Zirkulierende Tumorzellen (CTC) beim metastasierten Mammakarzinom

Bahriye Aktas

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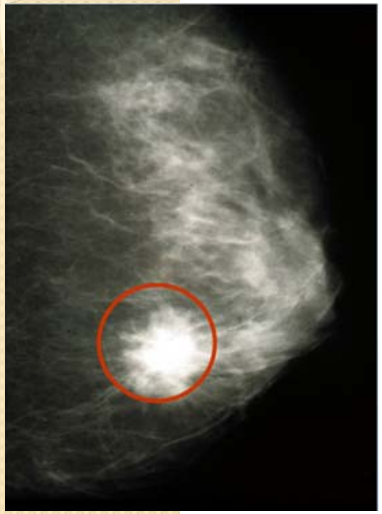
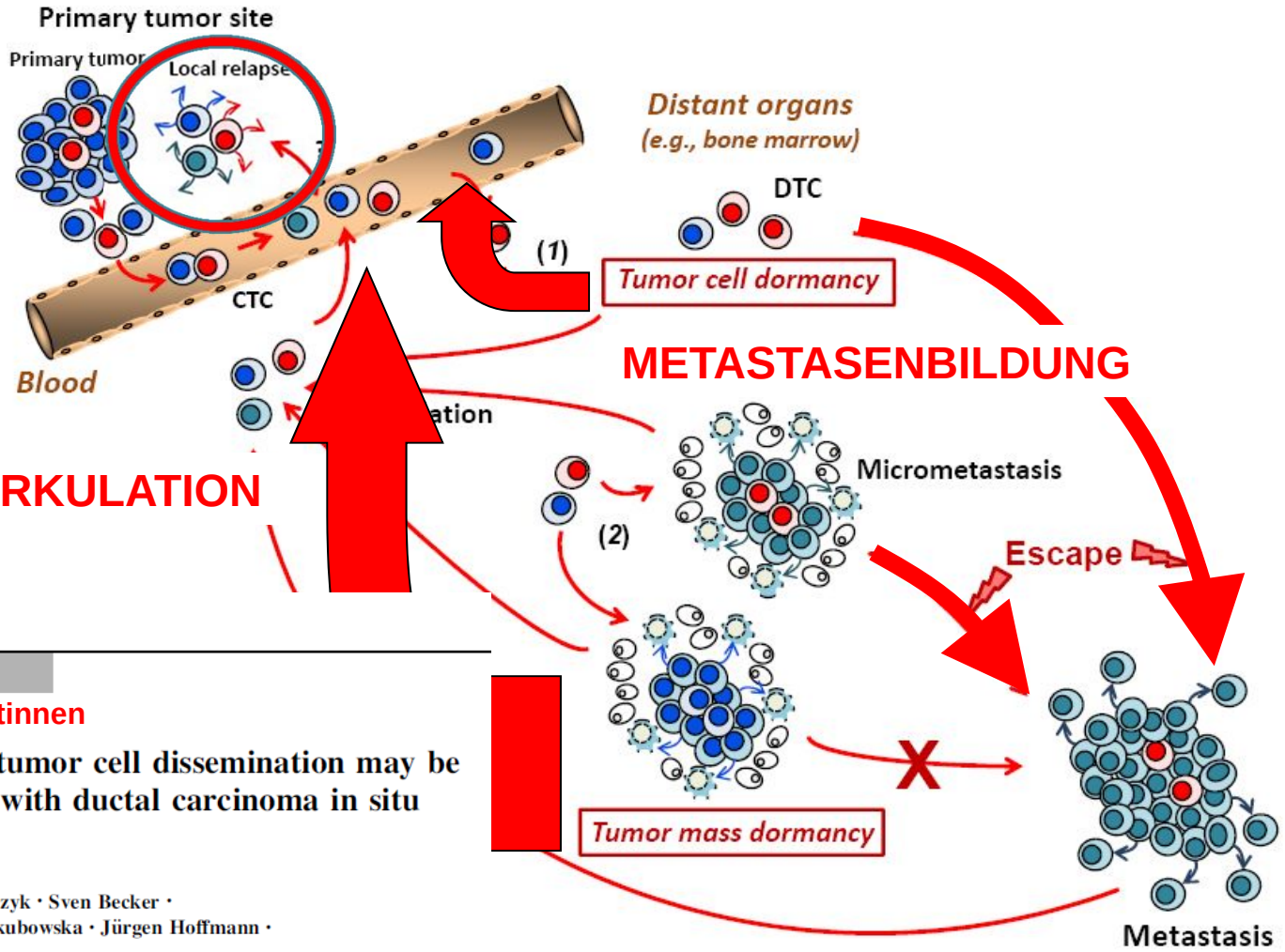
ubze
uni-brustzentrum
essen

Das Mammakarzinom- eine systemische Erkrankung!





Breast Cancer Res Treat
DOI 10.1007/s10549-011-1478-2

PRECLINICAL STUDY

CTC-pos: 34/266 (13%) Patientinnen

Hematogenous and lymphatic tumor cell dissemination may be detected in patients diagnosed with ductal carcinoma in situ of the breast

Malgorzata Banys · Ines Gruber · Natalia Krawczyk · Sven Becker · Ralph Kurth · Diethelm Wallwiener · Jolanta Jakubowska · Jürgen Hoffmann · Ralf Rothmund · Annette Staebler · Tanja Fehm

Pantel et al., Nat. Rev Clin. Oncol 2009

Sind CTC im Blut maligne?

