Universitätsklinikum Leipzig

UNIVERSITÄT LEIPZIG
Medizinische Fakultät

Neues über die Tumorzelle – wissen wir mehr?

Dr. Ivonne Nel
ivonne.nel@medizin.uni-leipzig.de

Forschungslabor der
Klinik und Poliklinik für Frauenheilkunde
Direktorin: Prof. Dr. med. Bahriye Aktas

DKG KREBSGESELLSCHAFT Zertifiziertes Gynäkologisches Krebszentrum

BRUSTZENTRUM

Klinischer Nutzen serieller CTC-Quantifizierung bei MBC

SABCS

San Antonio Breast Cancer Symposium, December 8-11, 2020

Clinical utility of serial circulating tumor cell (CTC) enumeration as early treatment monitoring tool in metastatic breast cancer (MBC) - a global pooled analysis with individual patient data

Janni et al. | 2020 SABCS | GS4-08

Weltweit gepolte Daten von CTC Analysen bei MBC mittels **CellSerch**
N=4079
Therapiebeginn und Follow-Up

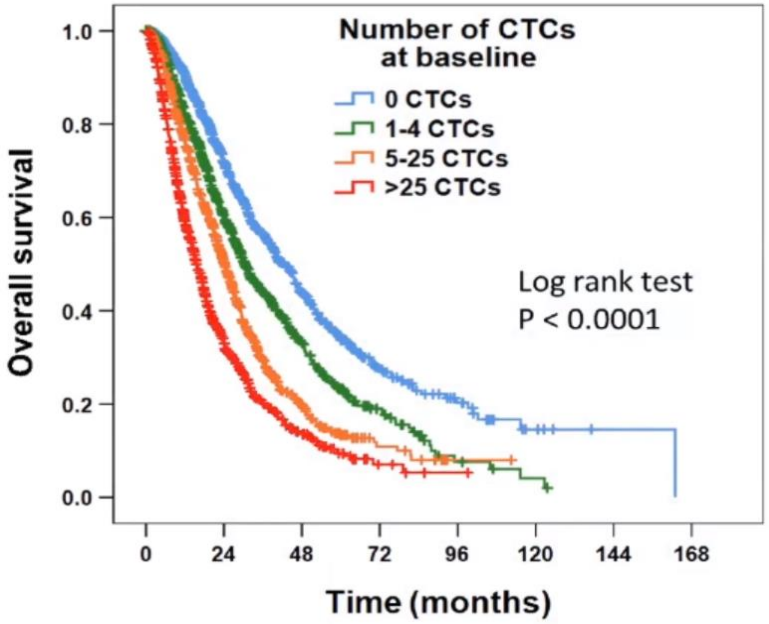
Ziel: prädiktive Rolle der CTC

Fokus: Gesamtüberleben
(N=3877 mit 2284 Ereignissen)

Cut Off ≥1 CTC und ≥5 CTC

Clinical Trial / Study / Institution	n	%
CALGB 40502 (Alliance)	455	11.2
CALGB 40503 (Alliance)	231	5.7
COMET	222	5.4
DETECT (ongoing)	273	6.7
IMMC-01	189	4.6
N1031	30	0.7
NSABP B-06	71	1.7
SWOG 0500	280	6.9
TBCRC 001	84	2.1
European pooled analysis (EPAC; including updated data sets)	1060	26.0
MDACC institutional study	387	9.5
Multi center Chinese study	220	5.4
Multi center Japanese study	106	2.6
Single institutional data (Athens, Aviano, Bruessels, Georgetown, Heraklion, Montpellier, Rome, Rotterdam)	471	11.5
TOTAL	**4079**	**100.0**

Klinischer Nutzen serieller CTC-Quantifizierung bei MBC

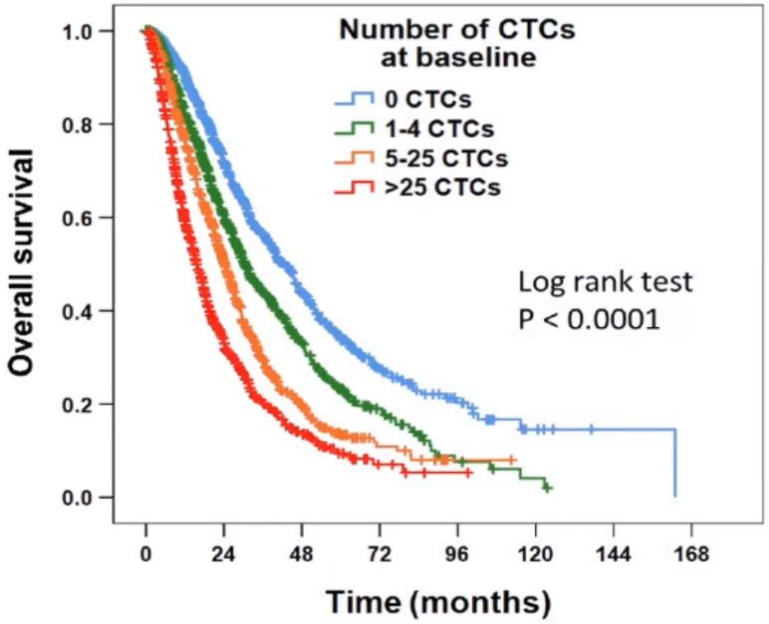


Überleben gemäß CTC count

	Median OS (months)	Hazard ratio	95 % CI	p-value
0 CTCs (n = 1058)	43.04	reference		
1-4 CTCs (n = 950)	30.55	1.44	1.27 – 1.63	< 0.0001
5-25 CTCs (n = 931)	24.16	2.01	1.78 – 2.26	< 0.0001
>25 CTCs (n = 938)	15.44	3.01	2.67 – 3.39	< 0.0001

Überleben gemäß CTC Status

Klinischer Nutzen serieller CTC-Quantifizierung bei MBC



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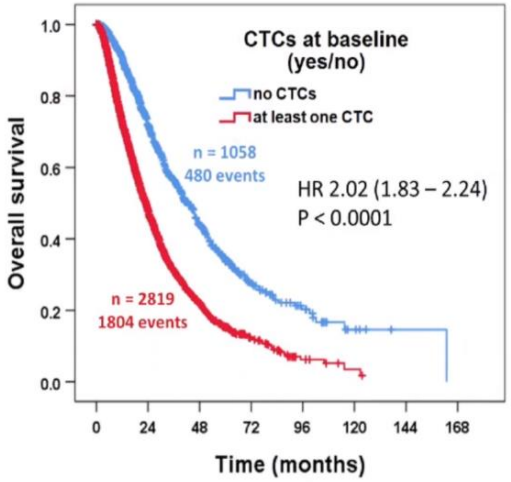

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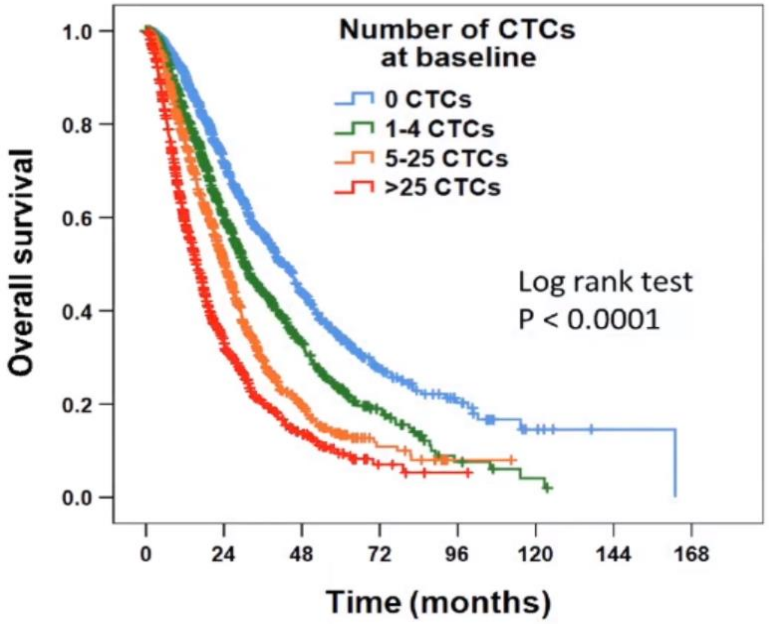

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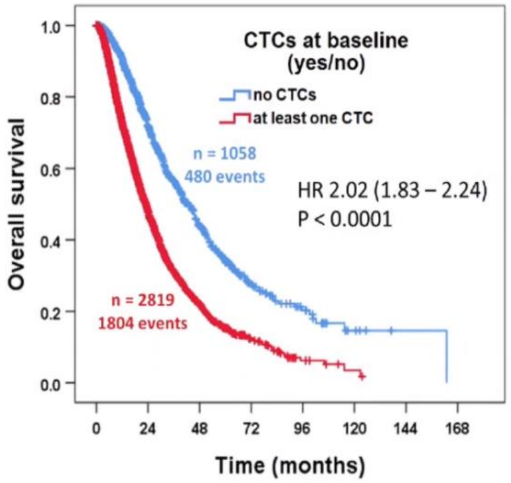
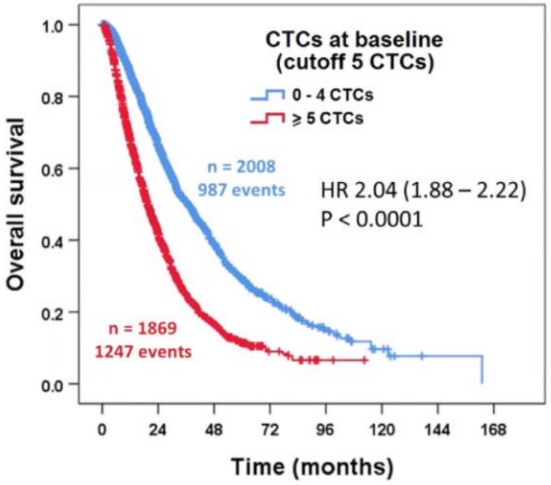
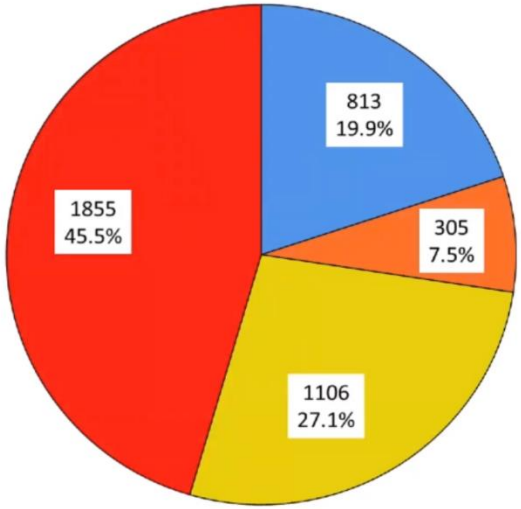




Klinischer Nutzen serieller CTC-Quantifizierung bei MBC

Change in CTC status from baseline to first follow up



CTC change group
(cutoff for CTC positivity: ≥ 1 CTC)

- CTC neg / CTC neg
- CTC neg / CTC pos
- CTC pos / CTC neg
- CTC pos / CTC pos

Time from baseline CTC assessment to first follow up CTC assessment:
Median: 29 days
Interquartile range: 26 – 54 days

