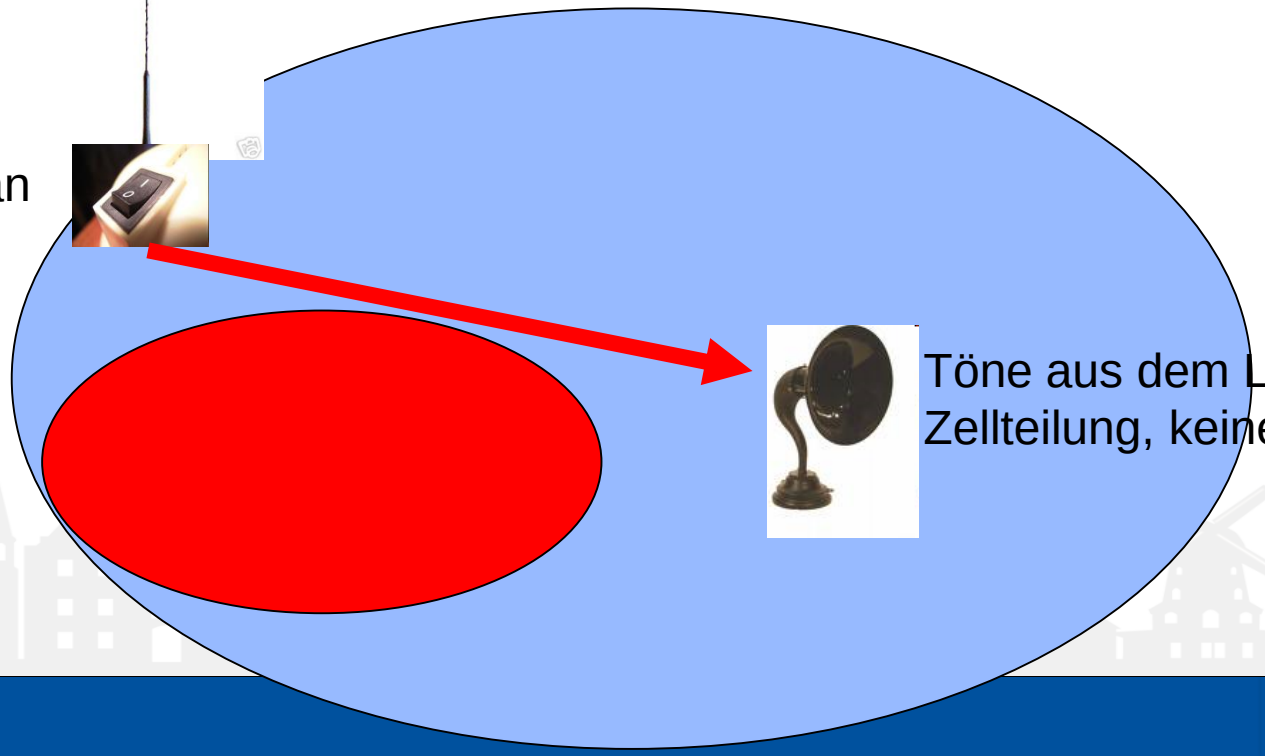
Töne aus dem Lautsprecher = Zellteilung, keinen Apoptose etc.

Krebszelle: Mutation

„veränderte Antenne“
Mutierter Rezeptor

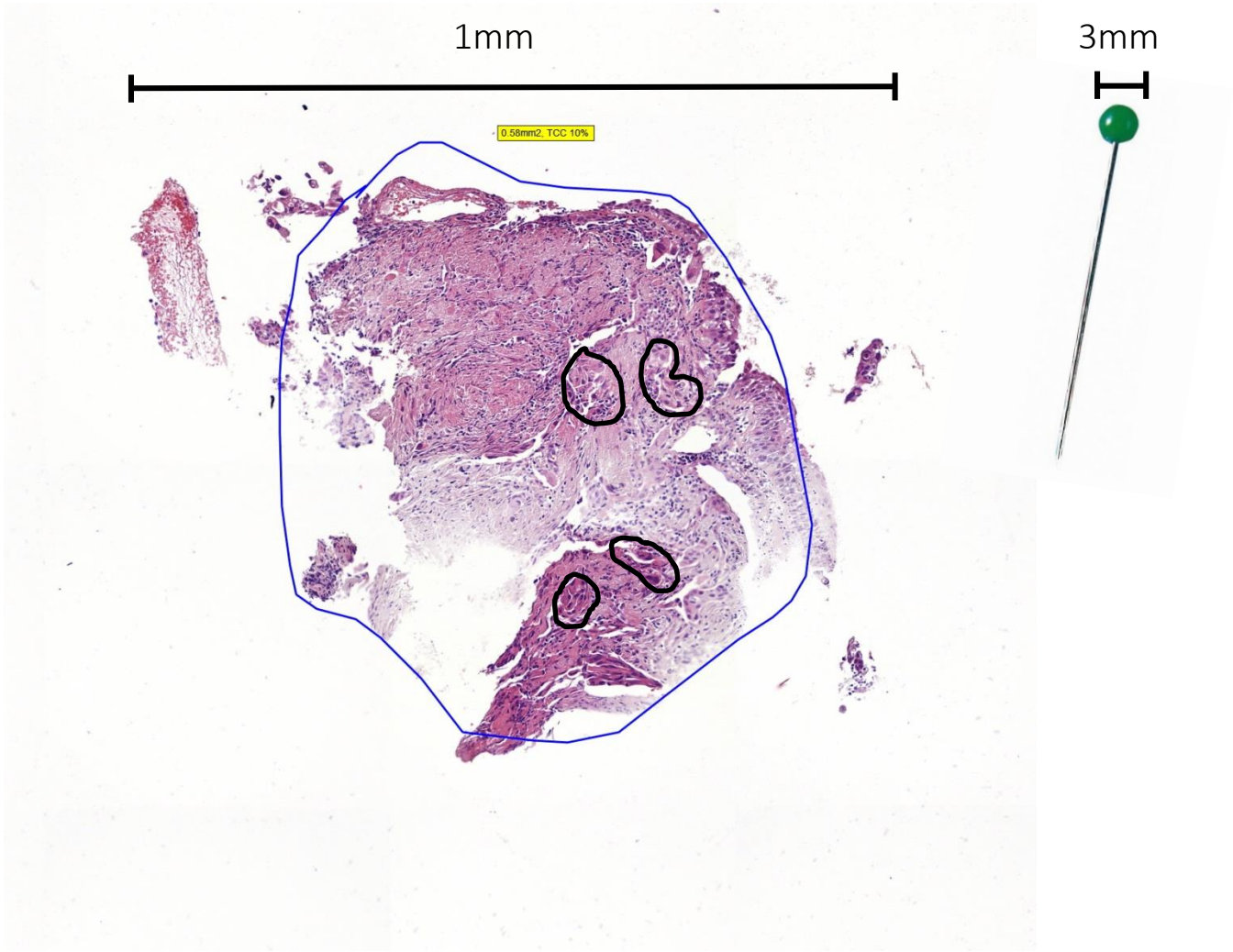
Radiowellen = Botenstoffe





Herausforderungen von Probenentnahmen

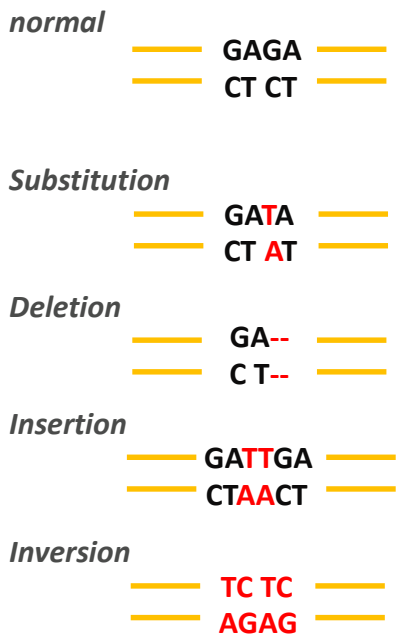
Sehr begrenztes Gewebe und wenig Tumorzellen



Herausforderungen in der Routine-Diagnostik

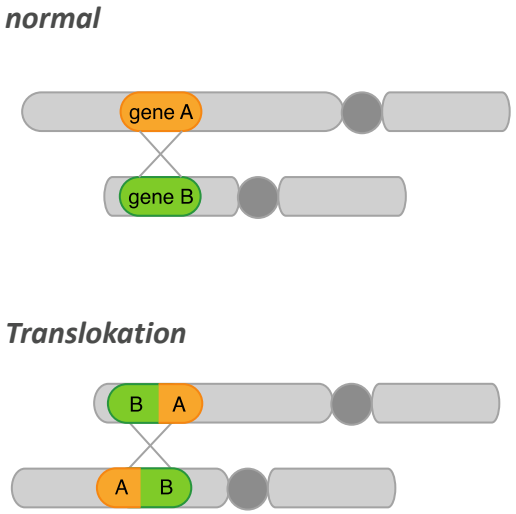
Different types of genomic alterations need to be detected