Vol. 8, 2073–2084, July 2002 Clinical Cancer Research

Advances in Brief

Cytogenetic Evidence That Circulating Epithelial Cells in Patients with Carcinoma Are Malignant[1]

Tanja Fehm, Arthur Sagalowsky, Edward Clifford, Peter Beitsch, Hossein Saboorian, David Euhus, Songdong Meng, Larry Morrison, Thomas Tucker, Nancy Lane, B. Michael Ghadimi, Kerstin Heselmeyer-Haddad, Thomas Ried, Chandra Rao, and Jonathan Uhr[2]

Cancer Immunobiology Center [T. F., S. M., T. T., N. L., J. U.] and Departments of Urology, Surgery, Pathology, and Oncology [A. S., E. C., P. B., H. S., D. E.], University of Texas Southwestern Medical Center, Dallas, Texas 75390; Vysis, Inc., Downers Grove, Illinois 60515 [L. M.]; National Cancer Institute, Bethesda, Maryland 20892 [B. M. G., K. H-H., T. R.]; and Immunicon Corporation, Huntingdon, Pennsylvania 19006 [C. R.]

Touch preparations from the primary tumors of 13 patients with aneusomic CECs were available. The pattern of aneusomy matched a clone in the primary tumor in 10 patients. *Conclusions:* We conclude that the vast majority of CECs in breast, kidney, prostate, and colon cancer patients are aneusomic and derived from the primary tumor.

Introduction

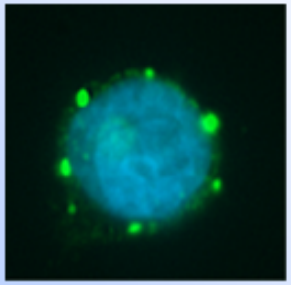
There are numerous reports of epithelial cells in the blood (1–13) and bone marrow (14–19) of patients with carcinoma. It has been shown that the presence of micrometastases in the bone marrow is an independent prognostic indicator of an aggressive tumor with a poor outcome (20–23). In contrast to bone marrow aspirates, however, blood samples can be obtained repeatedly and easily. Longitudinal studies of CECs[3] show that their levels

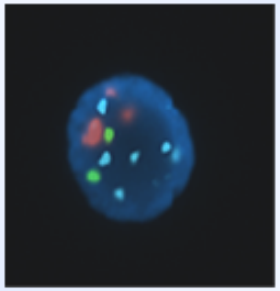
Detektion von numerischen chromosomalen Aberrationen
=
Beweis der Malignität

Fehm T, Uhr J et al., Clin Cancer Res 2002

Total	n=134 CTC
Diploid	18 (13%)
Aneuploid	**116 (87%)**
- Monosomy	4 (3%)
- Polysomy	96 (85%)
- combination	16 (12%)

Identifizierung Beweis der Malignität





CTC mit numerischen Aberrationen

Gibt es schlafende Zellen?

Featured Article

Circulating Tumor Cells in Patients with Breast Cancer Dormancy

Songdong Meng,[1] Debasish Tripathy,[2] Eugene P. Frenkel,[2] Sanjay Shete,[4] Elizabeth Z. Naftalis,[5] James F. Huth,[5] Peter D. Beitsch,[5] Marilyn Leitch,[5] Susan Hoover,[5] David Euhus,[5] Barbara Haley,[5] Larry Morrison,[6] Timothy P. Fleming,[7] Dorothee Herlyn,[8] Leon W. M. M. Terstappen,[9] Tanja Fehm,[10] Thomas F. Tucker,[1] Nancy Lane,[1] Jianqiang Wang,[1] and Jonathan W. Uhr[1]

[1]Cancer Immunobiology Center, [2]Department of Medicine, Komen Breast Cancer Center, and [3]Center for Breast Care, University of Texas Southwestern Medical Center, Dallas, Texas; [4]Department of Epidemiology, University of Texas M. D. Anderson Cancer Center, Houston, Texas; [5]Dallas Breast Center, Dallas, Texas; [6]Vysis, Inc., Downers Grove, Illinois; [7]Department of Surgery, University of Washington, St. Louis, Missouri; [8]Wistar Institute, Philadelphia, Pennsylvania; [9]Immunicon Corporation, Huntingdon, Pennsylvania; and [10]Department of Gynecology and Obstetrics, University of Tubingen, Tubingen, Germany

ABSTRACT

Purpose: The purpose of this study was to test the

Conclusions: The CTCs that are dying must be replenished every few hours by replicating tumor cells somewhere in the tissues. Hence, there appears to be a balance between tumor replication and cell death for as long as 22 years in dormancy candidates. We conclude that this is one mechanism underlying tumor dormancy.