Klinischer Nutzen serieller CTC-Quantifizierung bei MBC

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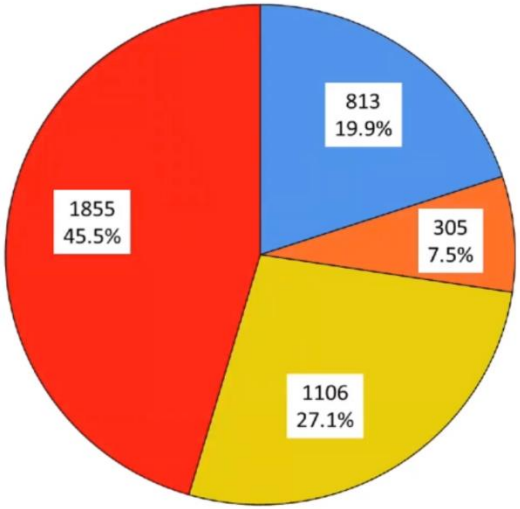
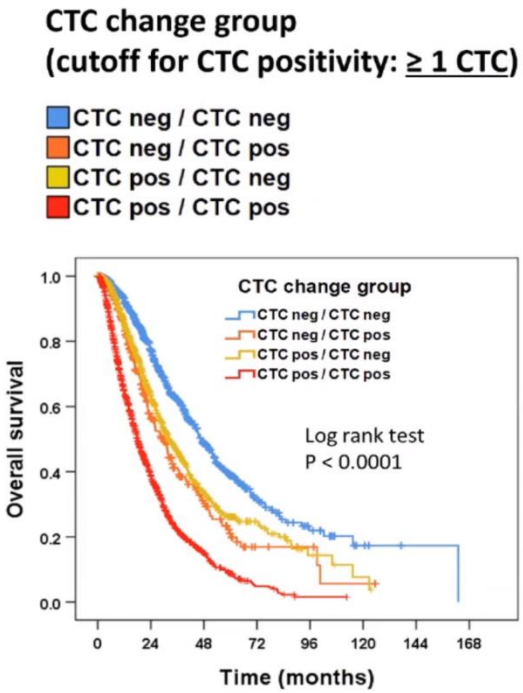




Überleben gemäß Änderung des CTC Status

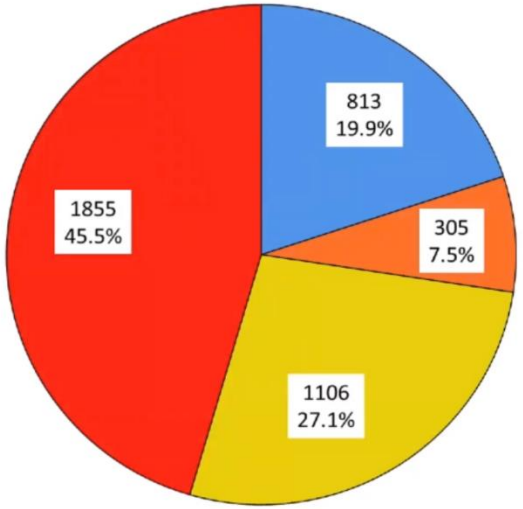
	Median OS (months)	Hazard ratio	95 % CI	p-value
neg/neg (n = 772)	47.05	reference		
neg/pos (n = 286)	29.67	1.74	1.43 – 2.10	< 0.0001
pos/neg (n = 1054)	32.20	1.52	1.32 – 1.74	< 0.0001
pos/pos (n = 1765)	17.87	3.15	2.78 – 3.57	< 0.0001

Note: Cutoff for CTC positivity ≥ 1 CTC)

Gesamtüberleben in Abhängigkeit zum **CTC Status** beim ersten Follow Up
Median: 29 Tage
IR: 26-54 Tage

Klinischer Nutzen serieller CTC-Quantifizierung bei MBC

Change in CTC status from baseline to first follow up



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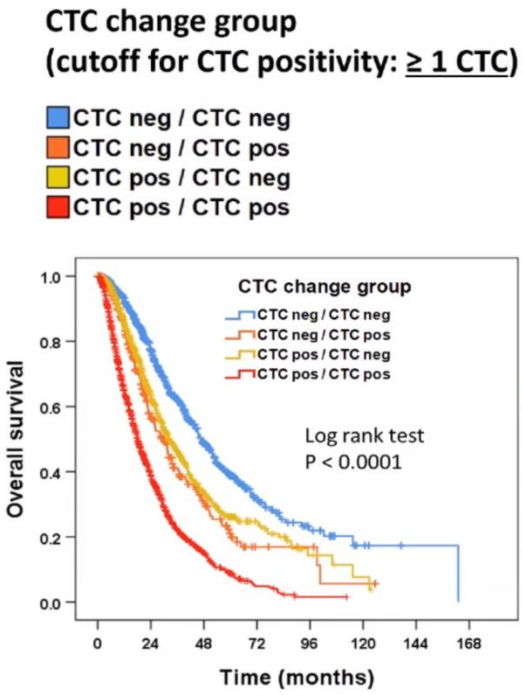

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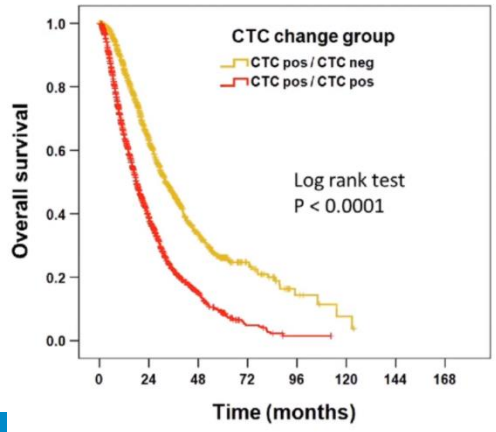


Only baseline CTC-positive groups
(i.e. CTC responders vs. CTC non-responders)

	Median OS (months)	Hazard ratio	95 % CI	p-value
pos/pos (n = 1765)	17.87	reference		
pos/neg (n = 1054)	32.20	0.49	0.44 – 0.54	< 0.0001

Note: Cutoff for CTC positivity ≥ 1 CTC)

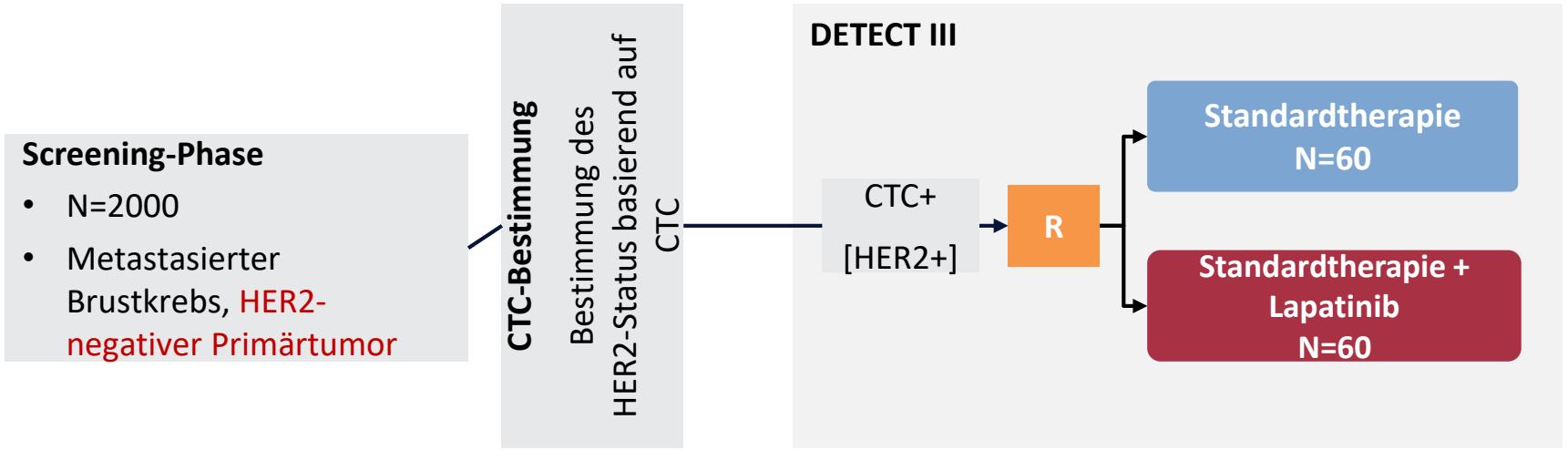
HER2 neg. Primarius & HER2 pos. CTC bei MBC

San Antonio Breast Cancer Symposium® - December 8-11, 2020

DETECT

Efficacy of the tyrosine kinase inhibitor lapatinib in the treatment of patients with HER2-negative metastatic breast cancer and HER2-positive circulating tumor cells – results from the randomized phase III DETECT III trial

Tanja Fehm[1], Volkmar Mueller[2], Maggie Banys-Paluchowski[3], Peter A. Fasching[4], Thomas W.P. Friedl [5], Andreas Hartkopf[6], Jens Huober[6], Christian Loehberg[4], Brigitte Rack[5], Sabine Riethdorf[7], Andreas Schneeweiss[8], Diethelm Wallwiener[6], Franziska Meier-Stiegen[1], Oliver Hoffmann[9], Lothar Müller[10], Pauline Wimberger[11], Eugen Ruckhaeberle[1], Jens-Uwe Blohmer[12], Klaus Pantel[7] and Wolfgang Janni[5] on behalf of the DETECT study group



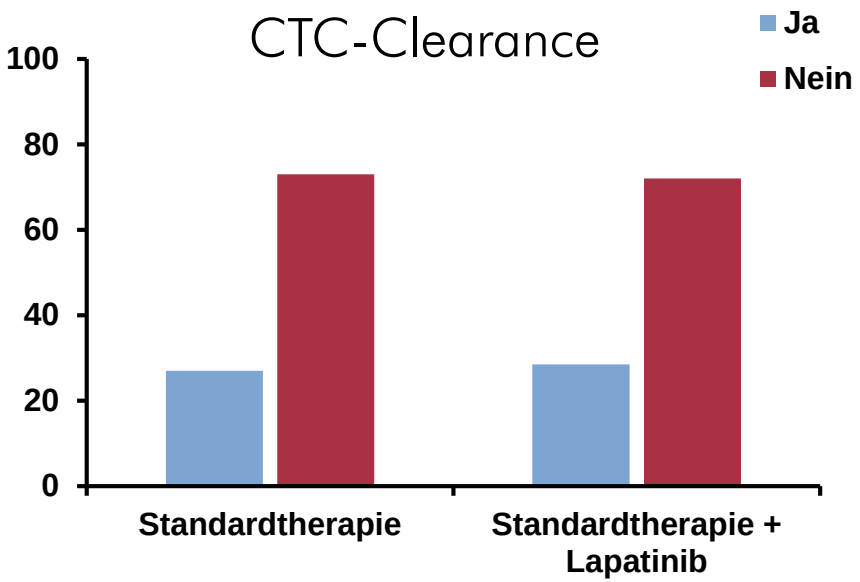
Fehm et al. | 2020 SABCS | PD3-12

105 Patientinnen prospektiv randomisiert
CTC Detektion und Phenotypisierung mittels **CellSearch**
HER2 positive: IHC score 2+ od 3+

Median CTC Baseline: 43 range (1-5500) in Standard-Arm
29 (range 1-7656) in Lapatinib-Arm

HER2 neg. Primarius & HER2 pos. CTC bei MBC

Erster Follow Up: 73 Tage nach Behandlungsbeginn (Median)



p=0.89 (26.7% vs. 28.2%)

p=0.64 (53.3% vs. 59%)

HER2 neg. Primarius & HER2 pos. CTC bei MBC

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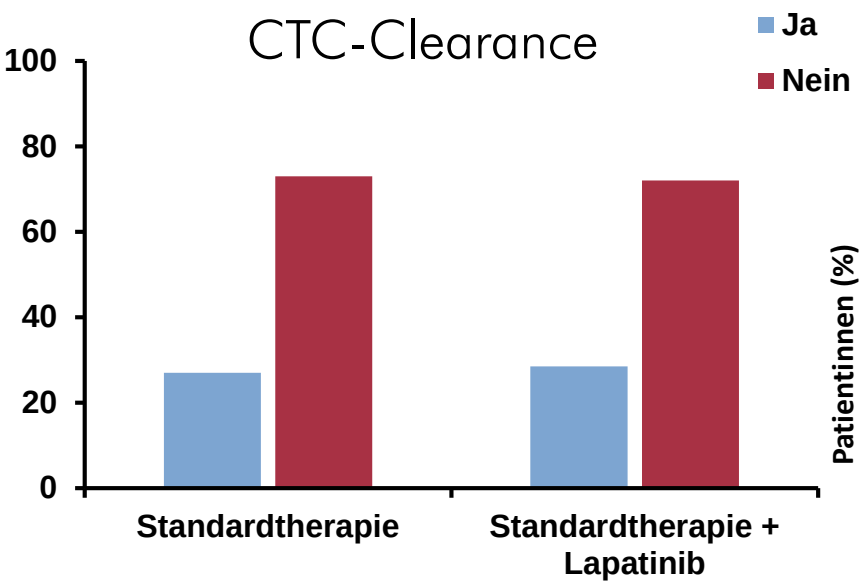