Punkmutationen und Deletionen



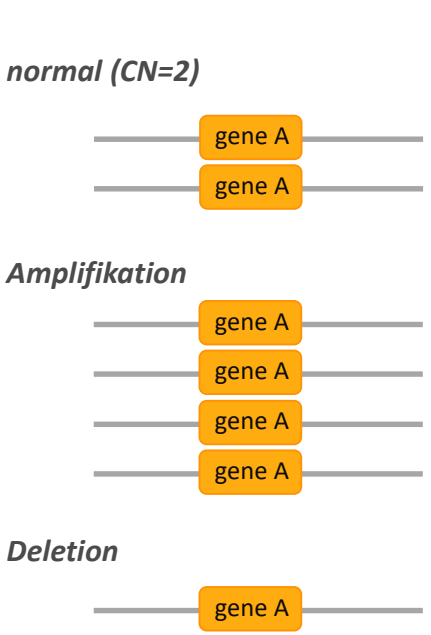
KRAS
BRAF
EGFR

Strukturelle Umlagerungen



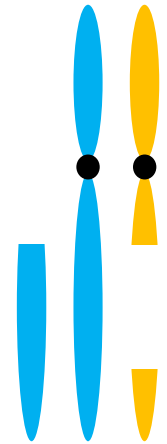
EML4-Alk
RET
ROS

Kopie-Zahl Veränderungen



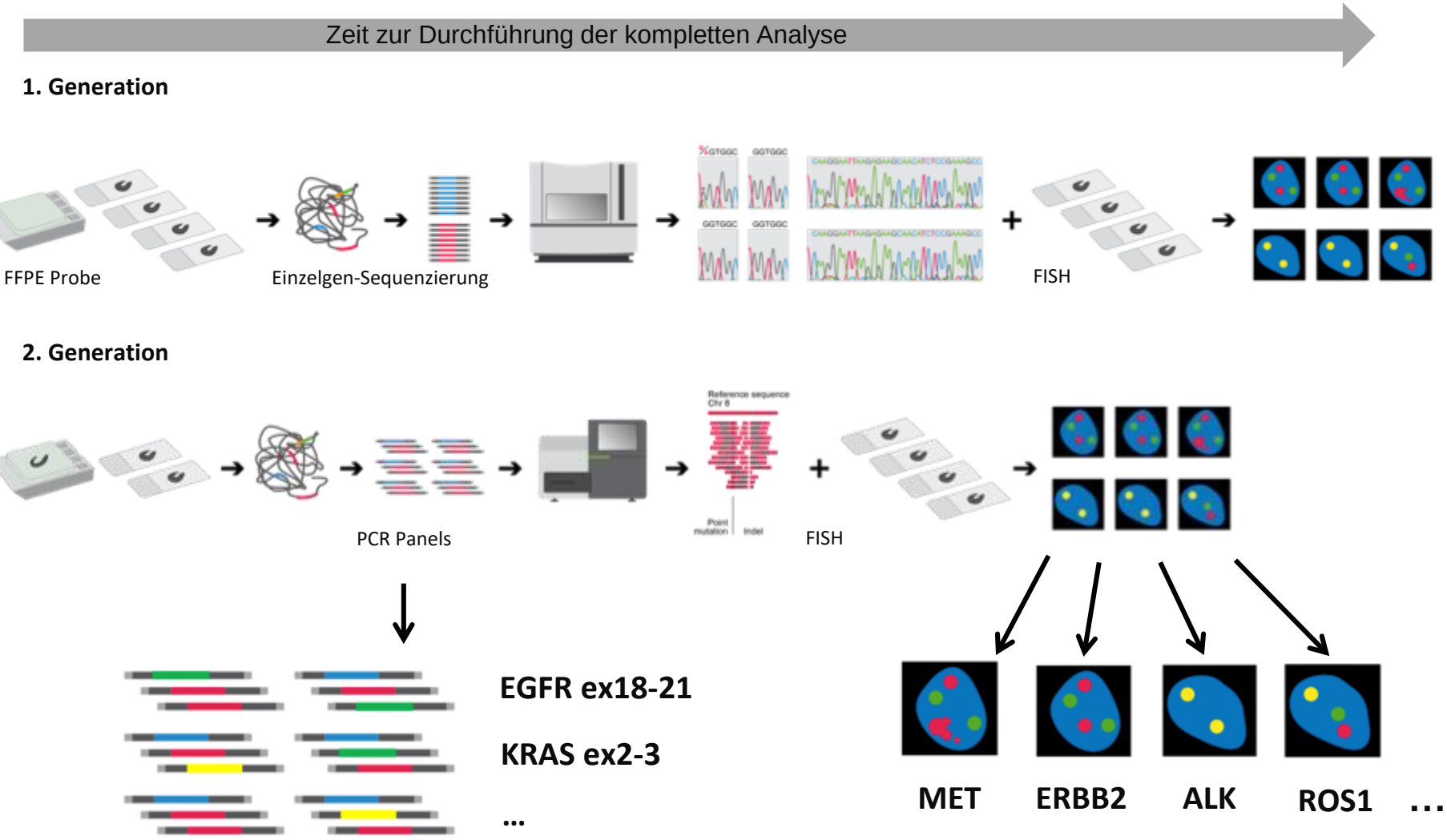
Her2
Met
EGFR

Komplexe Marker wie TMB, HRD, MSI



Standard-Technologie zur Krebsgenom-Diagnostik

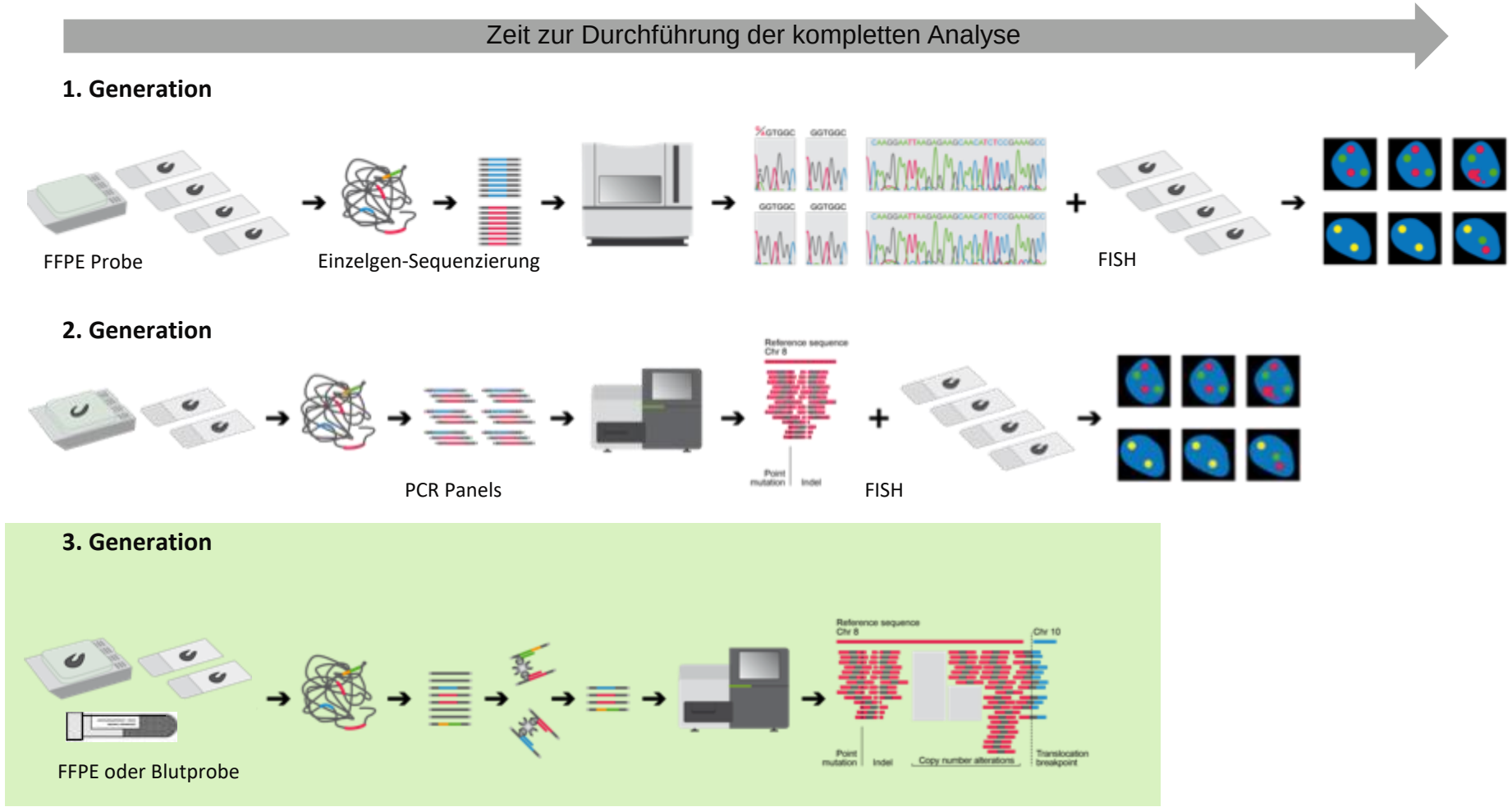
Hochsensitive Multiplex-PCR plus FISH



Figures from: ***Heuckmann*** *&* ***Thomas****, Ann Oncol. 2015*

Die nächste Generation der Krebsgenom-Diagnostik

Hochsensitive, umfassende NGS-basierte Analyse



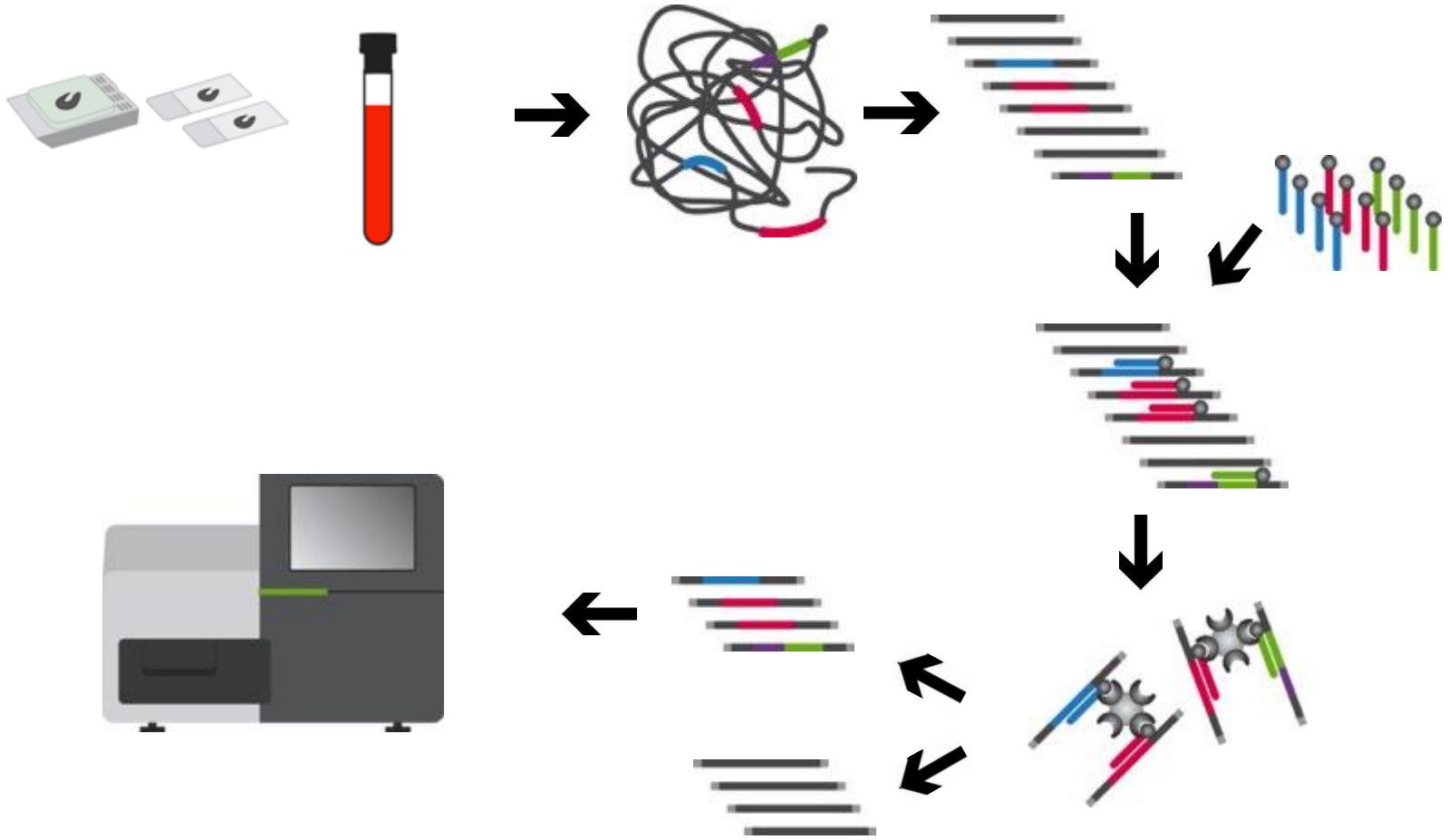
Figures from: ***Heuckmann*** *&* ***Thomas****, Ann Oncol. 2015*