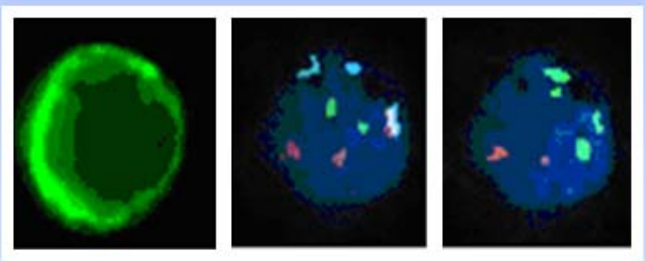
INTRODUCTION

Recurrence of tumor can occur a prolonged time after removal of the primary tumor. These very long intervals that some patients have before recurrence are not consistent with constant kinetic growth of tumor cells, so there must be a dormant state in the tumor cell population. Short-term presence of circulating tumor cells (CTCs) or marrow tumor cells may represent residual disease and is known to be associated with a higher risk of recurrence (1). However, CTCs in patients in long remissions who are most likely cured of disease (dormancy candidates) could represent an altogether different process and may provide important insights into mechanisms of tumor control. Our objective was to determine whether very sensitive techniques could detect these tumor cells in such a population of patients whose risk of recurrence at this point in time is minimal and to further characterize these tumor cells. Experimental tu-

Meng, Fehm, Uhr et al., Clin Cancer Res 2004

- 43 Mammakarzinompatientinnen ohne Anzeichen der Erkrankung
- 8-22 Jahre nach Ersterkrankung
- 13 (30%) Patientinnen mit 1-2 CTCs !
- 1 weiteres Jahr ohne Rezidiv

(1 Jahr Follow-up)



„Schlafende“ Tumorzelle im peripheren Blut.

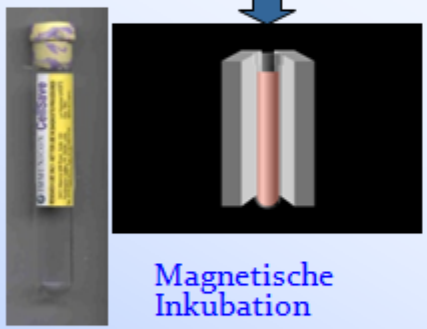
Fazit:

CTCs können zu jedem Zeitpunkt der Erkrankung im Blut gefunden werden!

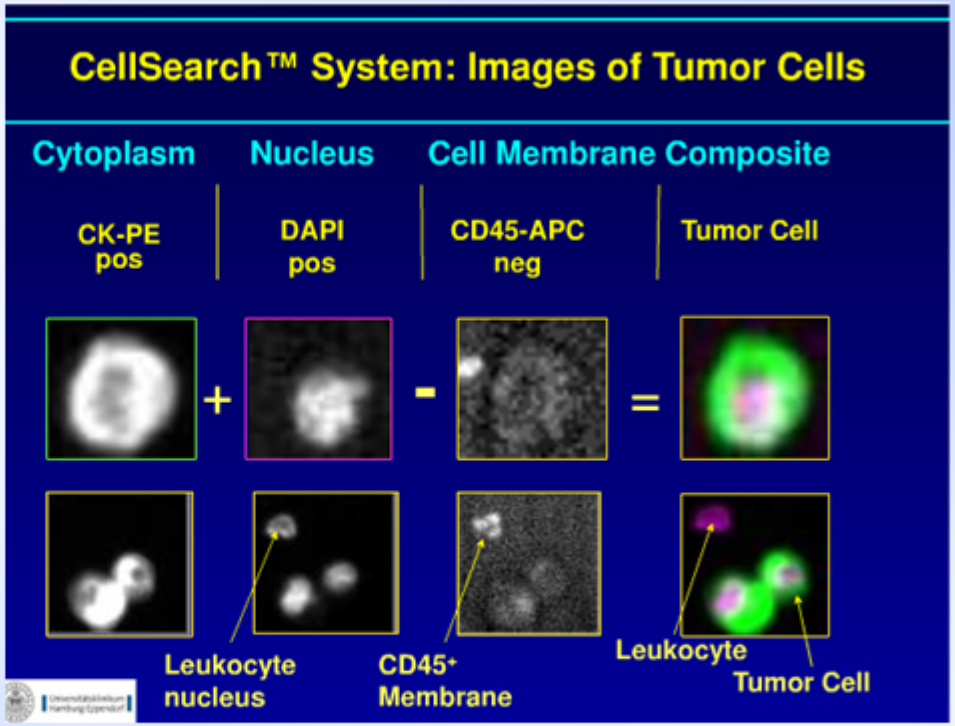
- **Vor OP**
- **Nach Abschluss aller Therapien**
- **In der progressionsfreien Zeit**
- **In der metastasierten Situation**

Gibt es eine Methode der Wahl?

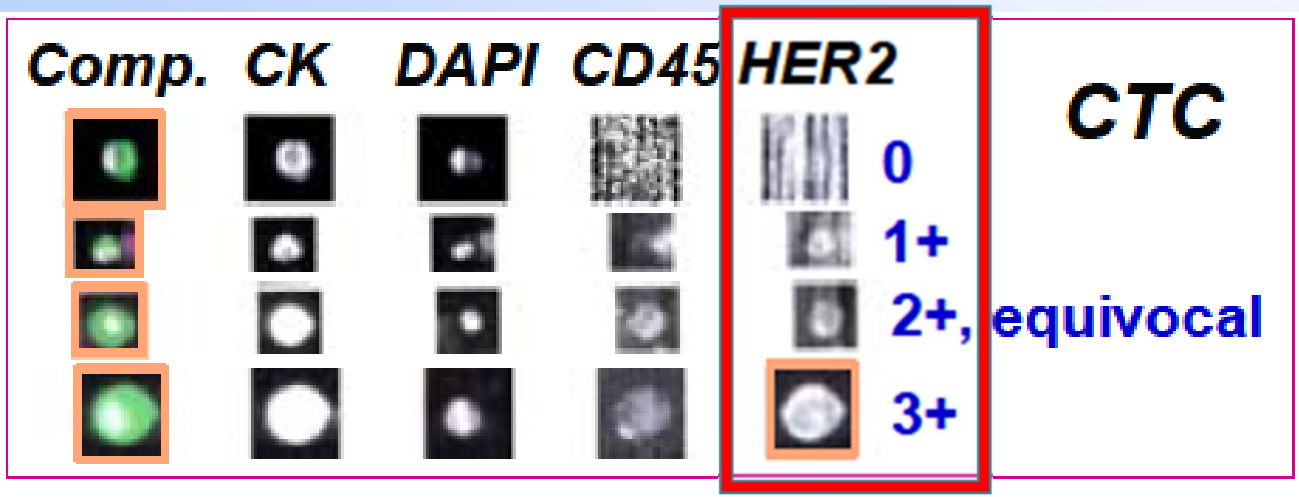
NEIN !!