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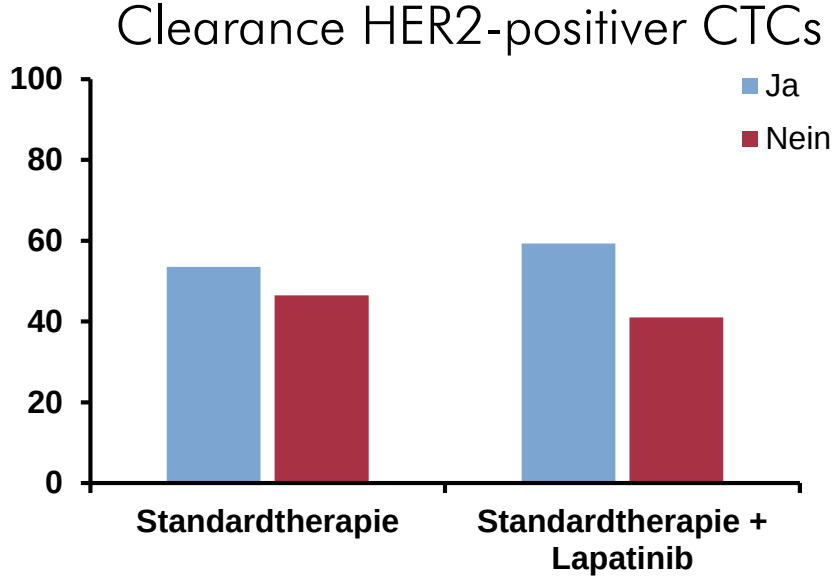

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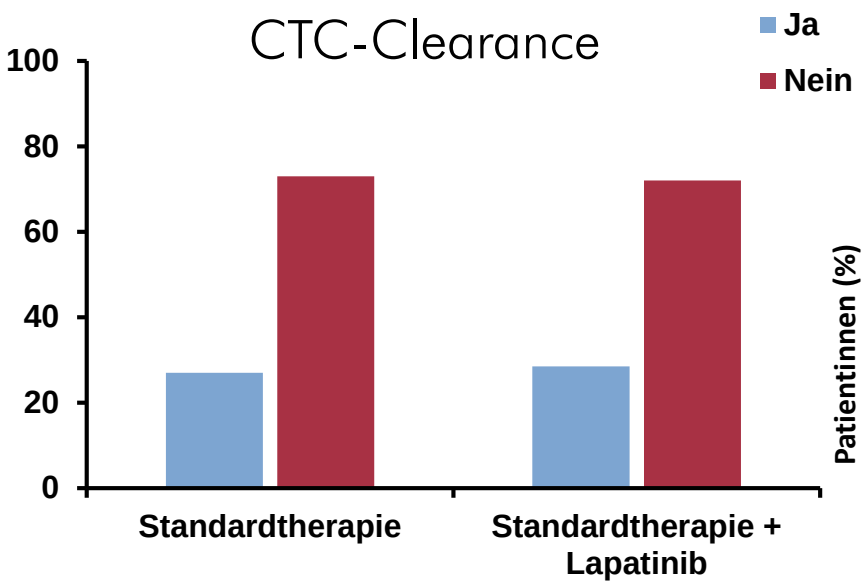

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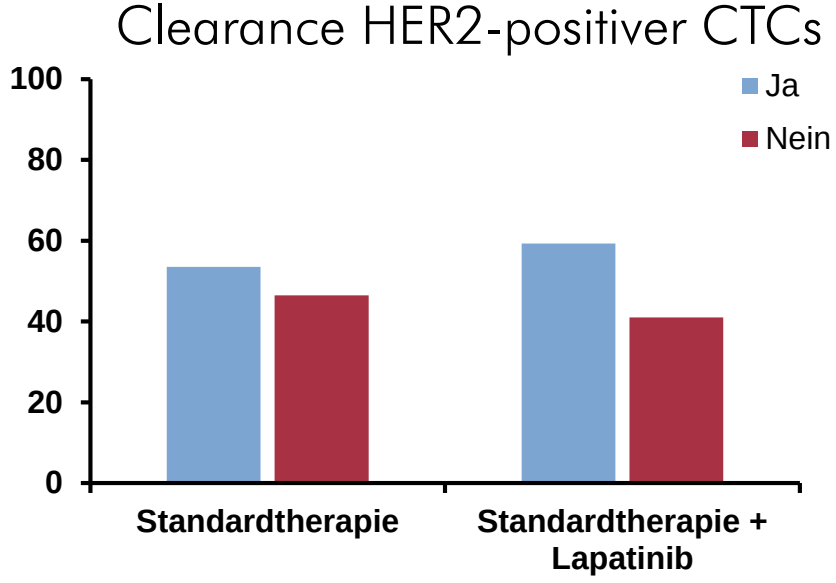


p=0.64 (53.3% vs. 59%)

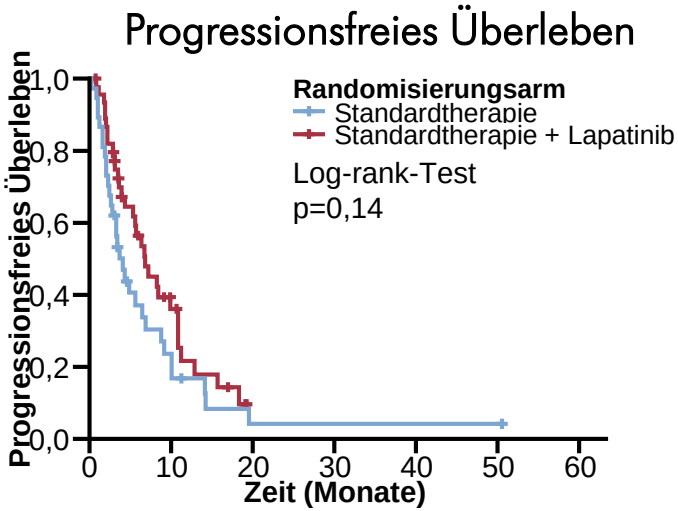
Letzter Follow Up: bei Behandlungsende bzw. Progress

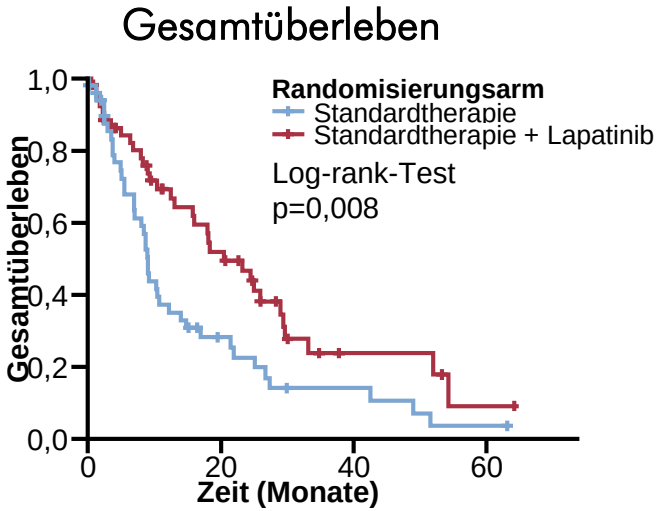
P=0.18 (33.3% vs 15.5%)

P=0.63 (57.1% vs. 50.0%)

Kein signifikanter Unterschied der CTC- bzw.- HER2-pos. CTC-Clearance zwischen den Standard-Therapie vs. Lapatinib/Standard- Arm bei erstem und letztem Follow-Up

HER2 neg. Primarius & HER2 pos. CTC bei MBC





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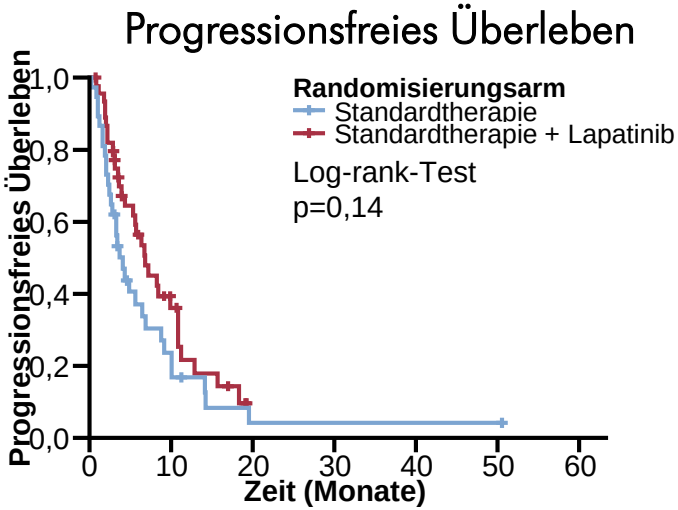
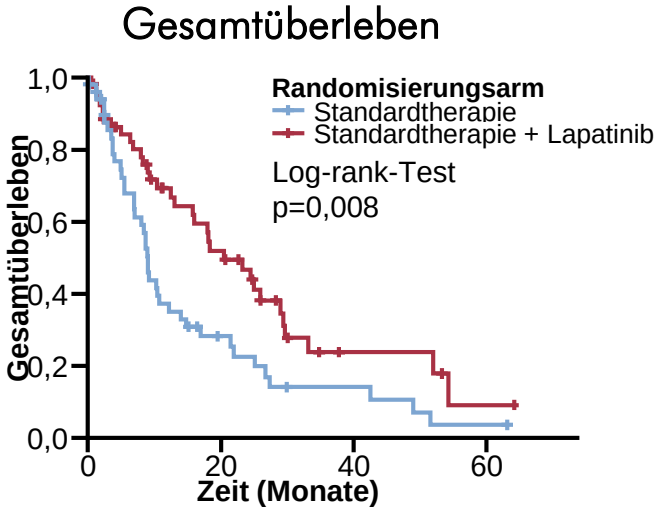
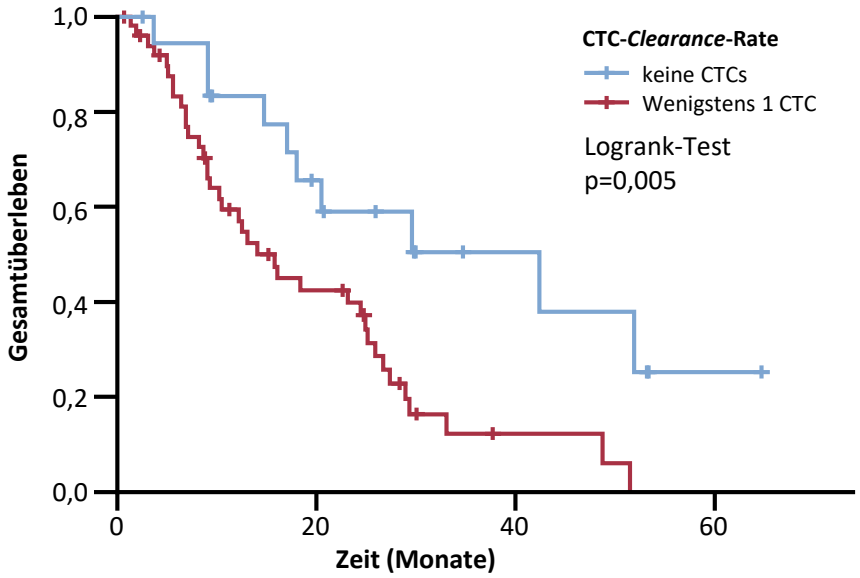