Menge der Sequenzierdaten konventionell vs. NGS

Notwendigkeit einer komplexen Bioinformatik

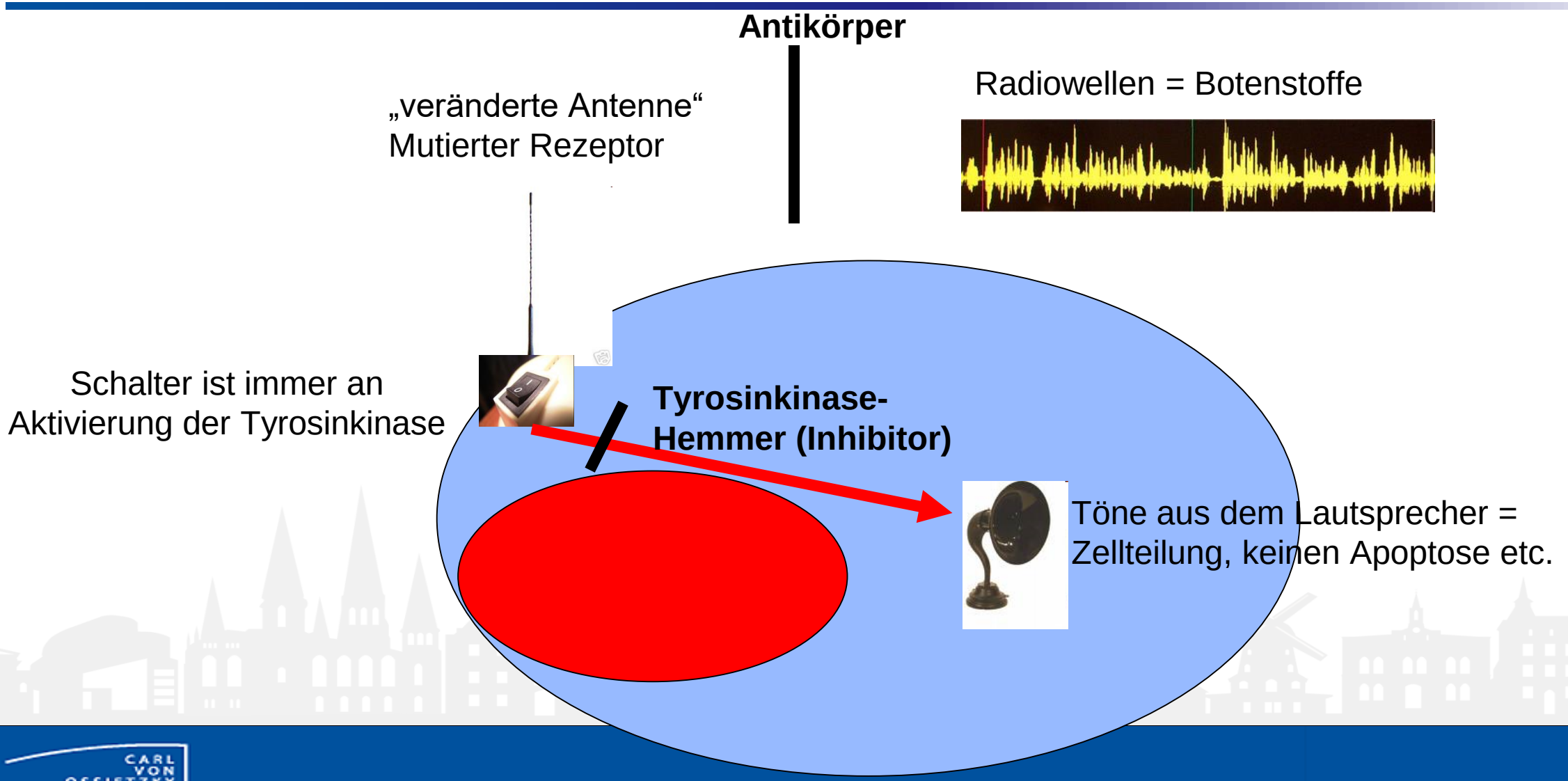
Die dritte Generation der Krebsgenom-Diagnostik

Hybrid-Capture Sequenzierung: Proben-Prozessierung

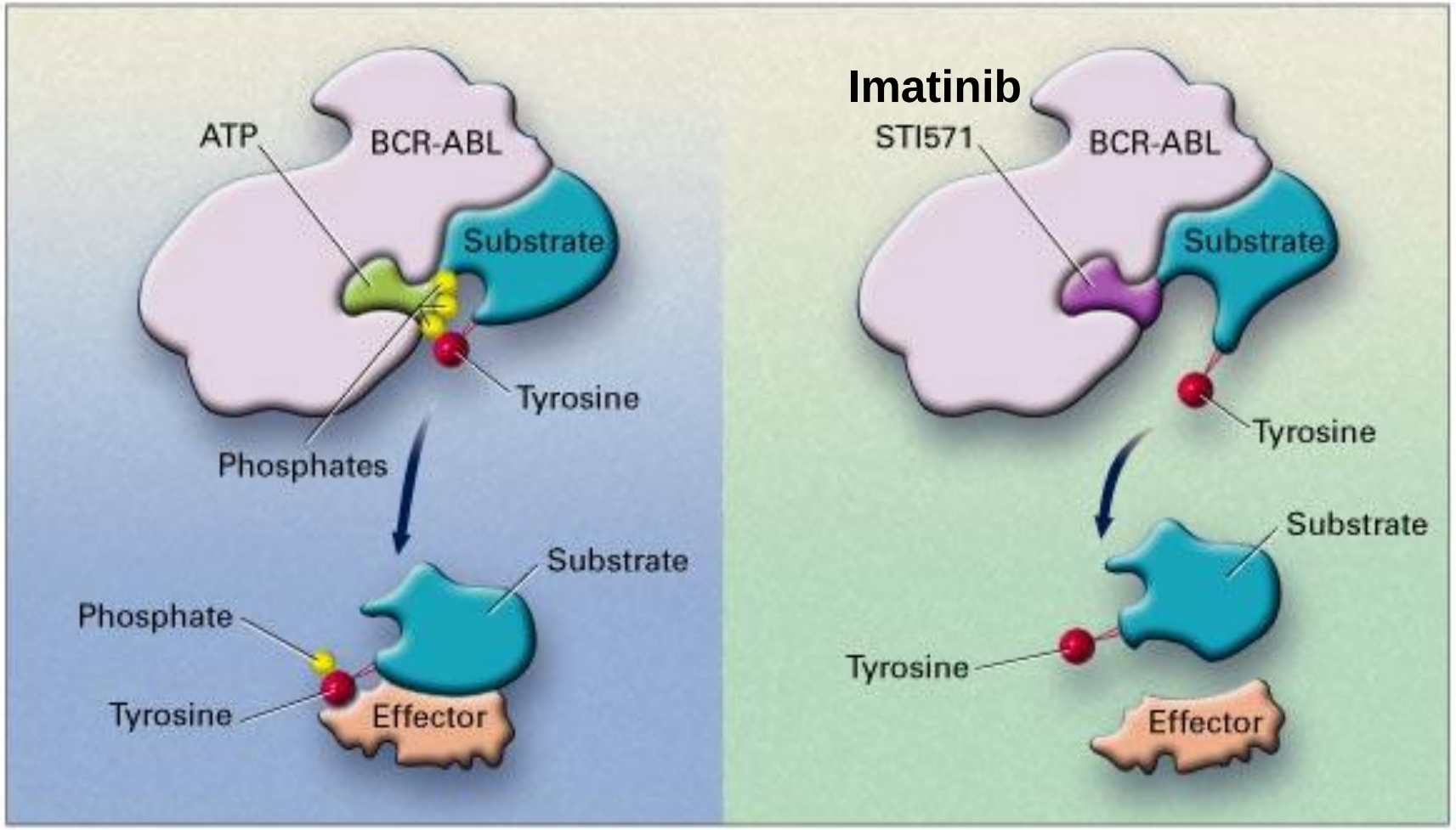


weniger als 200ng (1/5000stel gramm) DNA nötig (etwa 50 Zellen im HE Schnitt)

Behandelte Krebszelle: zielgerichtete Therapie, Präzisionsmedizin, molekulare Therapie

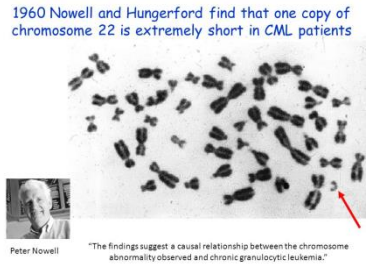


Beispiel Präzisionsonkologie: chronische myeloische Leukämie

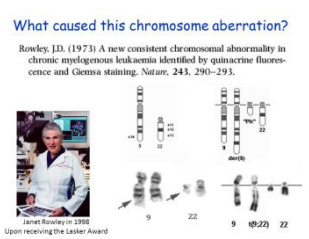


BCR-ABL+ chronische myeloische Leukämie (CML)