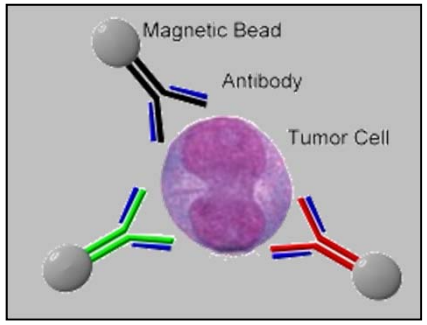
Magnetische Inkubation

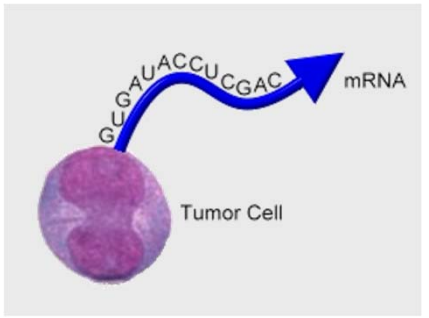


- Immunomagnetische Separation mit EpCAM-Ferromagnetpartikeln
- Färbung mit pan zytokeratin Antikörper A45B/B3 (CK8, 18, 19)

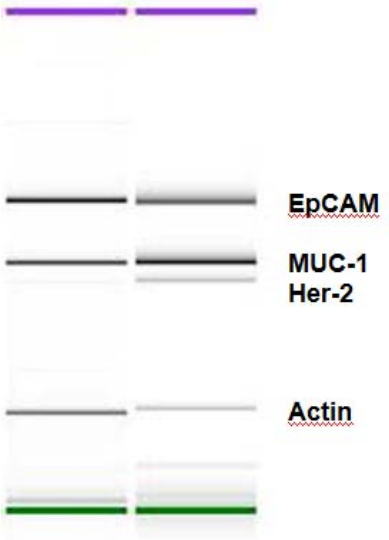


Molekularbiologischer Nachweis von CTC



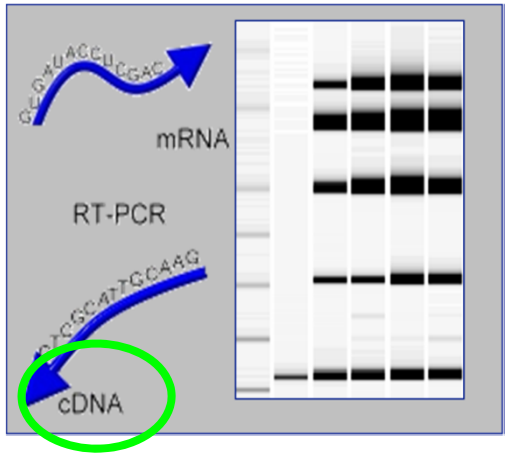


1: CTC-Test: „Brust“



ER (305 bp)
PR (270 bp)

Expression von ER/PR



Haben CTC eine Bedeutung in der metastasierten Situation?