Gesamtüberleben
Nach initialem
HER2-CTC-Status



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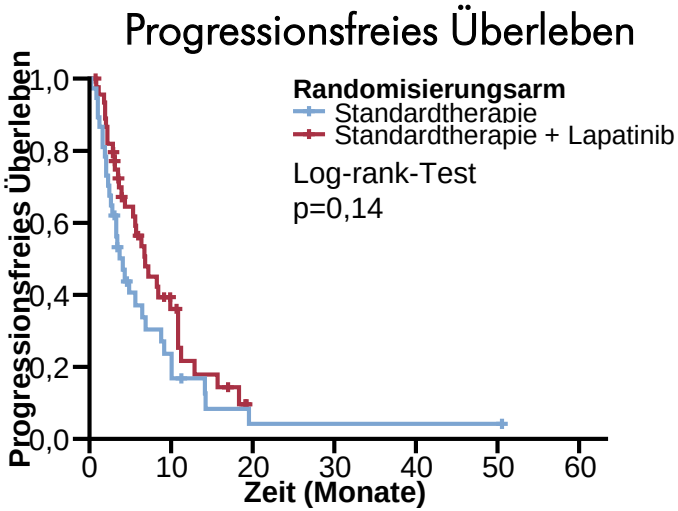

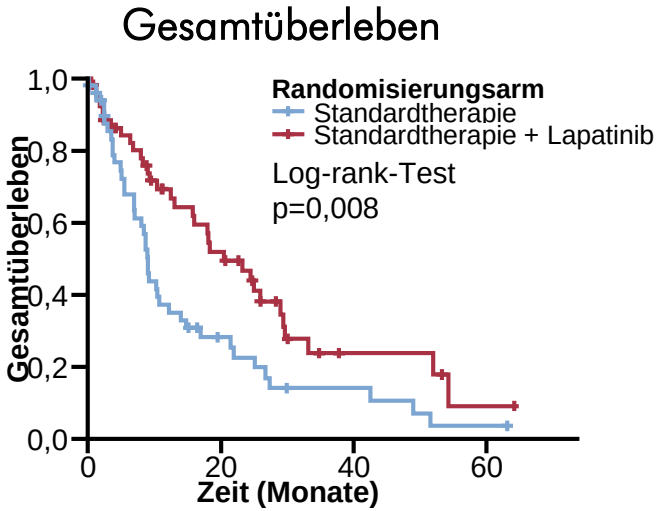

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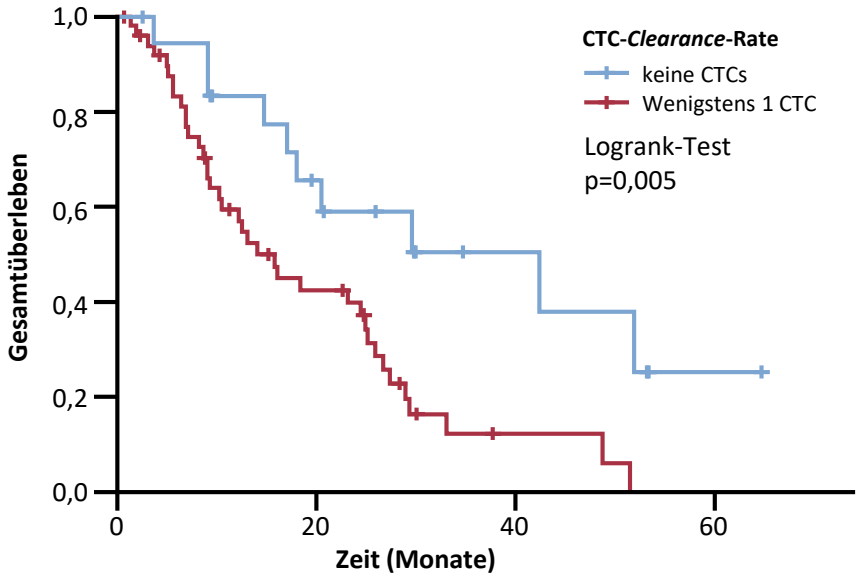

-Lapatinib verbesserte Gesamtüberleben bei HER2+CTCs

-Nachteil der Studie:
Cut-off bei 1 CTC
HER2 Expression ist heterogen!

HER2 pos Primarius & HER2 pos CTC bei MBC

Department of Medicine-Hematology and Oncology - Feinberg School of Medicine
San Antonio Breast Cancer Symposium – December 8-11, 2020. | Abstract Number#1751 - Poster: PS2-11

CTC-HER2+ a novel subset in Stage IV aggressive: molecular correlations, outcome and clinical characteristics in metastatic breast cancer (MBC)

Paolo D'Amico[1-2-3], Qiang Zhang[1], Lorenzo Gerratana[1], Youbin Zhang[1], Ami Shah[1], Carolina Reduzzi[1], Andrew Davis[1], Saya Jacob[1], Firas Wehbe[1], Amir Behdad[1], Giuseppe Curigliano[1-2-3] and Massimo Cristofanilli[1]
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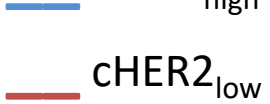
247 Blutproben von MBC Patientinnen mit
pos HER2 FISH Amplifikation in Gewebebiopsie
vor neuer Therapielinie

HER2+CTCs mittels CellSearch:
kategorisiert 0,1+,2+,3+

Population mit >5 CTCs, Stadium IV

cHER2 ratio (Summe 2+ & 3+ CTCs) /Gesamt HER2+ CTCs
-> cut-off bei 0.75: **cHER2 high vs. cHER2 low** Subgruppen

PFS in beiden Subgruppen



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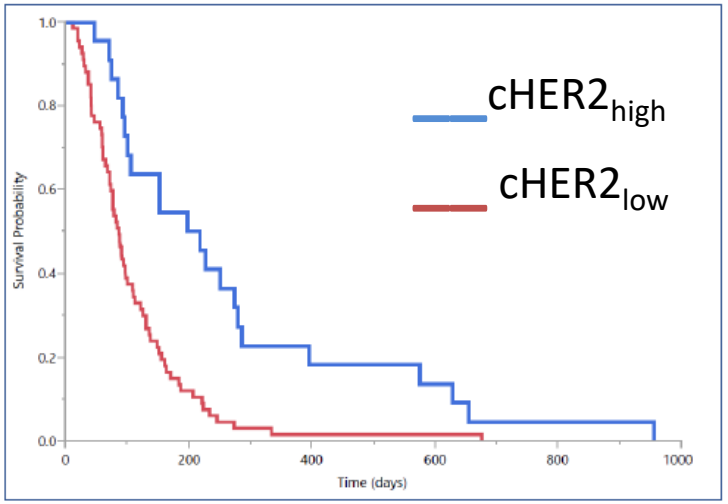

89 Events: 67 $cHER2_{high}$ vs. 22 $cHER2_{low}$
Median TTP: 87 Tage high vs. 209 Tage low

HER2 pos Primarius & HER2 pos CTC bei MBC

ctDNA aus Plasma mit Guardant360 NGS Assay analysiert

ERBB2 Mutationen häufiger in **cHER2 high** ($p<0.05$)

ERBB2 in beiden Subgruppen

$cHER2_{high}$

$cHER2_{low}$

HER2 pos Primarius & HER2 pos CTC bei MBC

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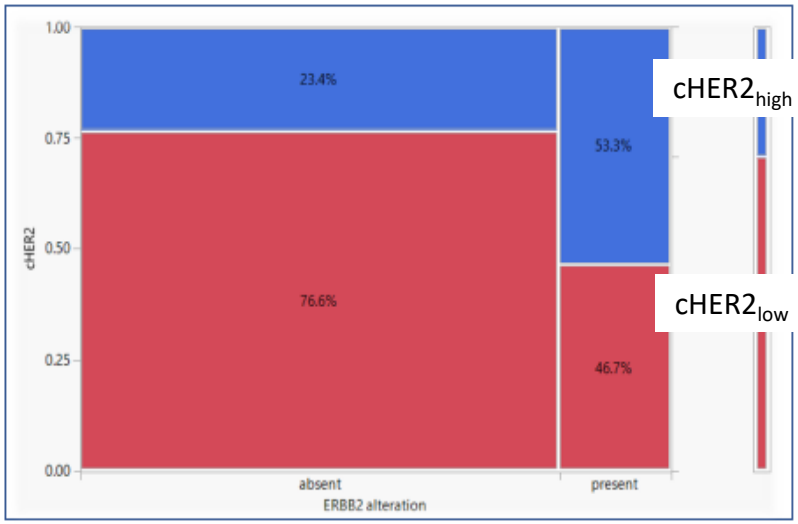
ERBB2 in beiden Subgruppen



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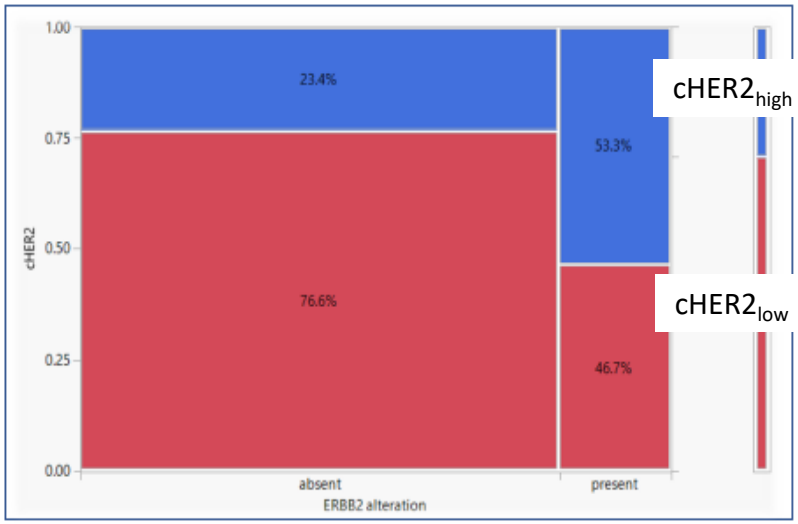
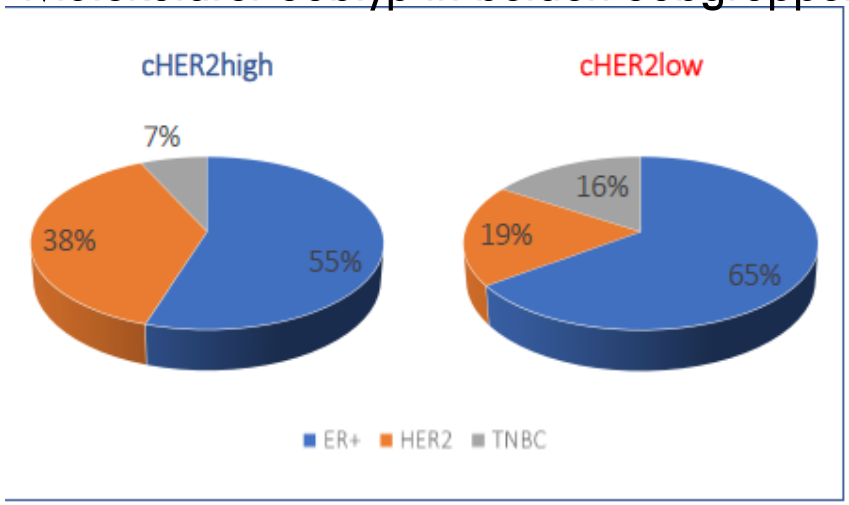


Molekularer Subtyp in beiden Subgruppen



HER2+ Subtyp mit 38% vs. 19% häufiger in **cHER2 high** ($p<0.05$)