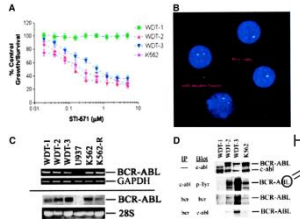
1960



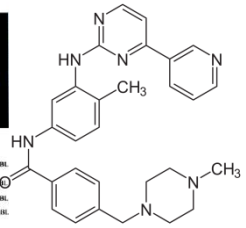
1972



1983



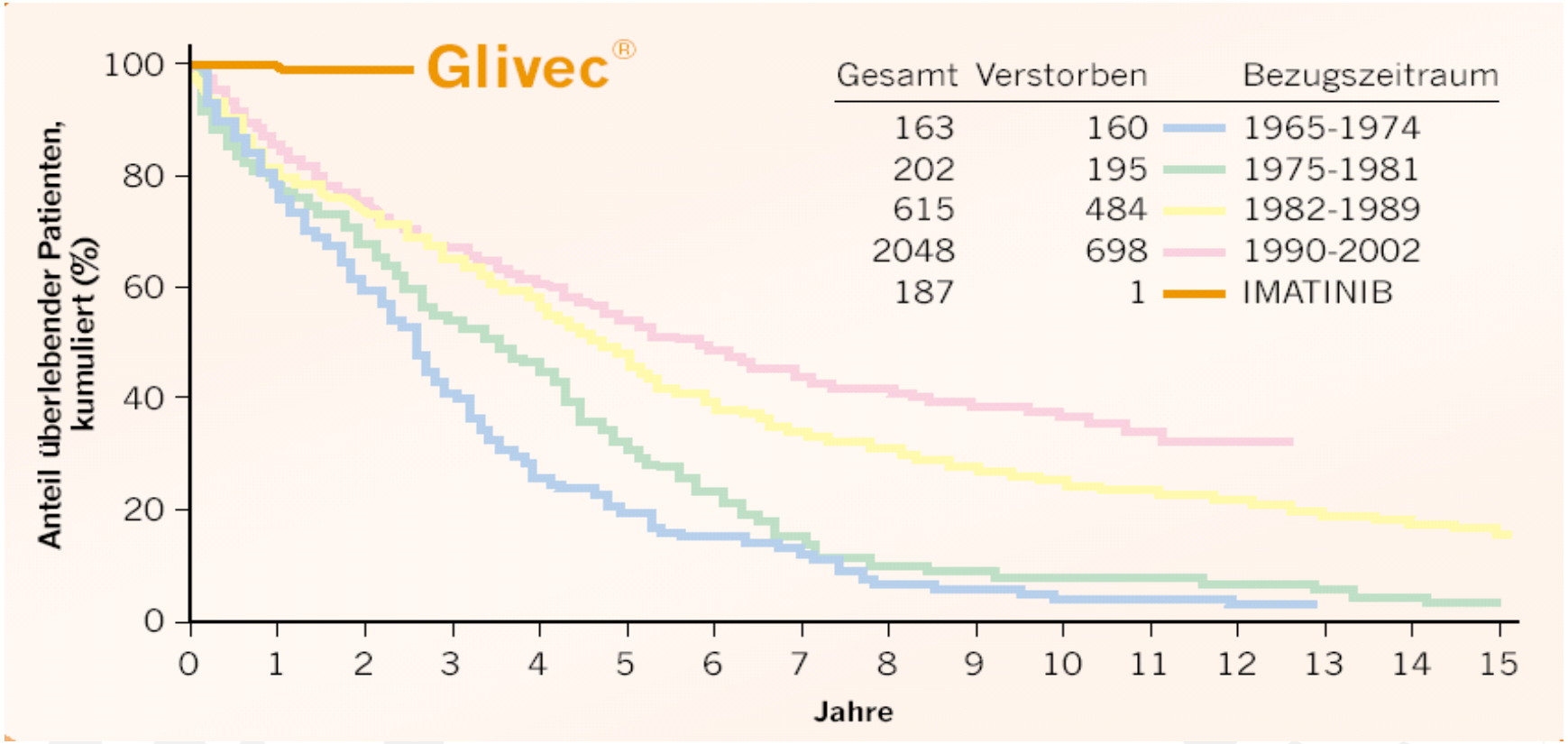
1984



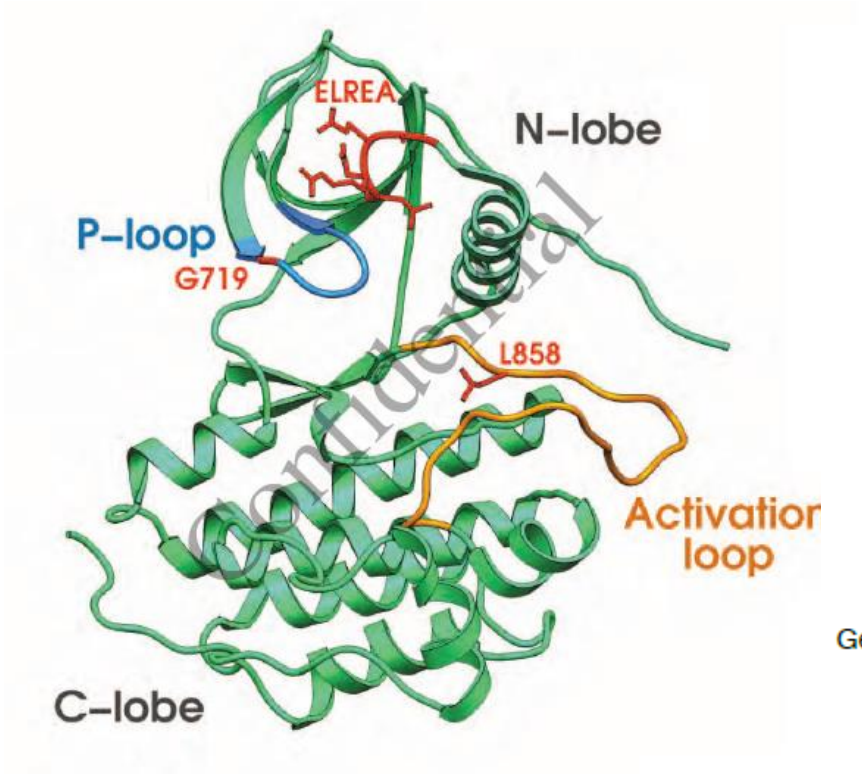
2001

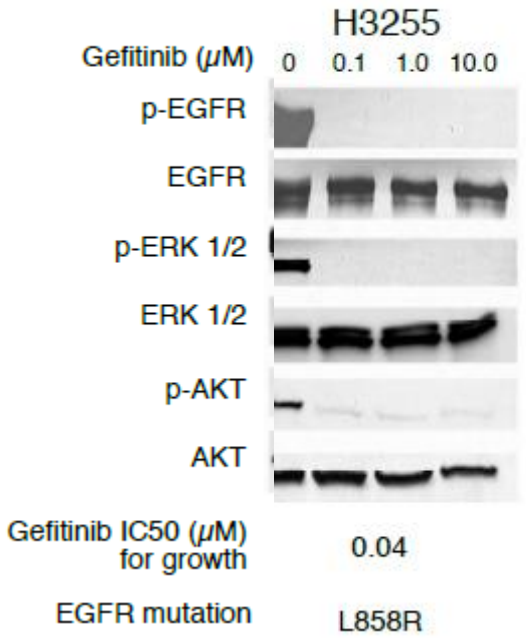
40 Jahre

Überleben Präzisionsonkologie vs. Chemotherapie



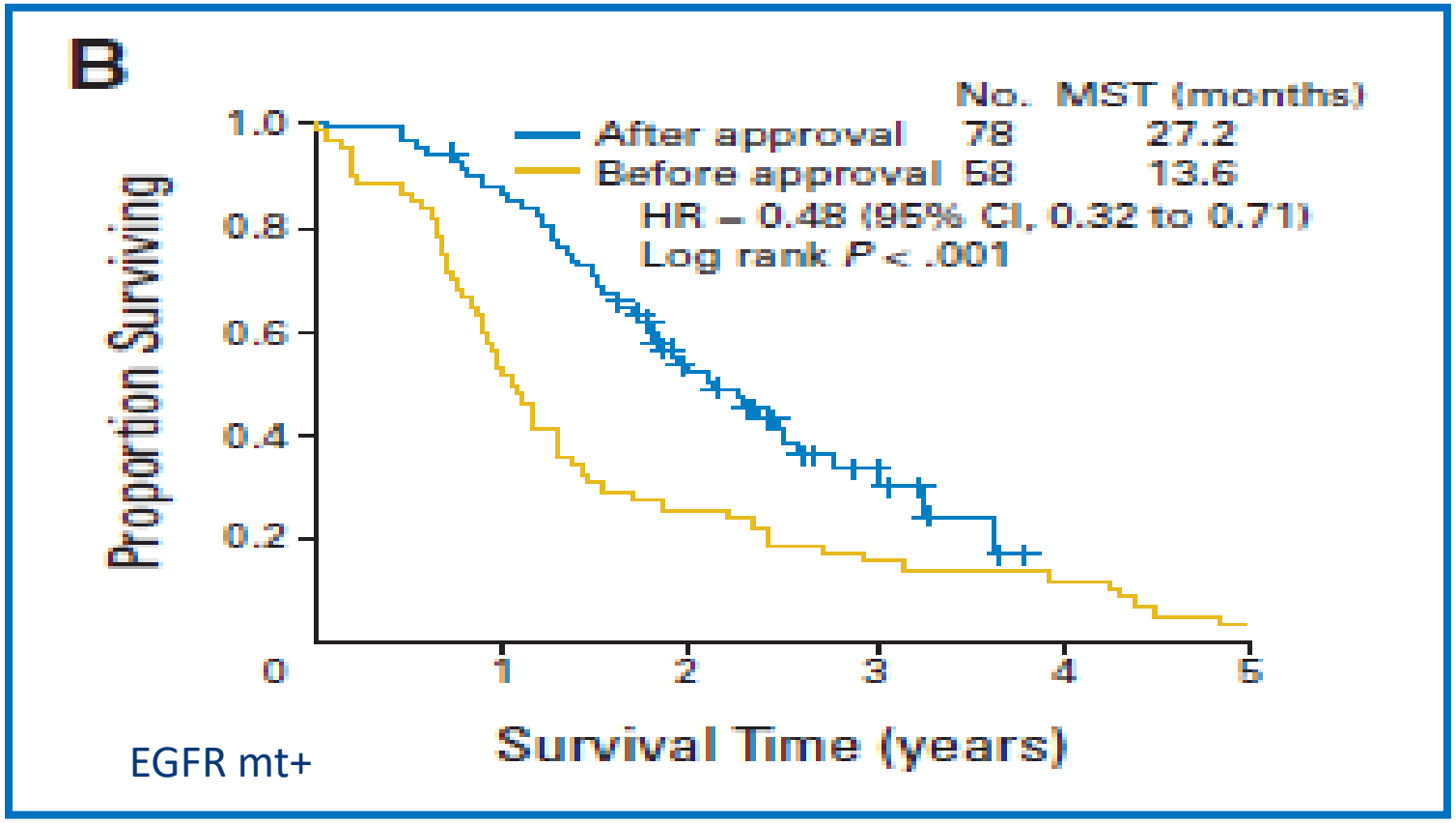
2004: Paradigma für Präzisionsonkologie: EGFR Tyrosinkinase-Mutation