Prognostische Bedeutung

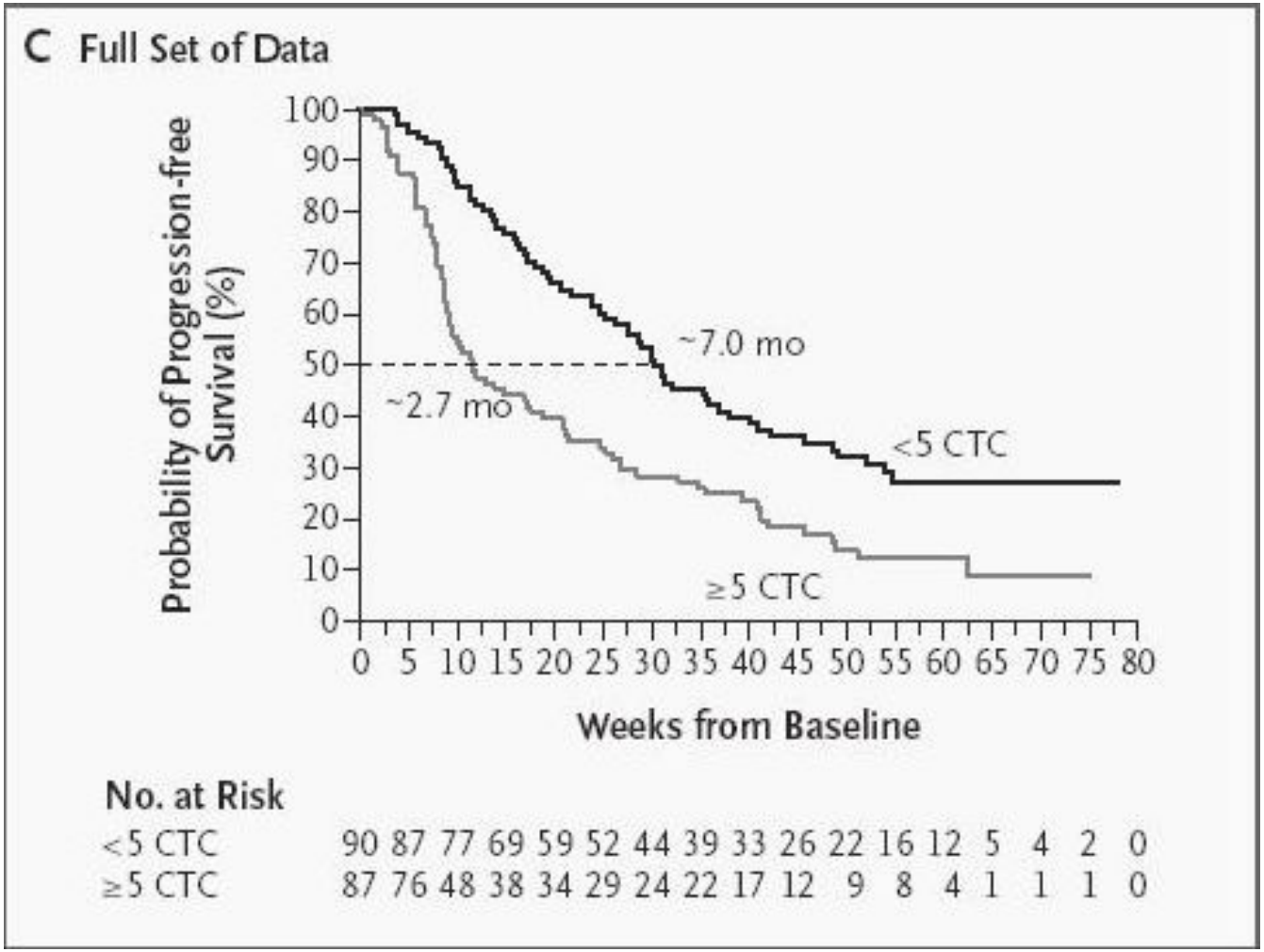
Therapiemonitoring

Optimierung von Therapien

Circulating Tumor Cells, Disease Progression, and Survival in Metastatic Breast Cancer

Massimo Cristofanilli, M.D., G. Thomas Budd, M.D., Matthew J. Ellis, M.B., Ph.D., Alison Stopeck, M.D., Jeri Matera, B.S., R.Ph., M. Craig Miller, B.S., James M. Reuben, Ph.D., Gerald V. Doyle, D.D.S., W. Jeffrey Allard, Ph.D., Leon W.M.M. Terstappen, M.D., Ph.D., and Daniel F. Hayes, M.D.

New Engl J Med, 2004



Circulating Tumor Cells, Disease Progression, and Survival in Metastatic Breast Cancer