In **cHER2 low** Subgruppe waren 65% HR+

HER2 pos Primarius & HER2 pos CTC bei MBC

ctDNA aus Plasma mit Guardant360 NGS Assay analysiert

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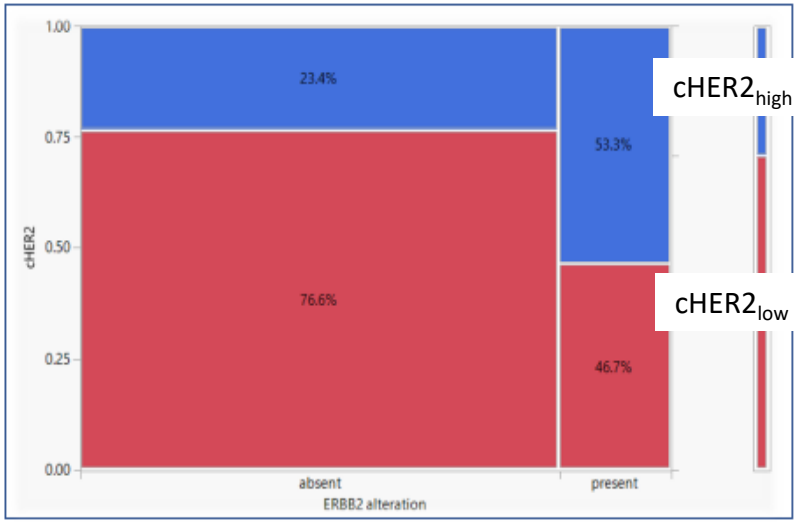
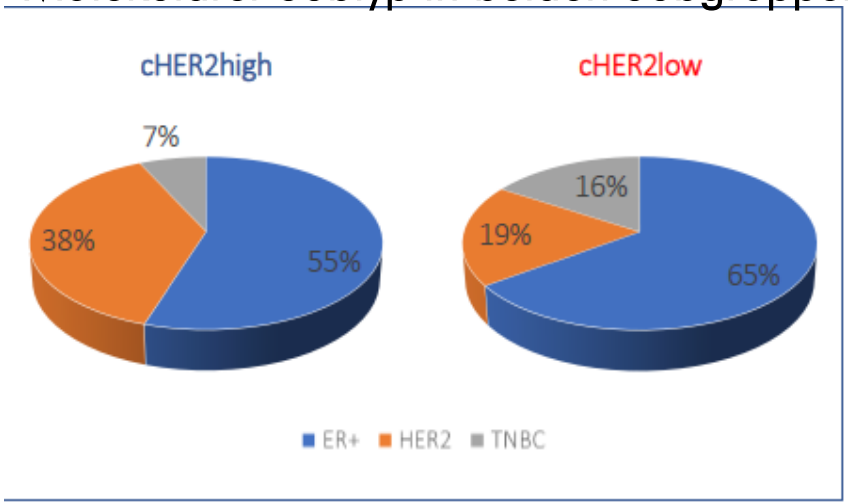
ERBB2 in beiden Subgruppen



Molekularer Subtyp in beiden Subgruppen



HER2+ Subtyp mit 38% vs. 19% häufiger in **cHER2 high** ($p<0.05$)

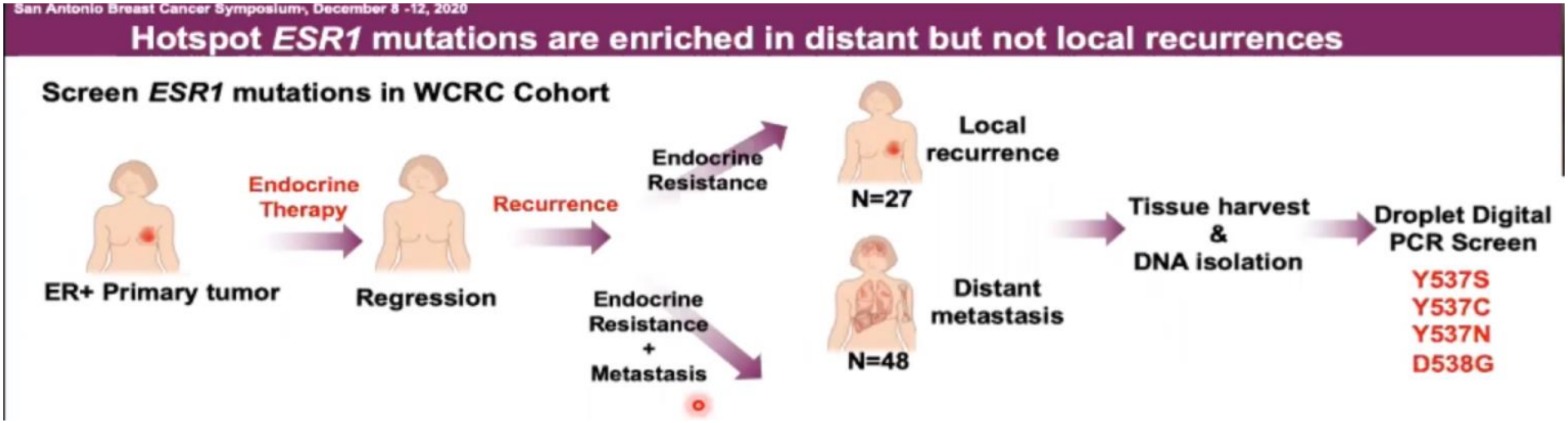
In **cHER2 low** Subgruppe waren 65% HR+

Bei MBC Stadium IV (aggressiv) spielt cHER2 Ratio eine **prognostische** Rolle

cHER2 high Patientinnen -> HER2 FISH Amplifikation im Tumorgewebe und
-> ERBB2 Mutation in ctDNA

ESR1 Mutationen und CTC cluster

Zheqi (Vaciry) Li, PhD
Postdoctoral Associate
Mentors: Steffi Oesterreich, PhD & Adrian Lee, PhD
Department of Molecular Pharmacology, University of Pittsburgh
Women's Cancer Research Center, UPMC Hillman Cancer Center



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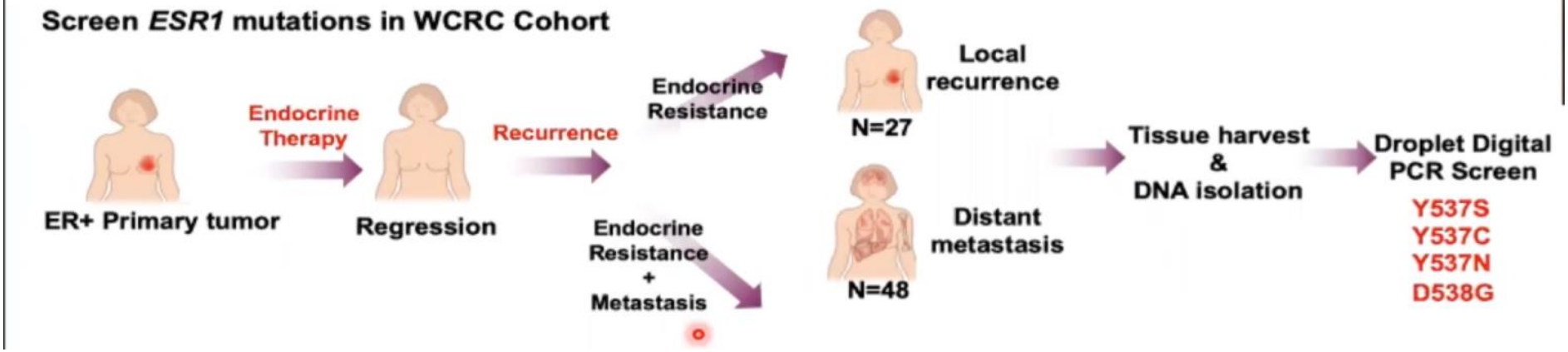
Hotspot *ESR1* mutations are enriched in distant but not local recurrences



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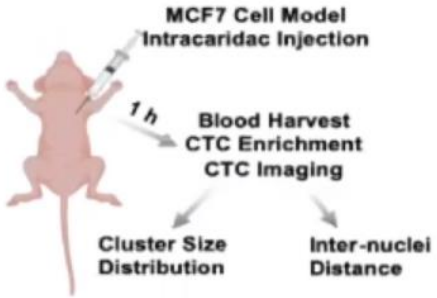
Y537S *ESR1* mutant cells form larger CTC clusters and promote metastasis *in vivo*



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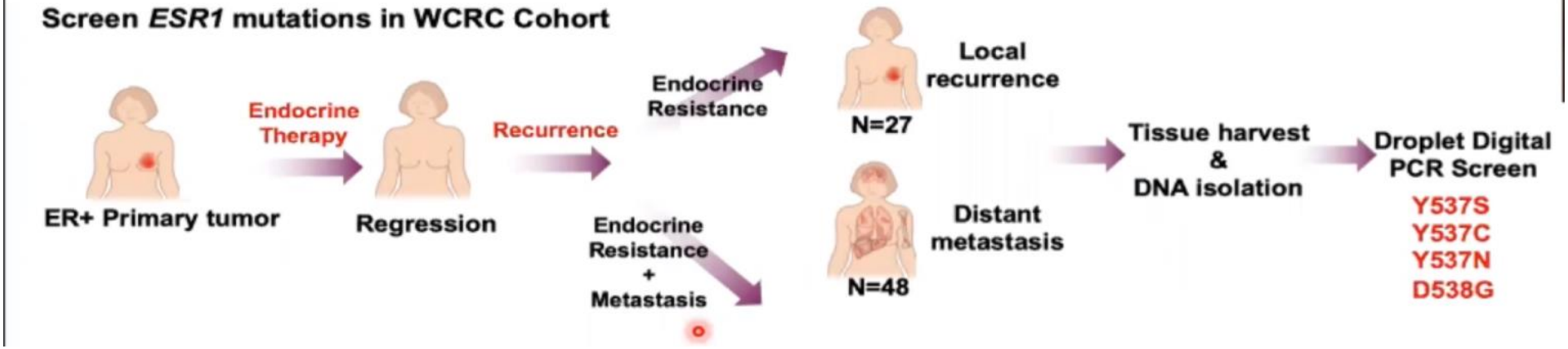

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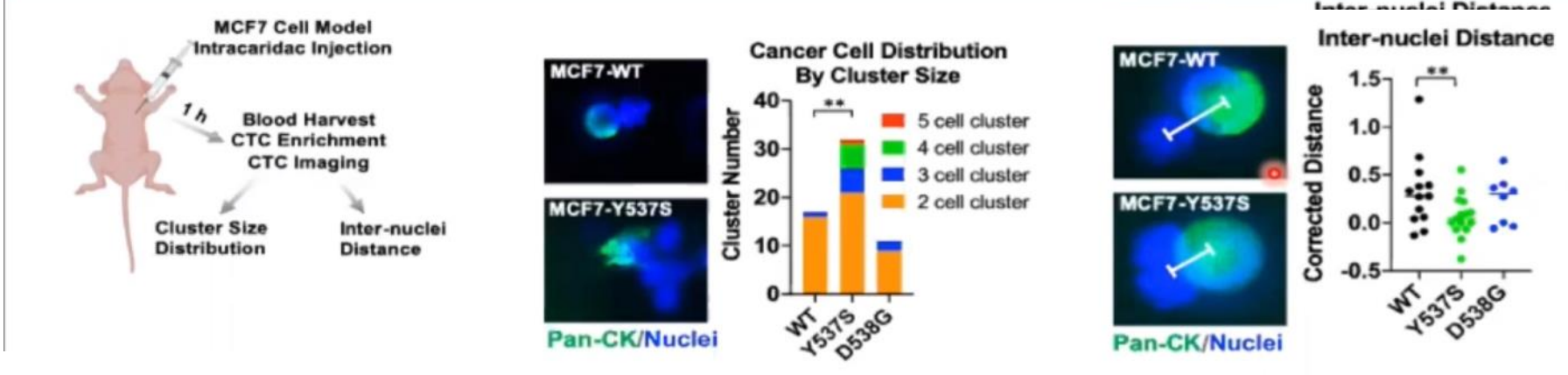


ESR1 Mutationen und CTC cluster bei MBC

ESR1 Mutationen und CTC cluster bei MBC

San Antonio Breast Cancer Symposium, December 8 -12, 2020

CTC clusters are significantly enriched in *ESR1* mutant breast cancer patients

Liquid Biopsy Workflow

151 MBC patients from Northwestern University Cohort

↓

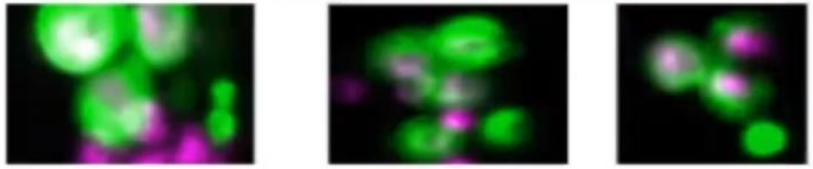
Two blood draws each patient

↓

CTC Enumeration CellSearch System

cfDNA-based *ESR1* mutation detection at Y537 and D538 sites

Representative Images of CTC clusters



Pan-Cytokeratin/Nuclei

This clinical study was in collaboration with Dr. Massimo Cristofanilli.