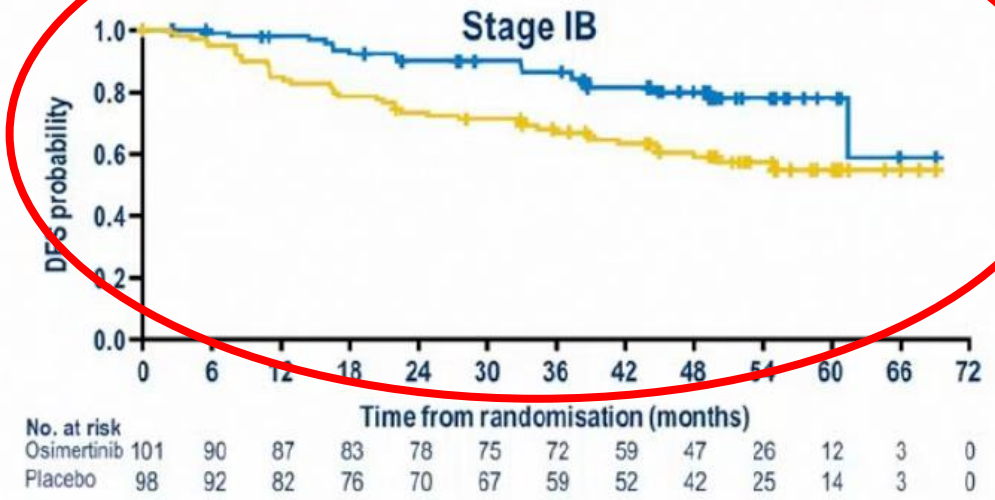
Paez et al., Science 2004

Gefitinib (Präzisionsonkologie) versus Chemotherapie: Überleben

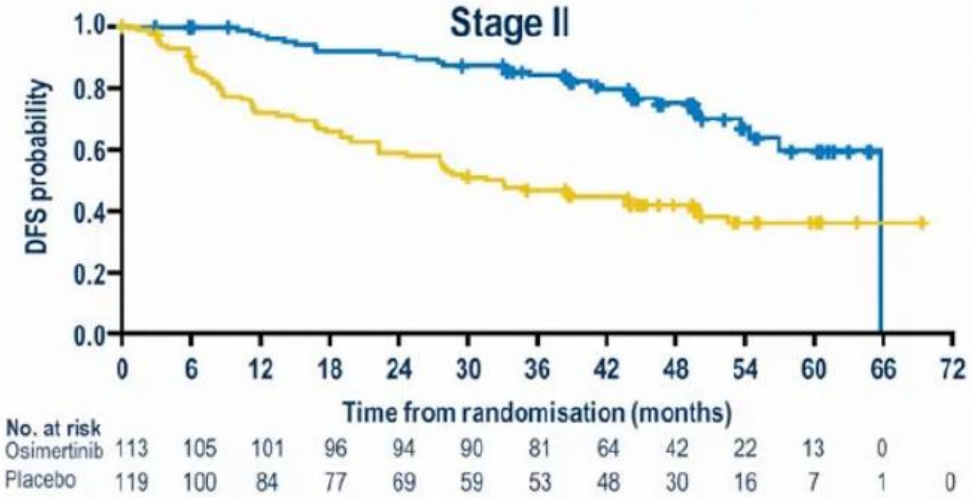


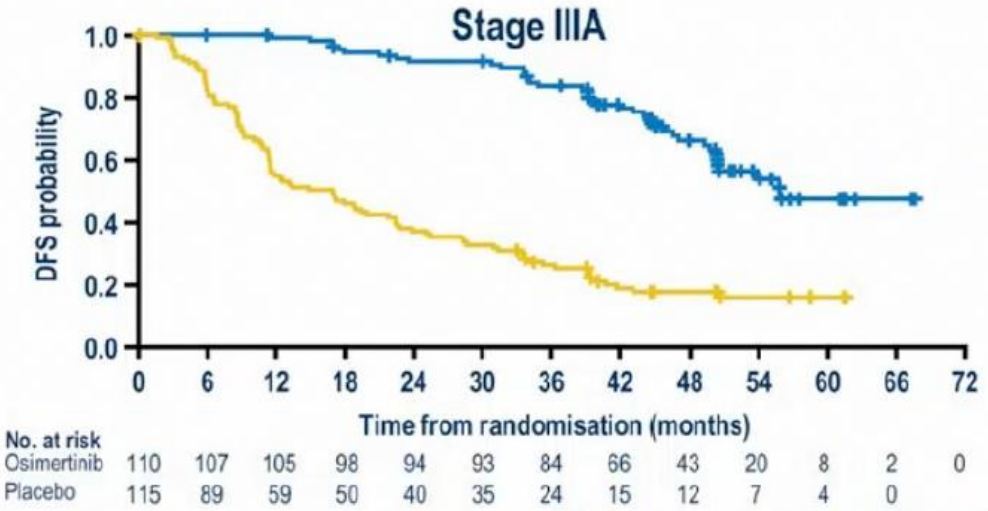
Takano et al. JCO 2008

UPDATED DFS BY STAGE (AJCC / UICC 8TH EDITION*)



	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (69, 87)	75 (65, 83)	66 (55, 75)
– Placebo	60 (49, 69)	43 (34, 52)	16 (10, 24)
Overall HR (95% CI)	0.44 (0.25, 0.76)	0.33 (0.21, 0.50)	0.22 (0.15, 0.31)





PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

DFS by investigator assessment; Tick marks indicate censored data.

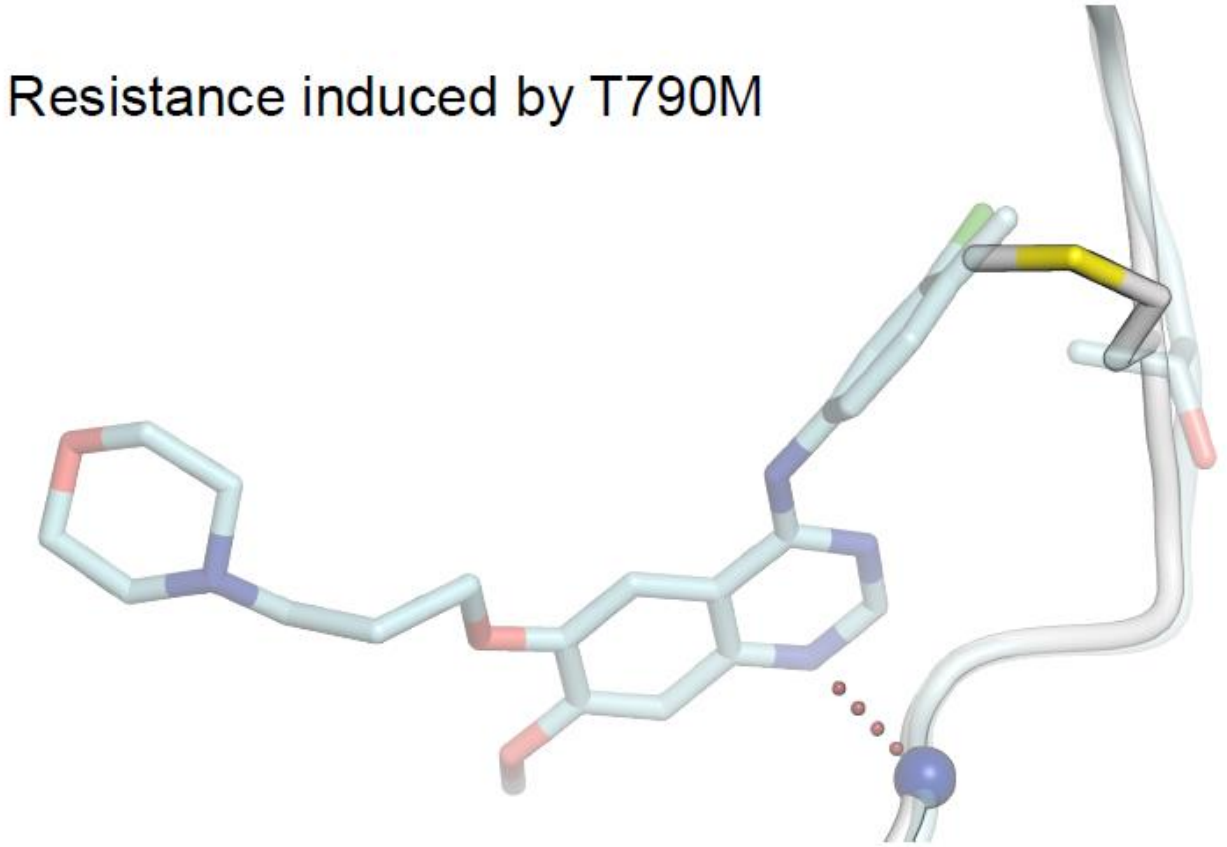
*Re-staging based on data captured in the Pathology at Diagnosis AJCC / UICC 8th edition manual, per investigator assessment requested before the primary analysis.

AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio

Data cut-off: April 11, 2022.

EGFR Gatekeeper Resistenzmutation

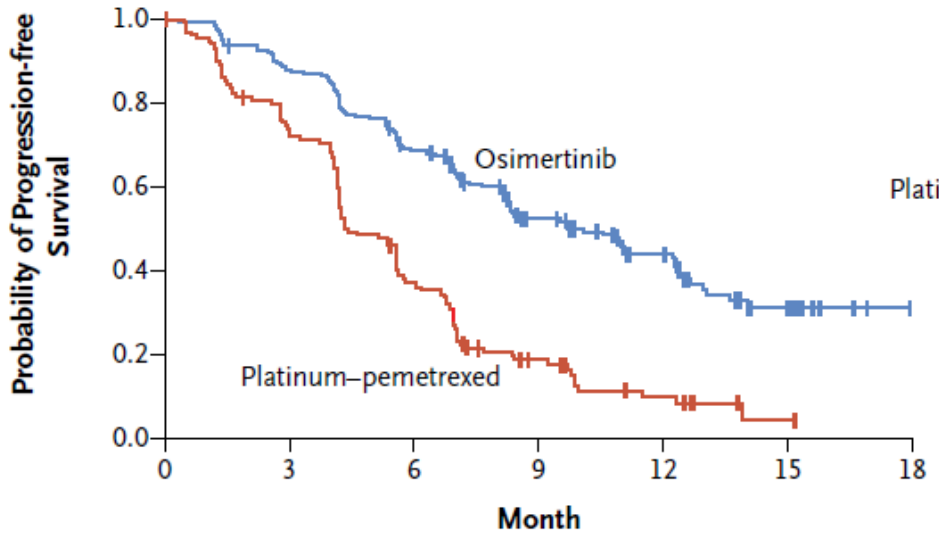
Apo EGFR-T790M
Yoshikawa et al., Oncogene 2012
PDB-code: 3UG1



Heuckmann, Rauh and Thomas, JCO 2012

AURA 3: Osimertinib vs. CTx nach TKI Versagen

A Patients in Intention-to-Treat Population



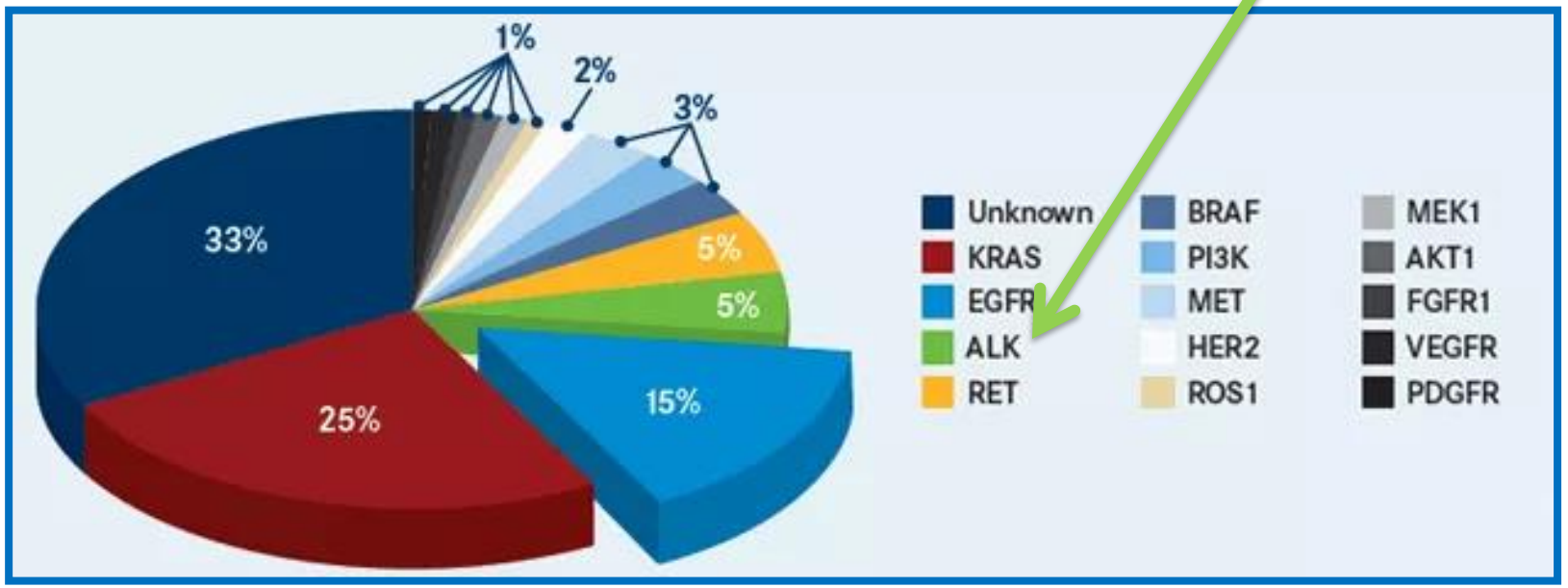
No. at Risk							
Osimertinib	279	240	162	88	50	13	0
Platinum–pemetrexed	140	93	44	17	7	1	0