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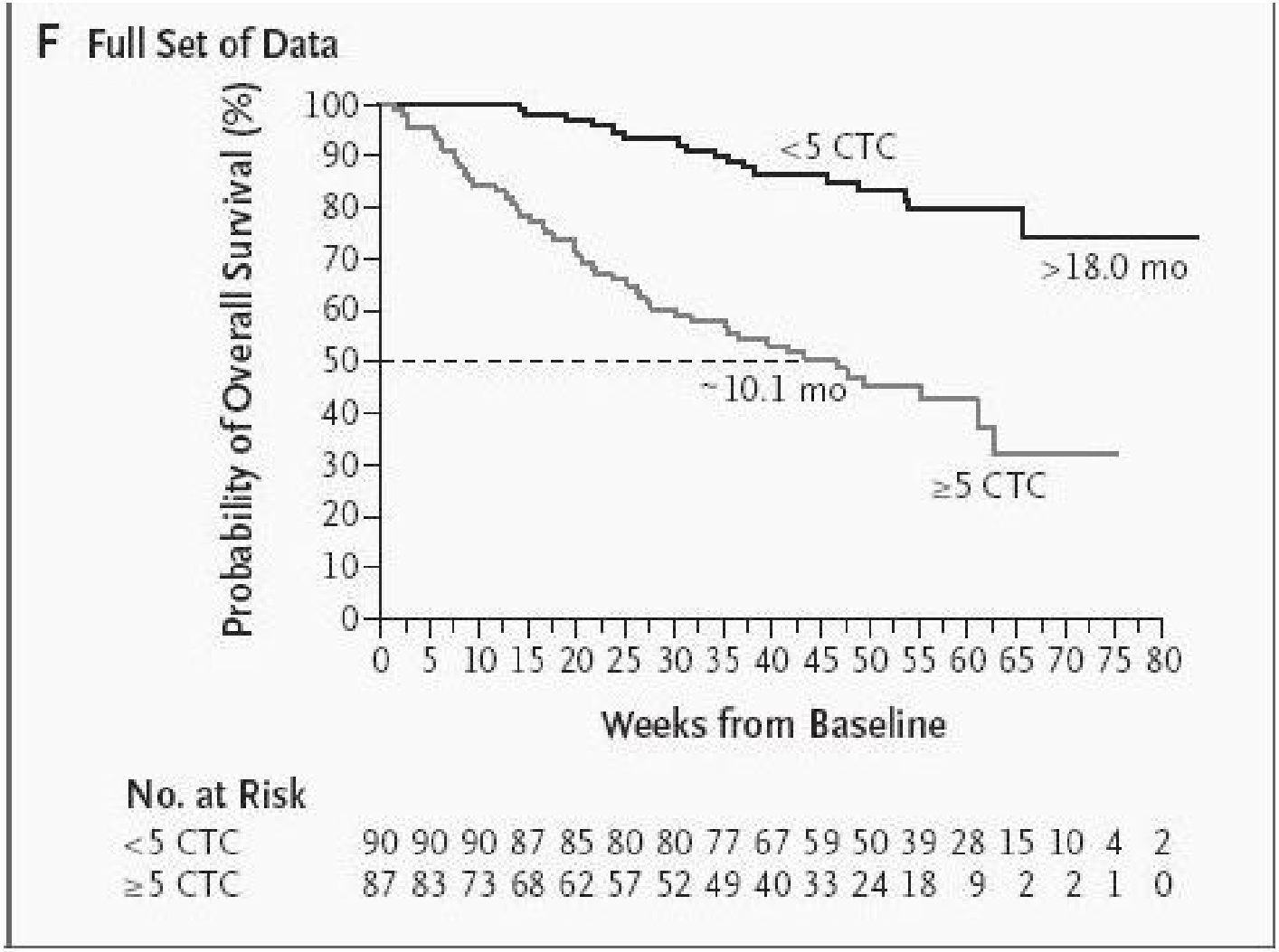
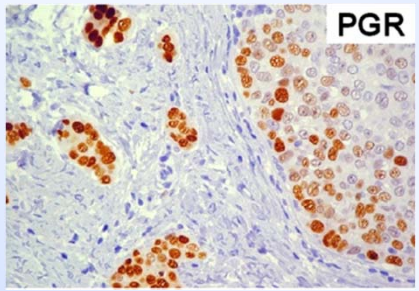
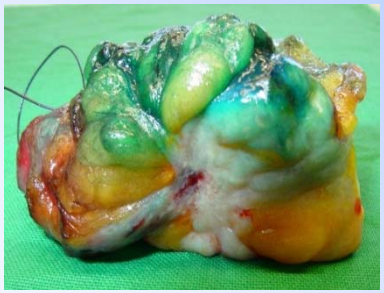


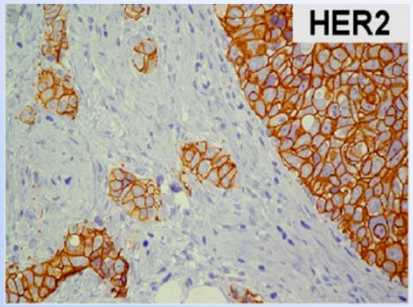
Therapieentscheidung aufgrund der Oberflächeneigenschaften des Primärtumors.

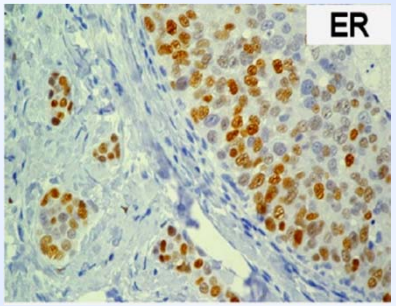
Therapiert wird die minimale Tumorresterkrankung, reflektiert durch CTC und DTC!

Untersuchungen am Tumor









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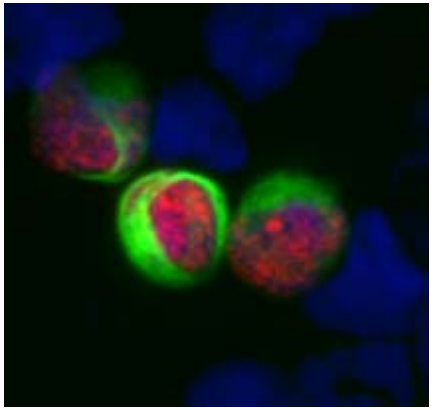
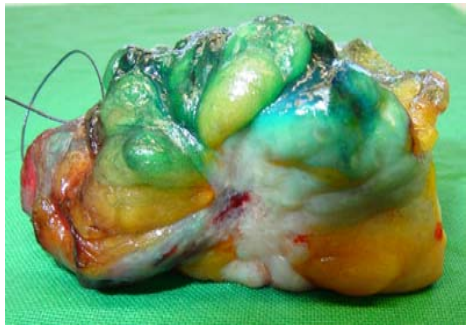
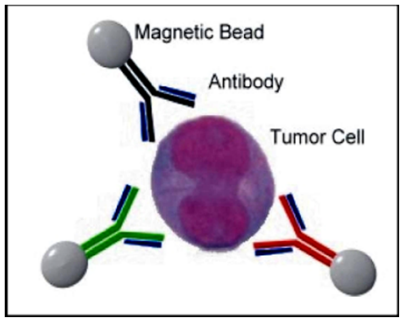