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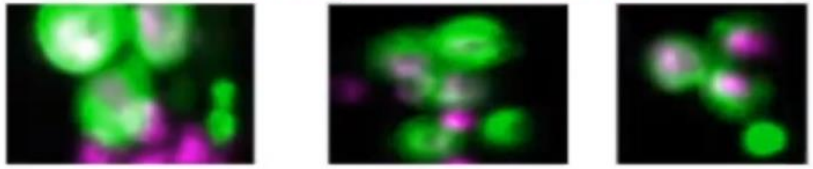

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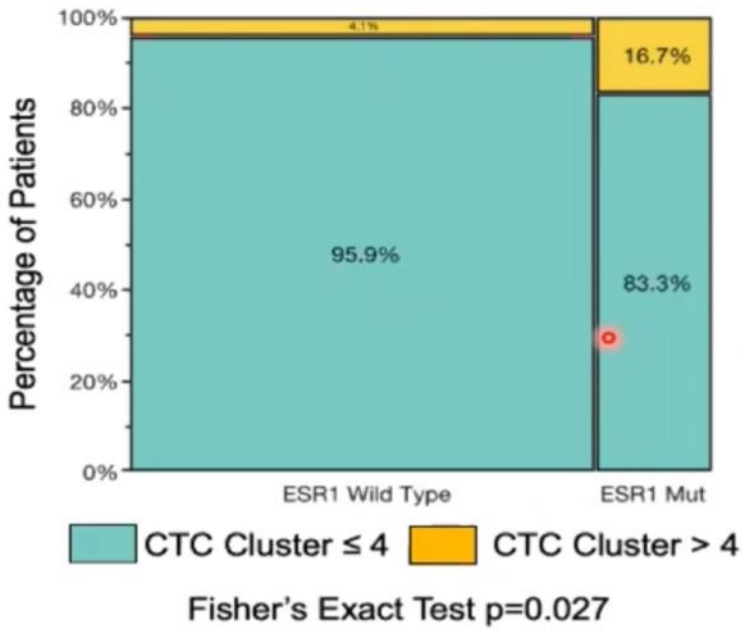

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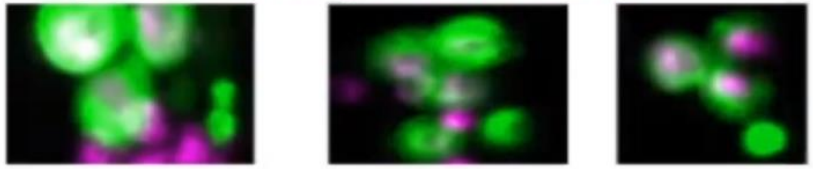

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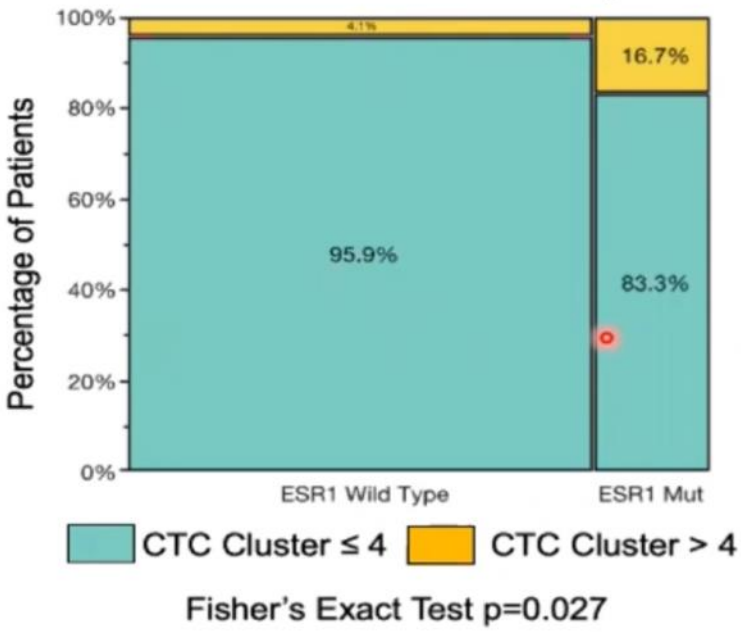

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CTC cluster >4 CTCs sind mit ESR1 Mutationen in ctDNA assoziiert

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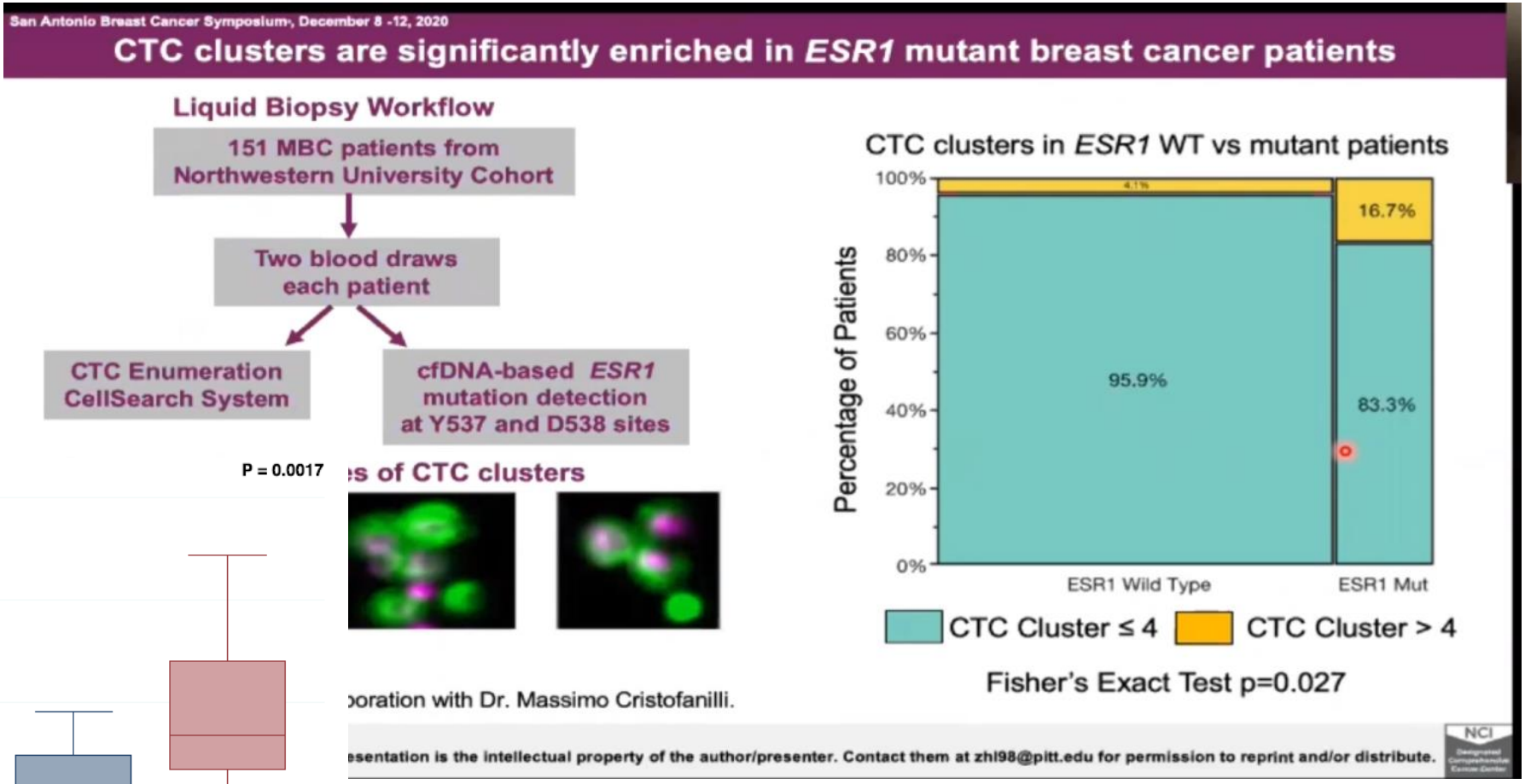

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Davis *et al. Breast Cancer Research* (2019) 21:137

ctDNA als Surrogat-Marker

Bekannt aus 2020:
ctDNA nach NACT bzw. im Follow-Up
mit Rezidivierung assoziiert:

TNBC > HER2+ > ER+

Response-Marker für NACT bei HER2+
(NeoALTTO)

- Prädiktiv nach NACT bei TNBC
BRE12-158 Trial

- Möglicher Marker für Therapie-
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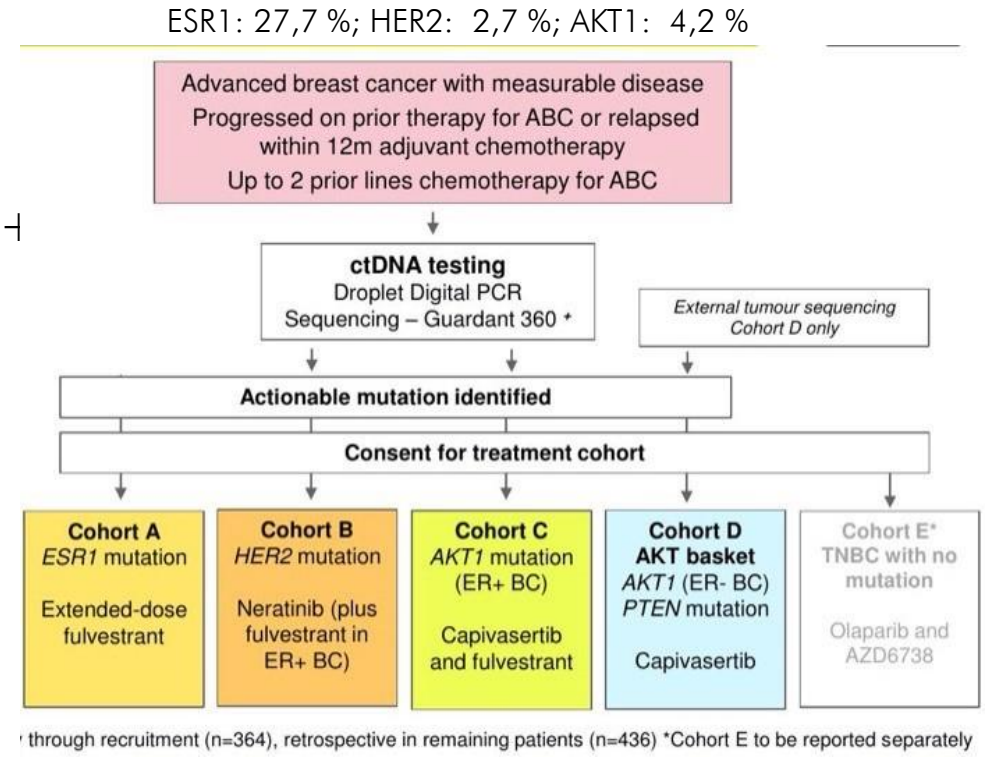

PlasmaMATCH Studie

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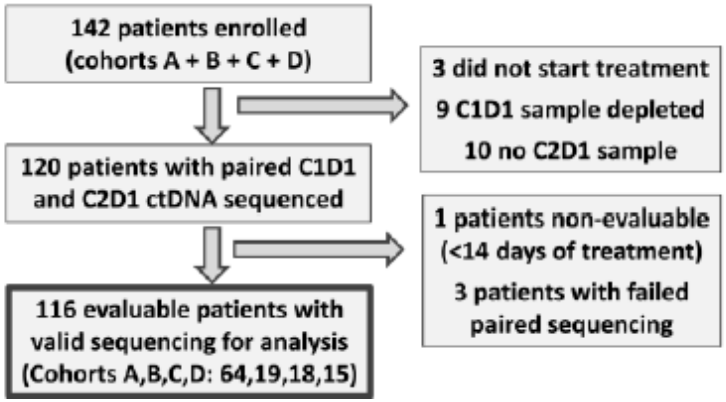