	No. of Patients	Median Progression-free Survival *mo (95% CI)*
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

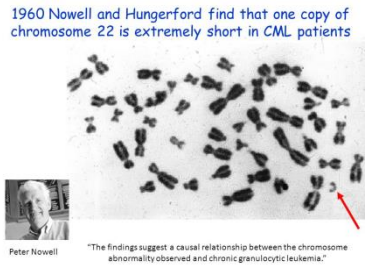
Mok et al., NEJM 2016

Genetische Klassifikation von NSCLC: 25%-30% mit onkogenen Treibern

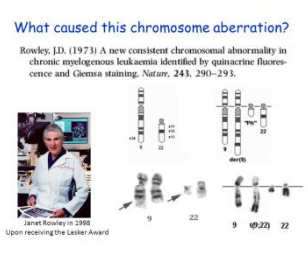


BCR-ABL+ CML

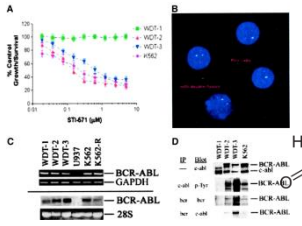
1960



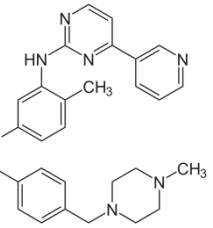
1972



1983



1984

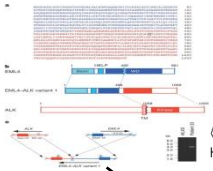


2001

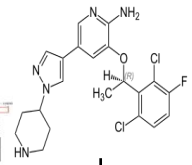
40 Jahre

ALK + NSCLC

2007



2010

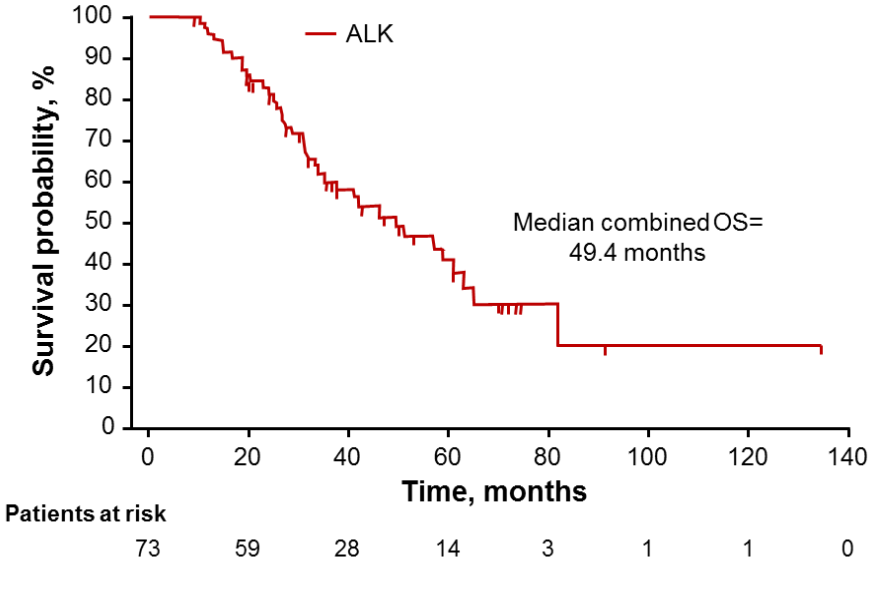


2012

5 Jahre

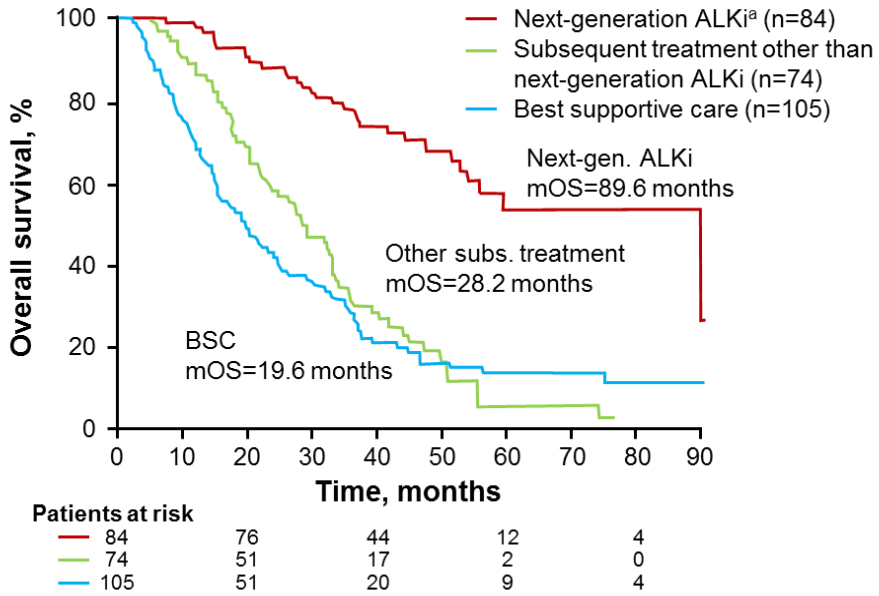
Sequentielle Therapie des ALK+ Lungenkarzinoms mit mehreren „nibs“

Crizotinib → ceritinib[1]



- Retrospective analysis of 73 ALK+ patients

Multiple ALK TKIs post-crizotinib[2]

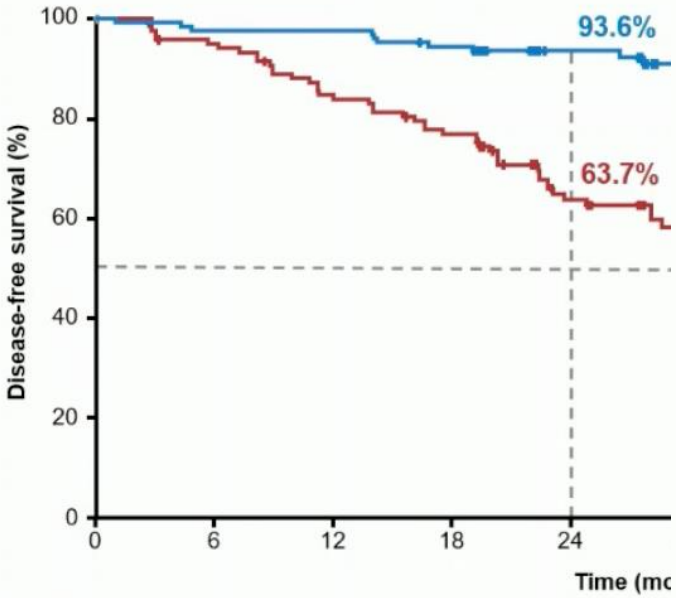


- Retrospective analysis of 214 ALK+ patients

[a]The next-generation ALKis administered were ceritinib, alectinib, ceritinib followed by alectinib, ceritinib followed by lorlatinib, or alectinib followed by ceritinib.
ALK, anaplastic lymphoma kinase; ALKi, ALK inhibitor; BSC, best supportive care; mOS, median overall survival; NSCLC, non–small cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.
1. Reprinted from Gainor JF, et al. Progression-free and overall survival in ALK-positive NSCLC patients treated with sequential crizotinib and ceritinib. *Clin Cancer Res*. 2015;21:2745-2752, with permission from AACR.
2. Adapted from Duruisseaux M, et al. *Oncotarget*. 2017;8:21903-21917 under the terms of the Creative Commons Attribution 3.0 license accessible at https://creativecommons.org/licenses/by/3.0/us/legalcode.

ALINA: primärer Endpunkt

Disease-free survival: ITT (stage IB–IIIA)*



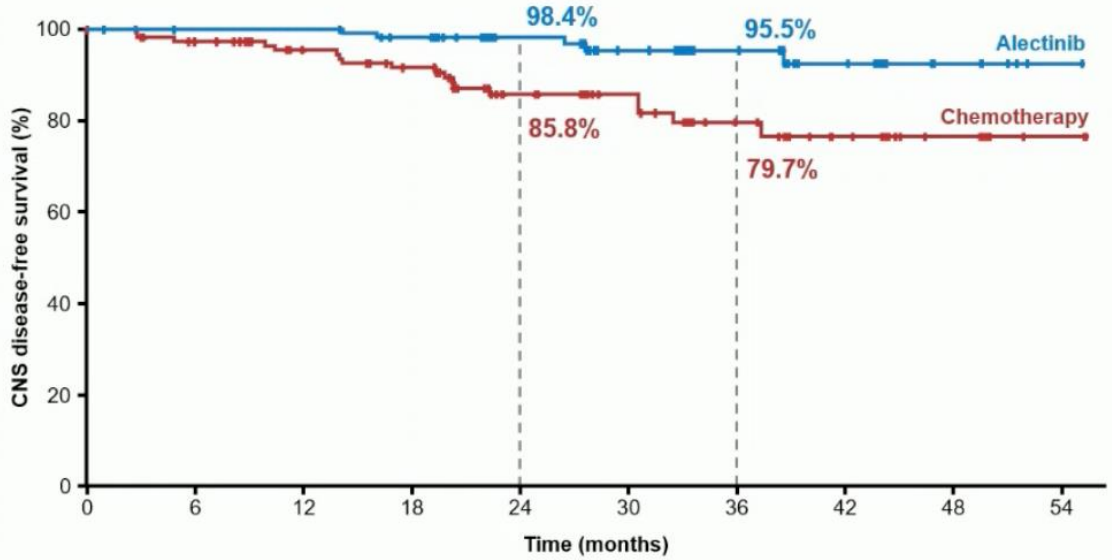
No. at risk

Alectinib	130	123	123	118	74
Chemo	127	112	98	89	55

Median survival follow

*Per a

CNS disease-free survival in the ITT population



No. at risk

Alectinib	130	124	124	118	74	55	39	22	10	3
Chemo	127	113	98	90	57	43	27	18	11	2

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	5	18
Death	1	4
Brain recurrence	4	14
CNS-DFS HR* (95% CI)	**0.22** (0.08, 0.58)	

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Data cut-off: 26 June 2023

*Stratified analysis with race and stage as stratification factors

CNS-DFS defined as time from randomisation to the first documented recurrence of disease in the CNS or death from any cause

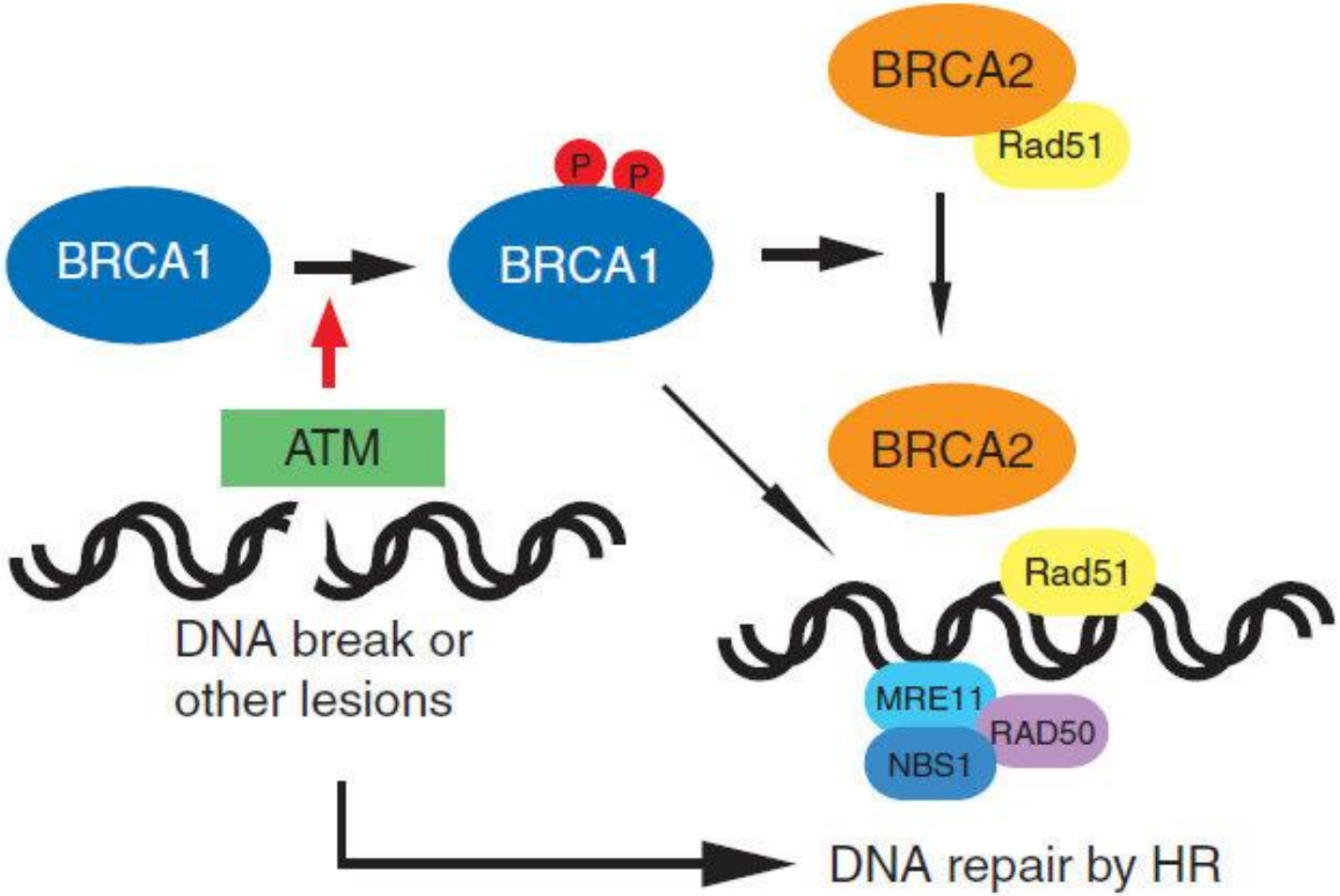
MADRID 2023 ESMO congress

MADRID 2023 ESMO congress

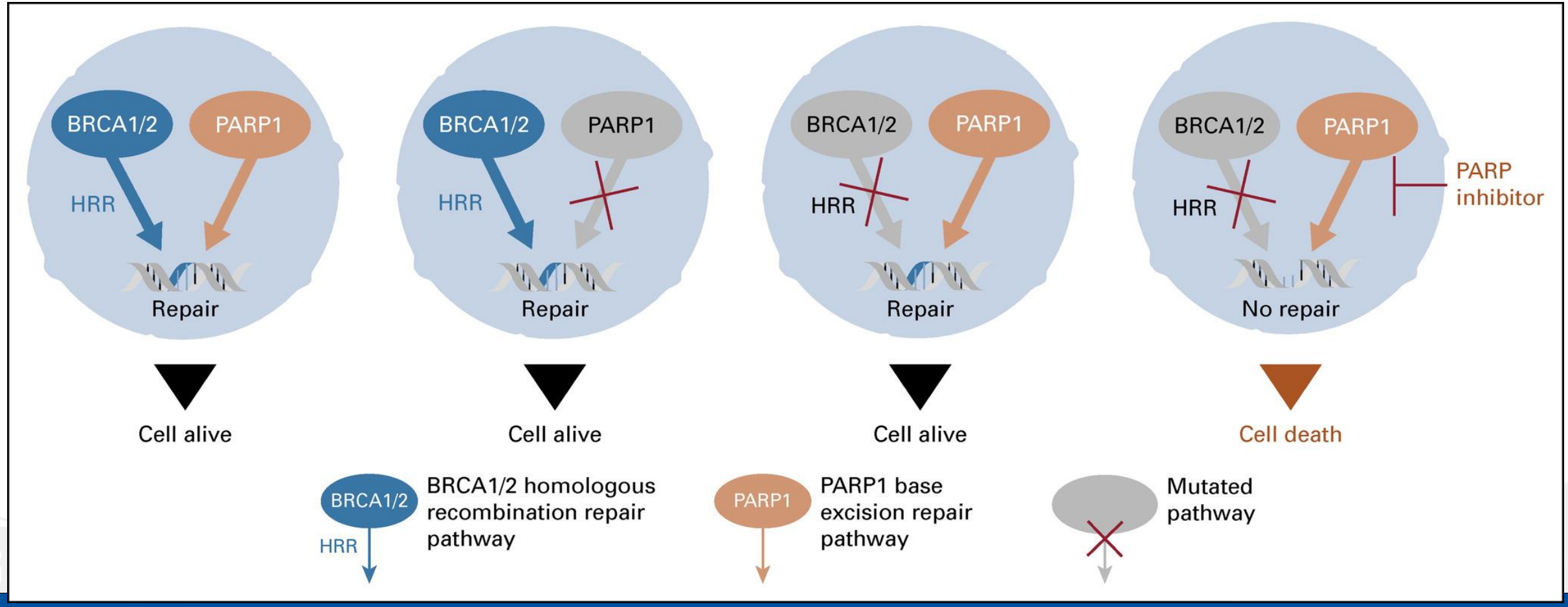
Solomn B et al, ESMO 2023

Was sind BRCA1 und BRCA2 Mutationen?

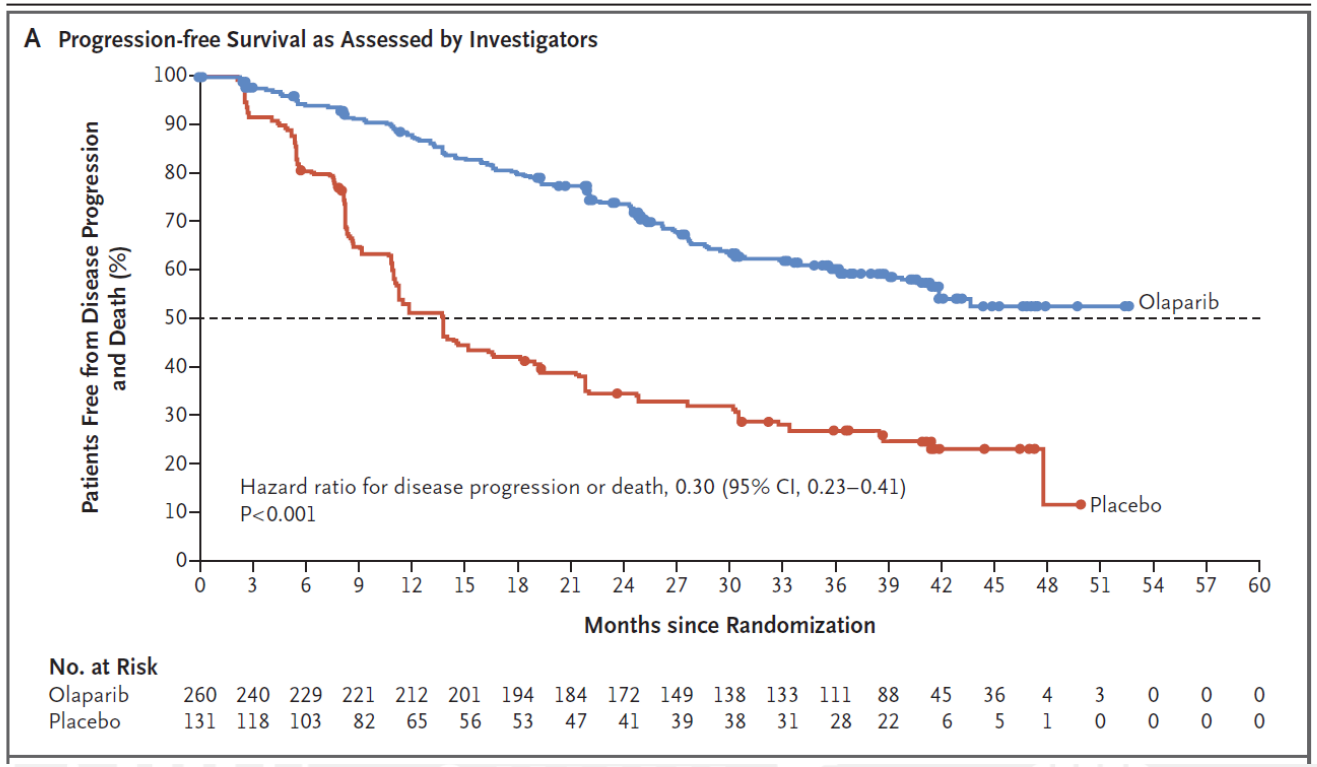
Defekte DNA Reperatur führt zu Krebs...