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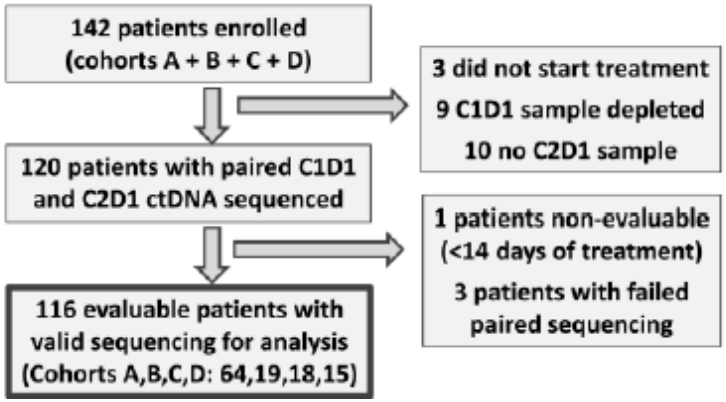

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	HR (95% CI)	P value	Peak Harrel's C-index
Maximum VAF in C1D1	2.42 (1.53-3.82)	**<0.001**	0.608
Maximum VAF at C1D1 or C2D1	2.59 (1.66-4.05)	**<0.001**	0.615
Mean VAF	2.44 (1.56-3.81)	**<0.001**	0.595
Mean VAF excluding *ESR1*	2.11 (1.35-3.29)	**0.001**	0.567
Weighted mean VAF	2.38 (1.53-3.68)	**<0.001**	0.619
Weighted mean excluding *ESR1*	1.47 (0.96-2.25)	0.08	0.571
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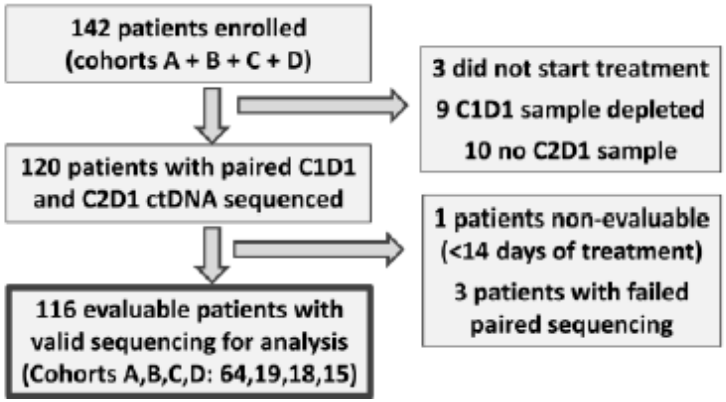

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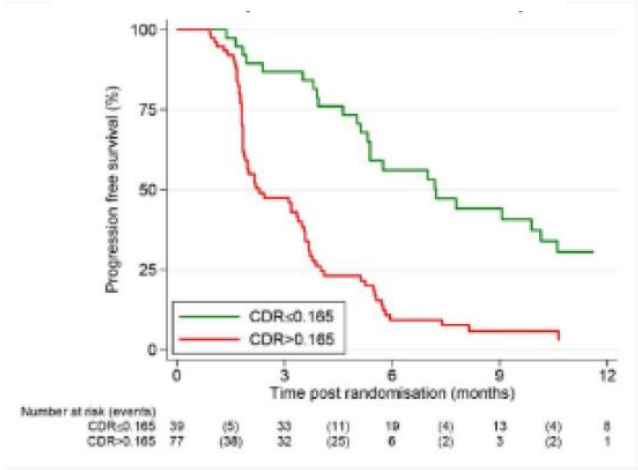
PFS 7.3 vs. 2.3 Monate



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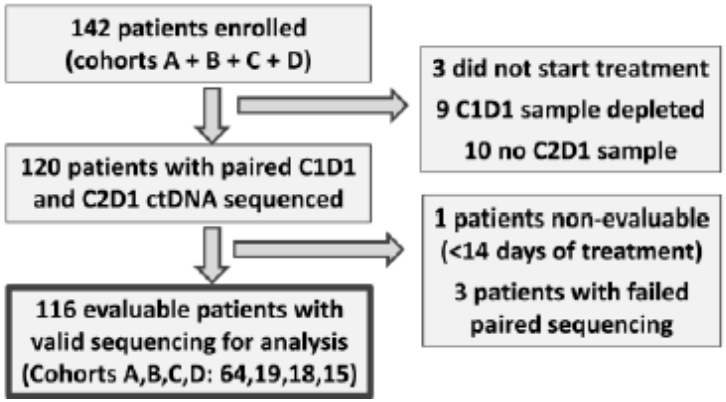

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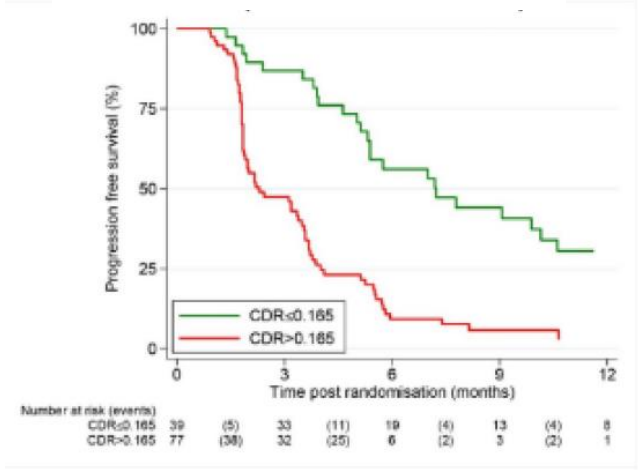
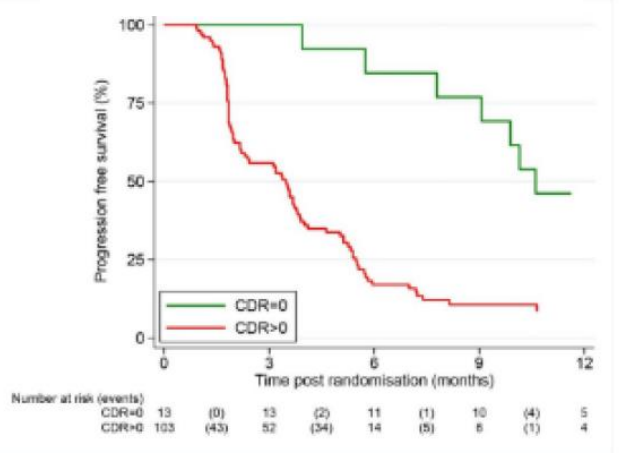


PFS 10.6 vs. 3.5 Monate



Frühe ctDNA Dynamik prädiktiv für Therapieansprechen bei MBC mit zielgerichteter Therapie

ctDNA als prädiktiver Biomarker in EBC

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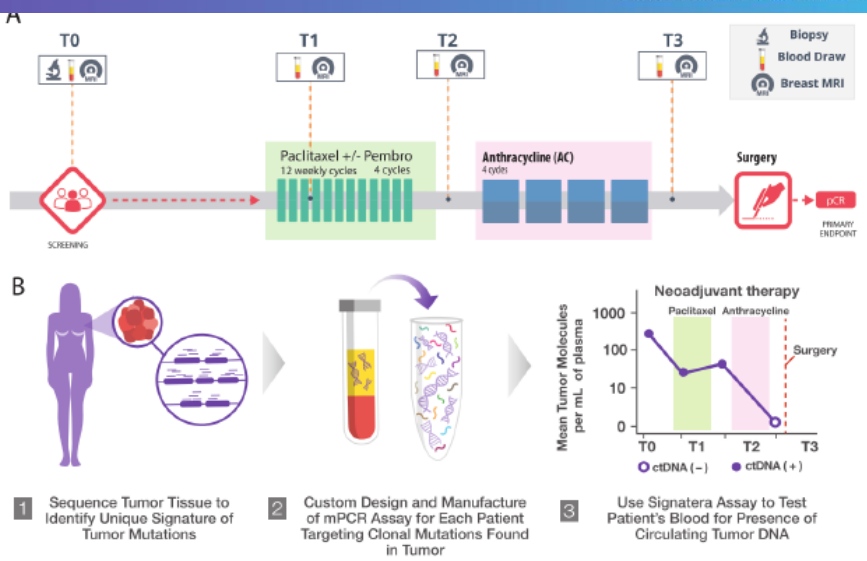
San Antonio Breast Cancer Symposium | San Antonio, Texas | December 9 - 11, 2020 #PD9-02

I-SPY Trial
NACT + Pembro
Verdoppelte pCR Rate
bei HR+ und TNBC

Nach 3 Jahren DRFS>95%

ctDNA prädiktiv für Response & Survival?



138 Patientinnen, 511 serielle Plasmaproben

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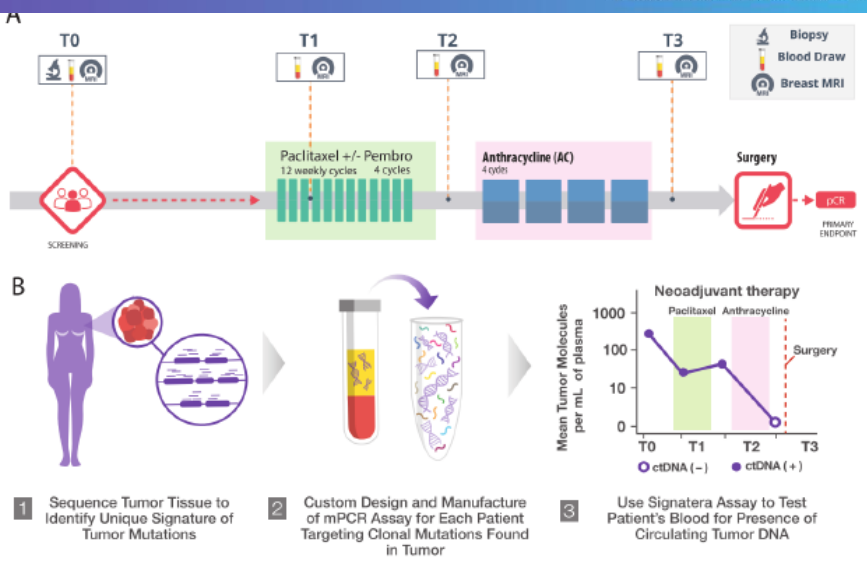

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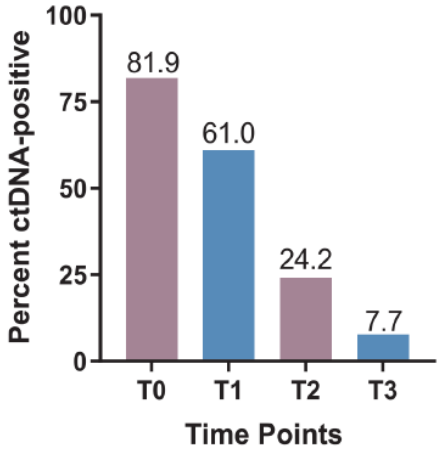

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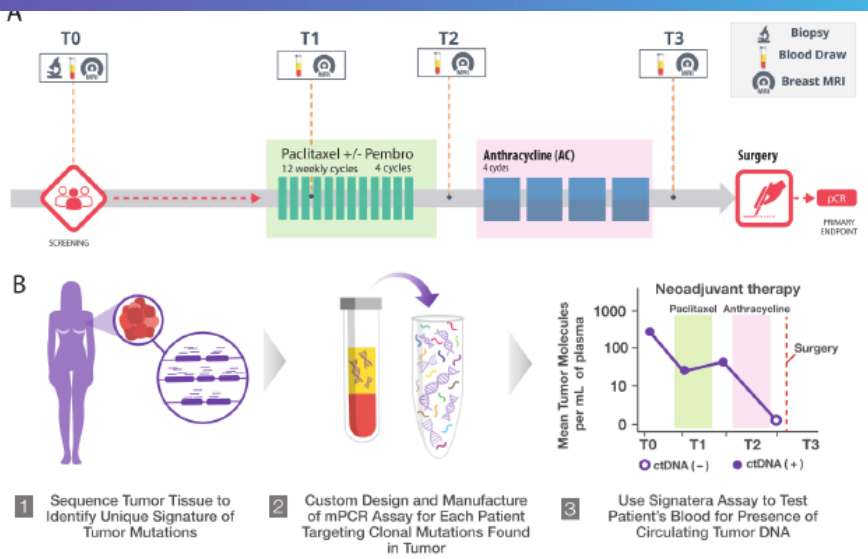