PARP-Inhibitoren

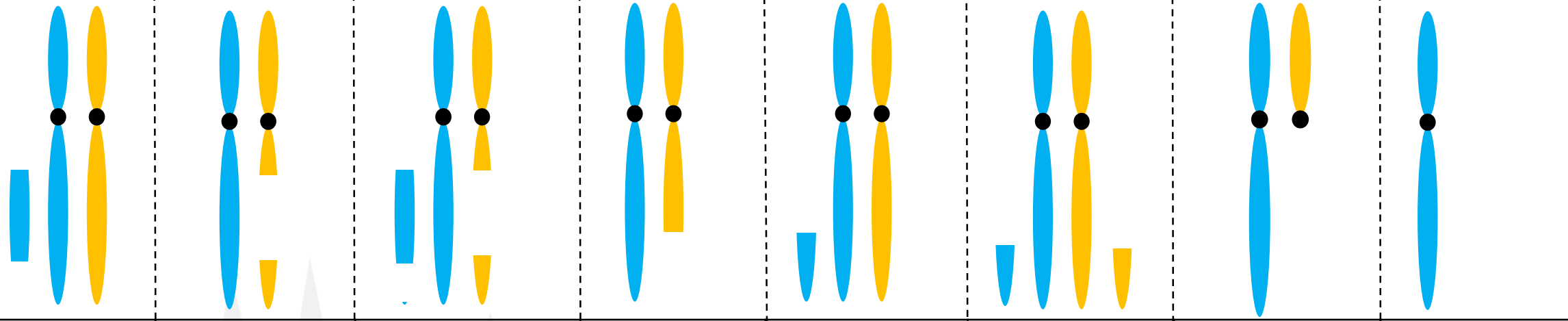


BRCA 1 und 2 mutiertes Ovarialkarzinom: rückfallfreies Überleben



Scoring genomic scars

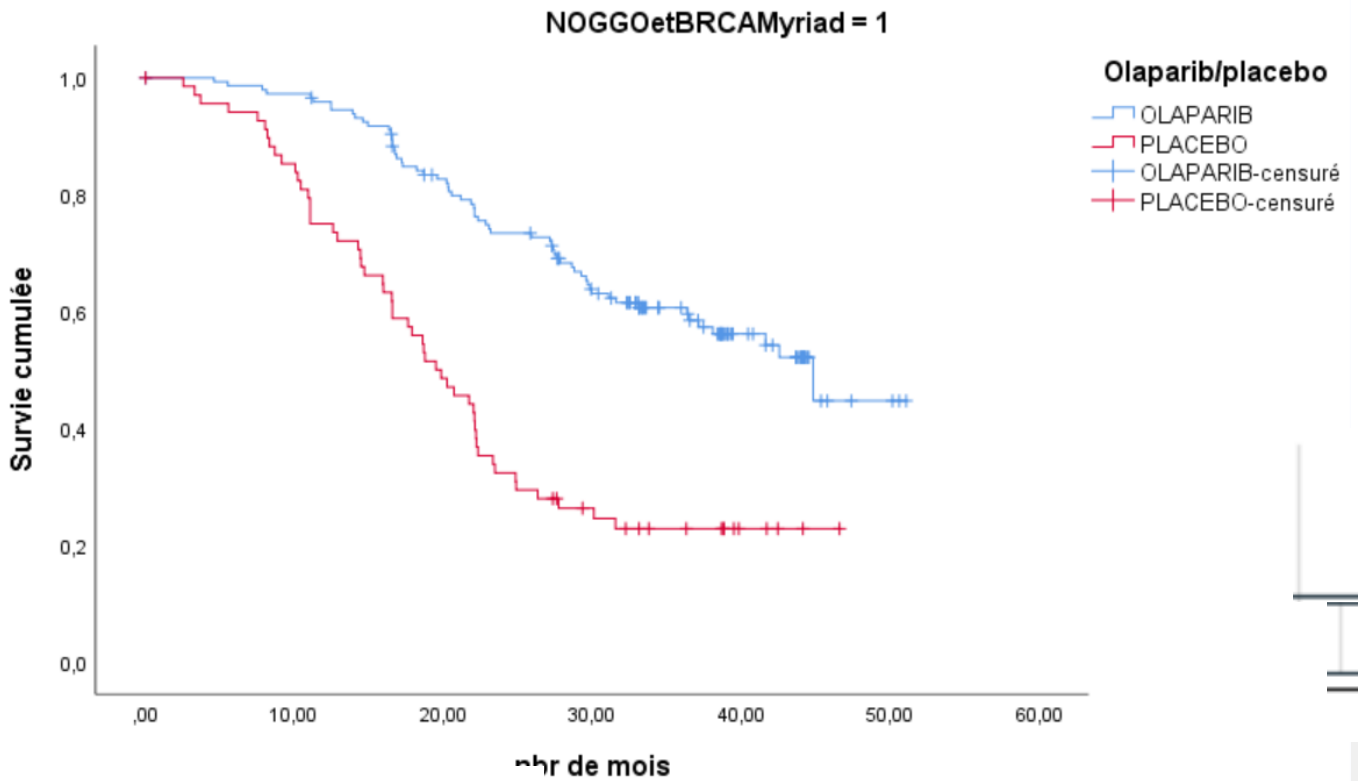
Evidence for Homologous Repair Deficiency and drug response



LST	x	x	x	x	x	x		
TAI				x	x			
LOH		x	x	x			x	

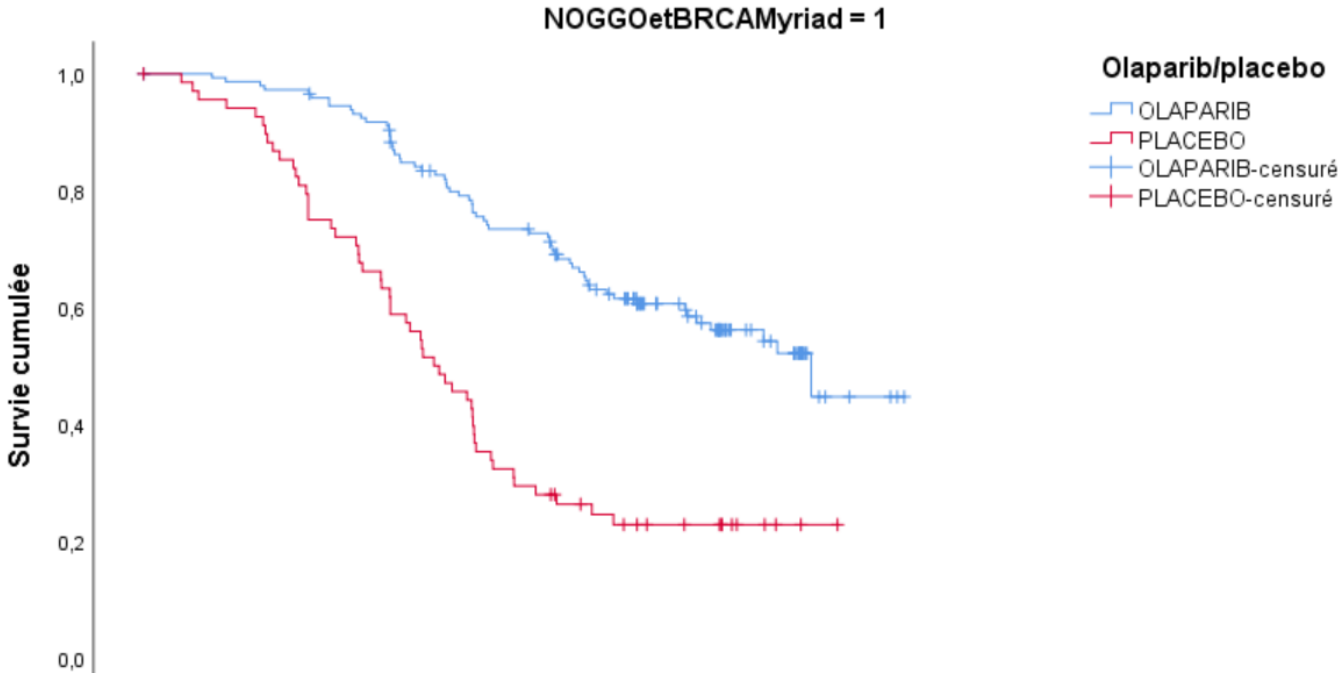
Watkins et al. (2014), Breast Cancer Research (modified)

Ursprünglicher Test (MYRIAD HRD test) bei Eierstockkrebs für PARPi bei HRD positiven Tumoren

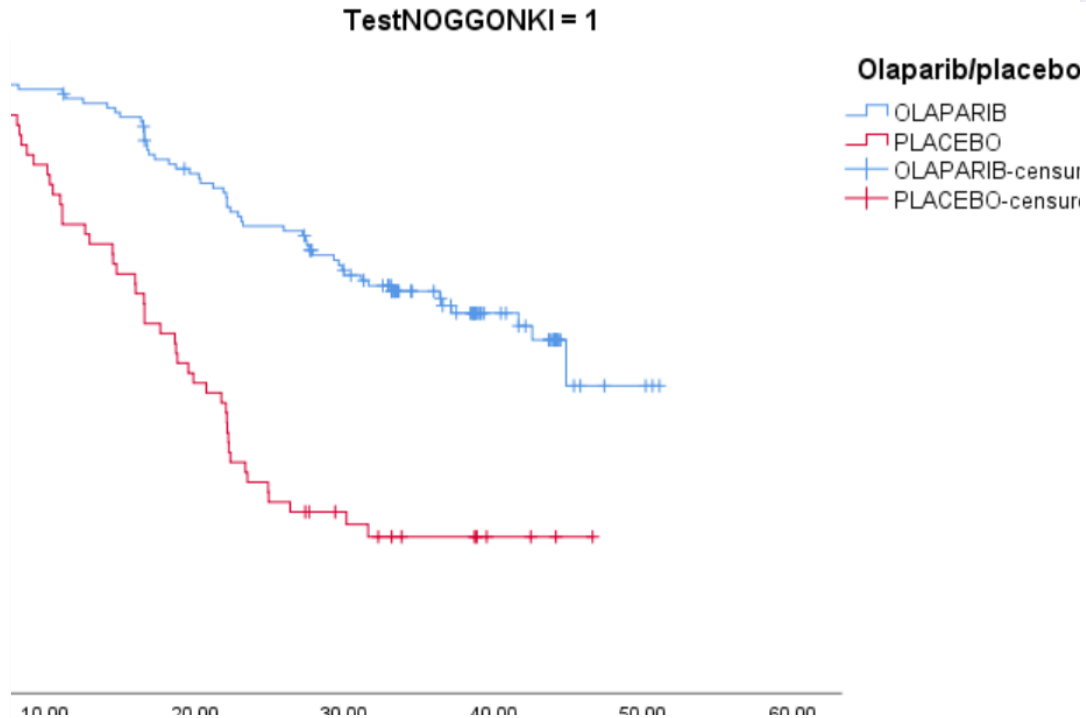


Sig.	Hazard ratio	95,0% CI of HR low	high
,000	,324	,221	,476

Neuer Test (NOGGO NKI test): ist sogar noch besser als ursprünglicher in der Studie verwendete Test (Myriad)



Sig.	Hazard ratio	95,0% CI of HR low	high
,000	,324	,221	,476



Sig.	Hazard ratio	95,0% CI of HR low	high
,000	,295	,197	,443

Zusammenfassung

- Umfassende genetische Testung bei jeder Krebserkrankung heute notwendig
- Genetische Testung läuft insbesondere über zertifizierten Krebszentren
- Pathologie muss akkreditiert sein und hohen Qualitätsanforderungen genügen
- Nur mit dem Nachweis von genetischen Veränderungen ist Präzisionsmedizin möglich
- Mit gezielter Krebstherapie werden tausende von Patientenjahren gewonnen bei hoher Lebensqualität

Lungenkrebsmedizin
Oldenburg

Vielen Dank für die Aufmerksamkeit!

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