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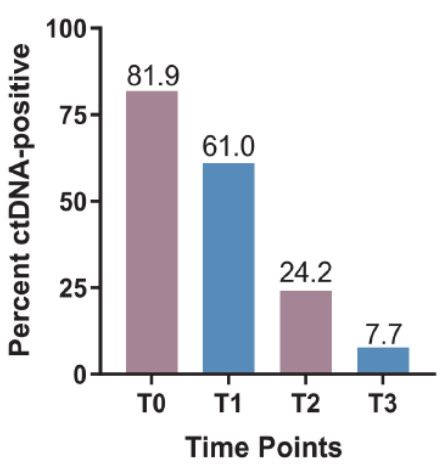

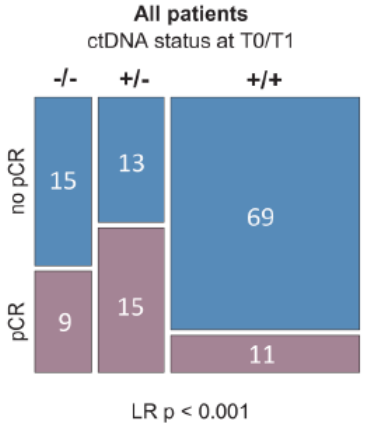

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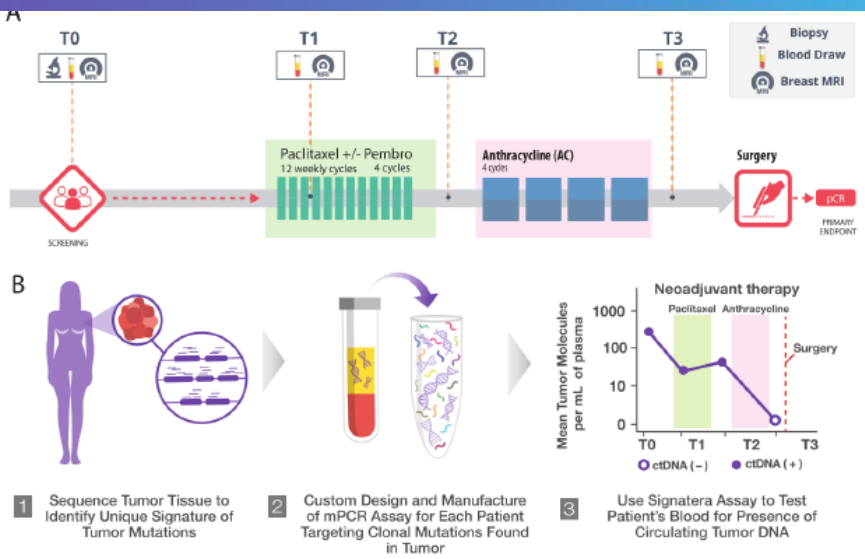

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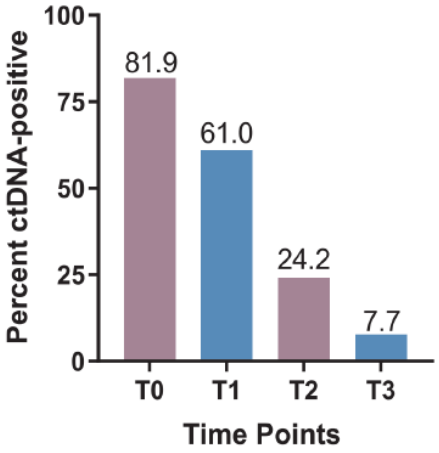

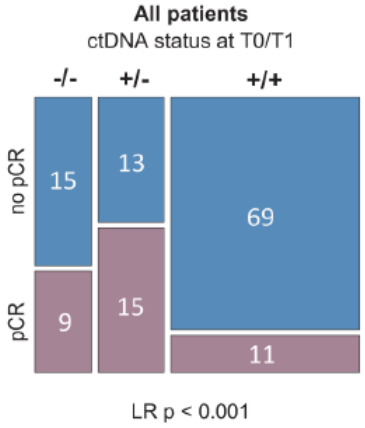

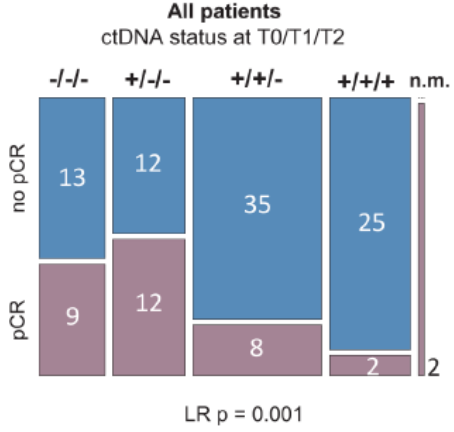

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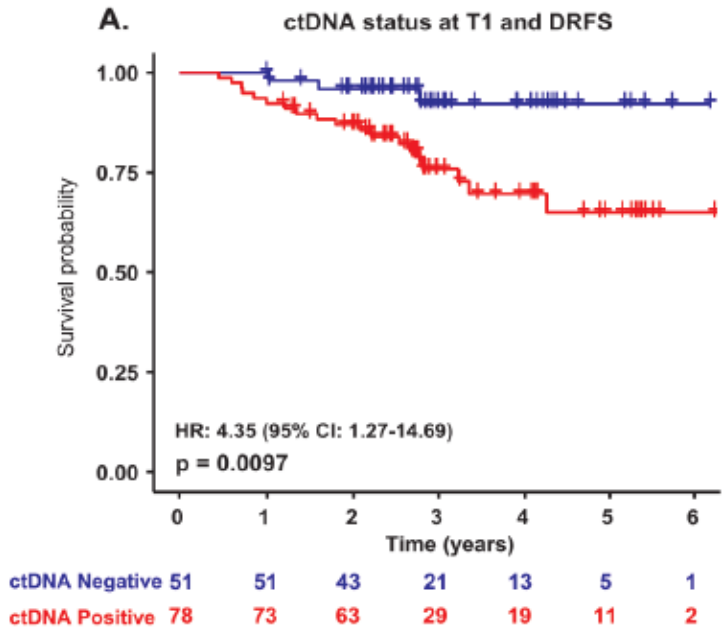

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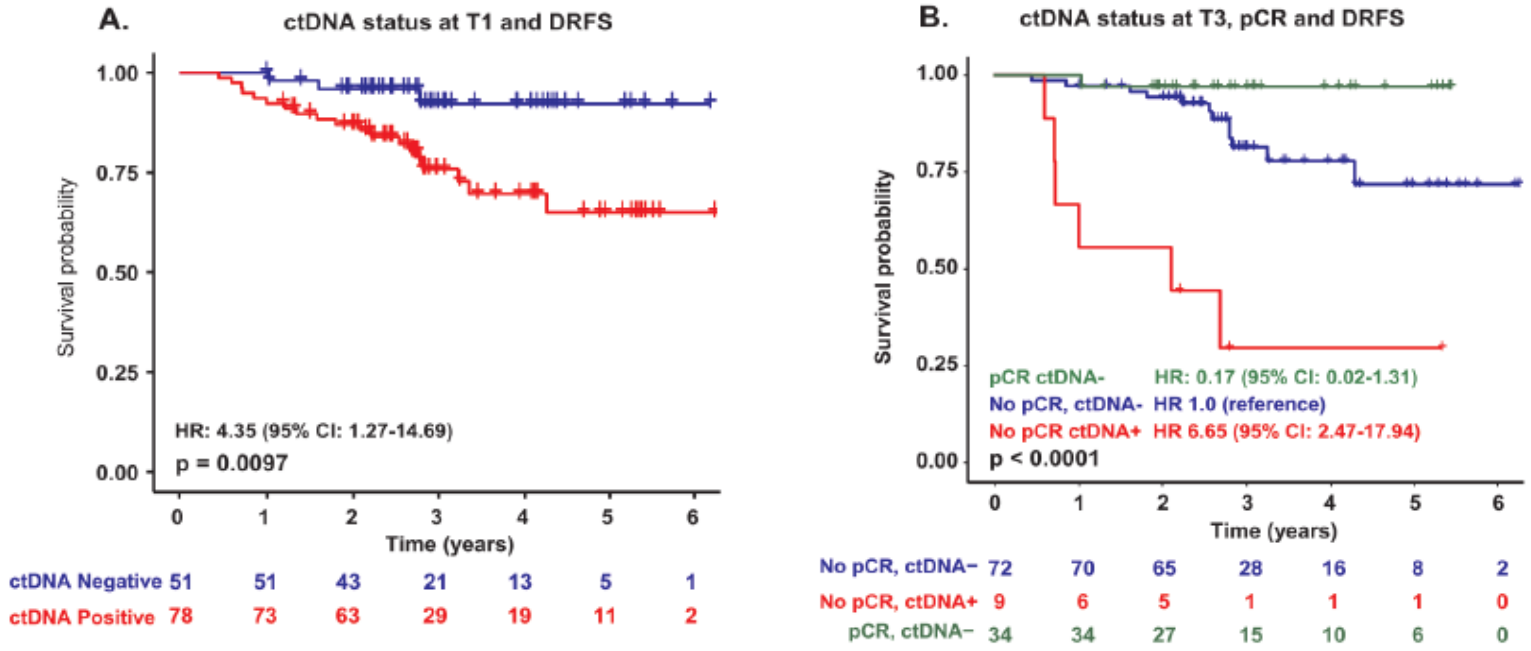


Frühzeitige ctDNA Clearance unter NACT signifikant mit pCR assoziiert
ctDNA nach NACT prädiktiv für schlechtes Outcome

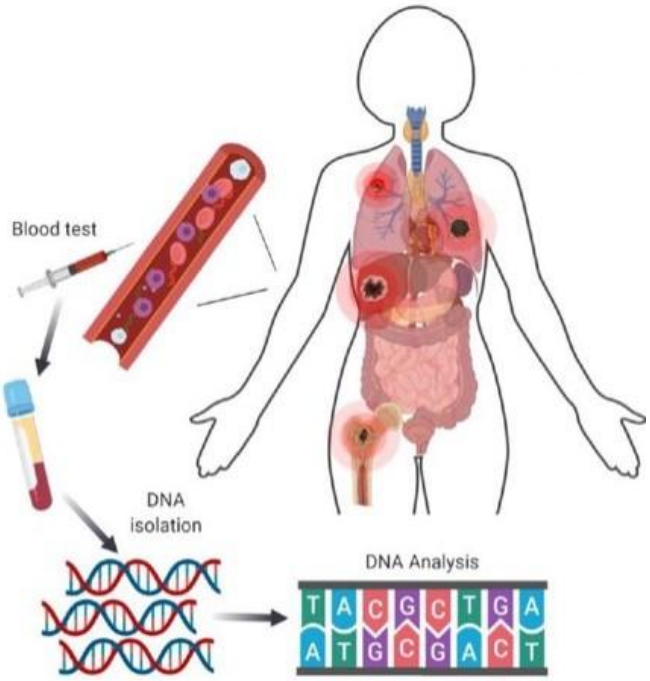
Zusammenfassung & Ausblick

CTCs:

Serielle Detektion ist prädiktiv,
Therapie basierend auf Phenotyp,
Scoring/Ratios

CTC-Cluster:

Mit ESR1 Mutationen assoziiert, Resistenz, Metastasen



ctDNA :

Minimal invasives Monitoring,
Frühe Dynamik prädiktiv für Response/Outcome zielgerichteter Therapien

Danke für Ihre Aufmerksamkeit!