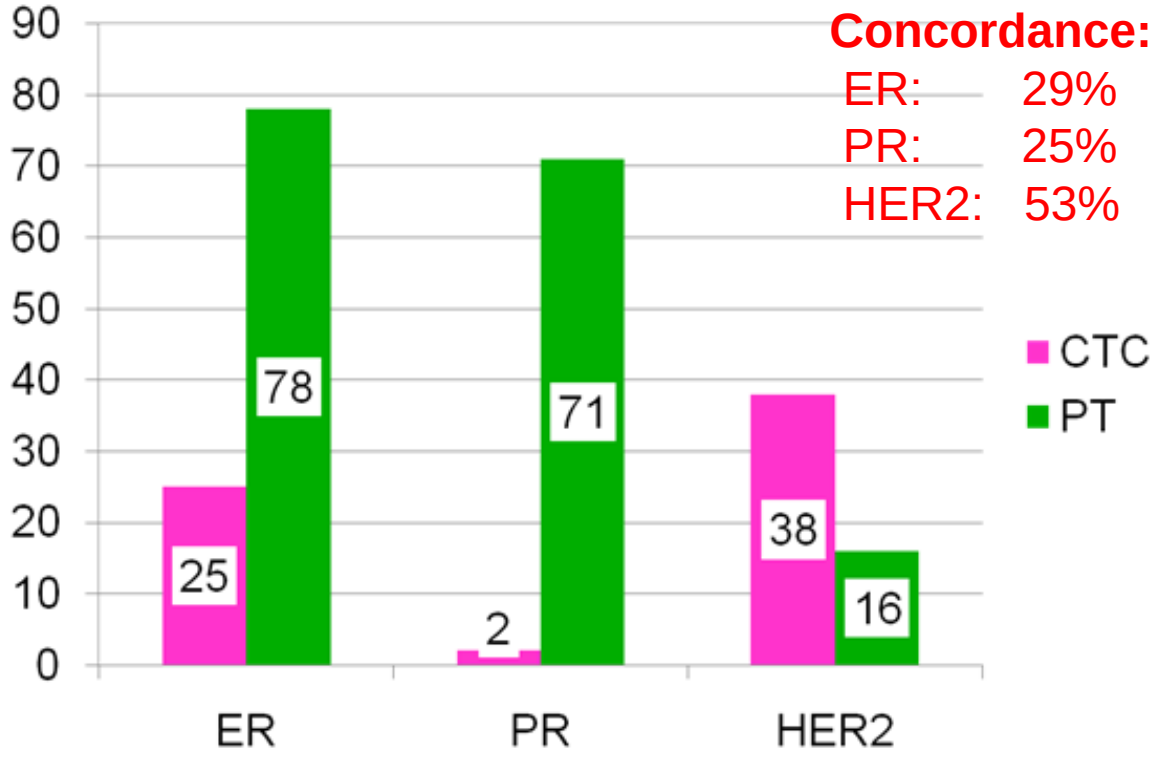
Vergleich der Expression von prädiktiven Markern auf CTC und dem Primärtumor in der Adjuvanz





N=431 Patientinnen

CTC-pos. 58/431 (13%)



Concordance:

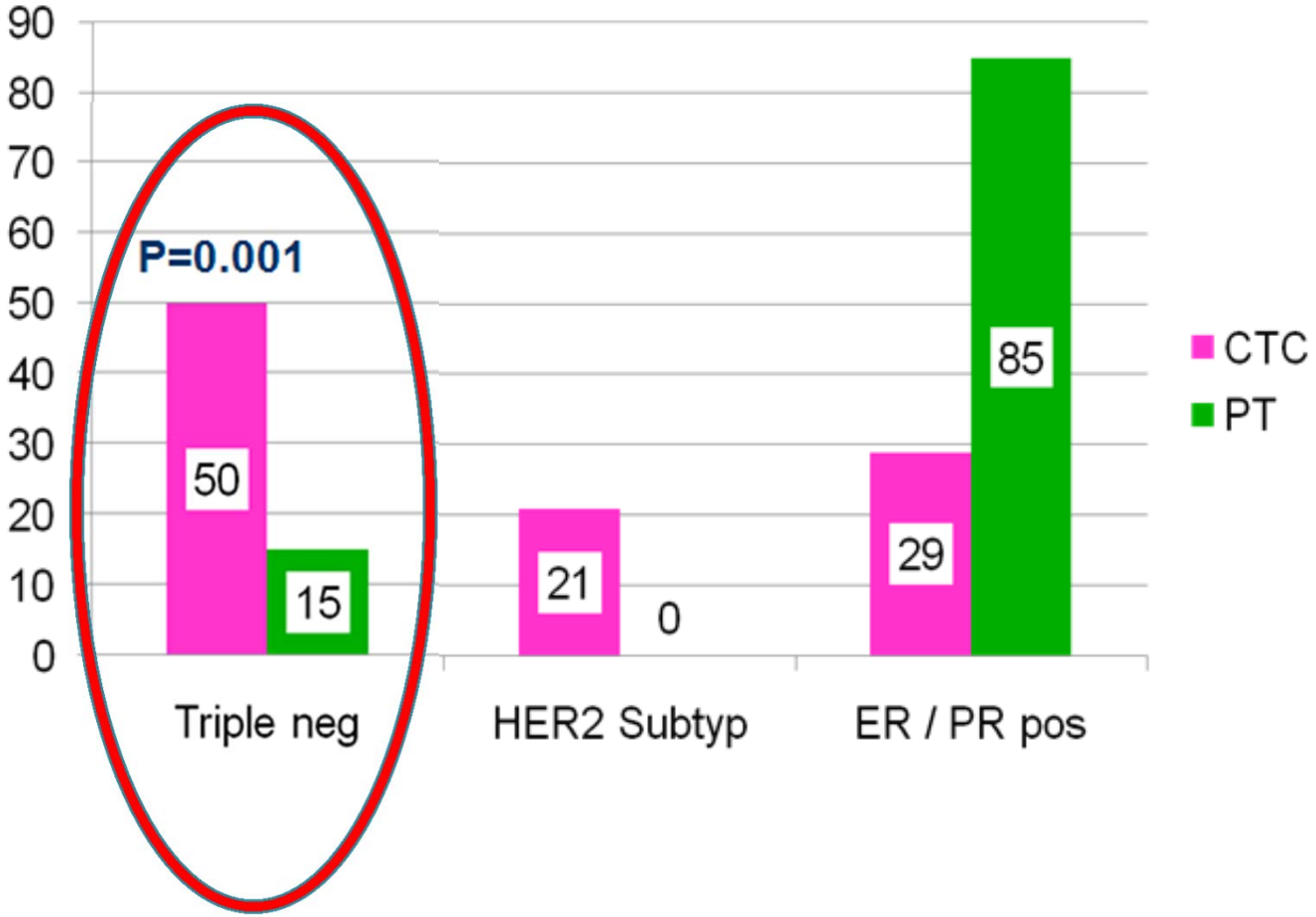
ER: 29%

PR: 25%

HER2: 53%

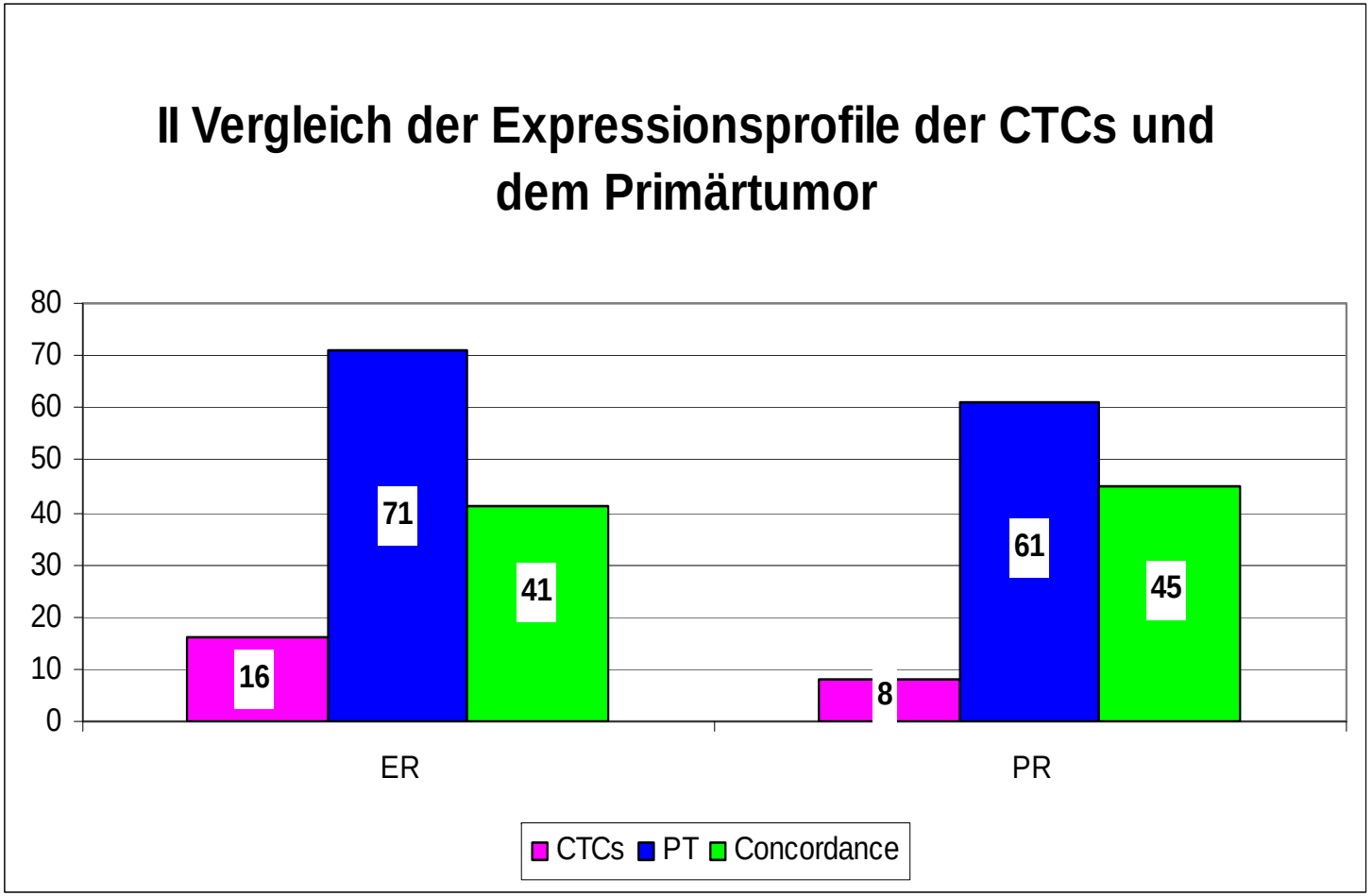
Fehm T, Kasimir-Bauer S et al,
Breast Cancer Res, 11(4) pR59, 2009

Expression von prädiktiven Markern in CTC und Primärtumor in der adjuvanten Situation



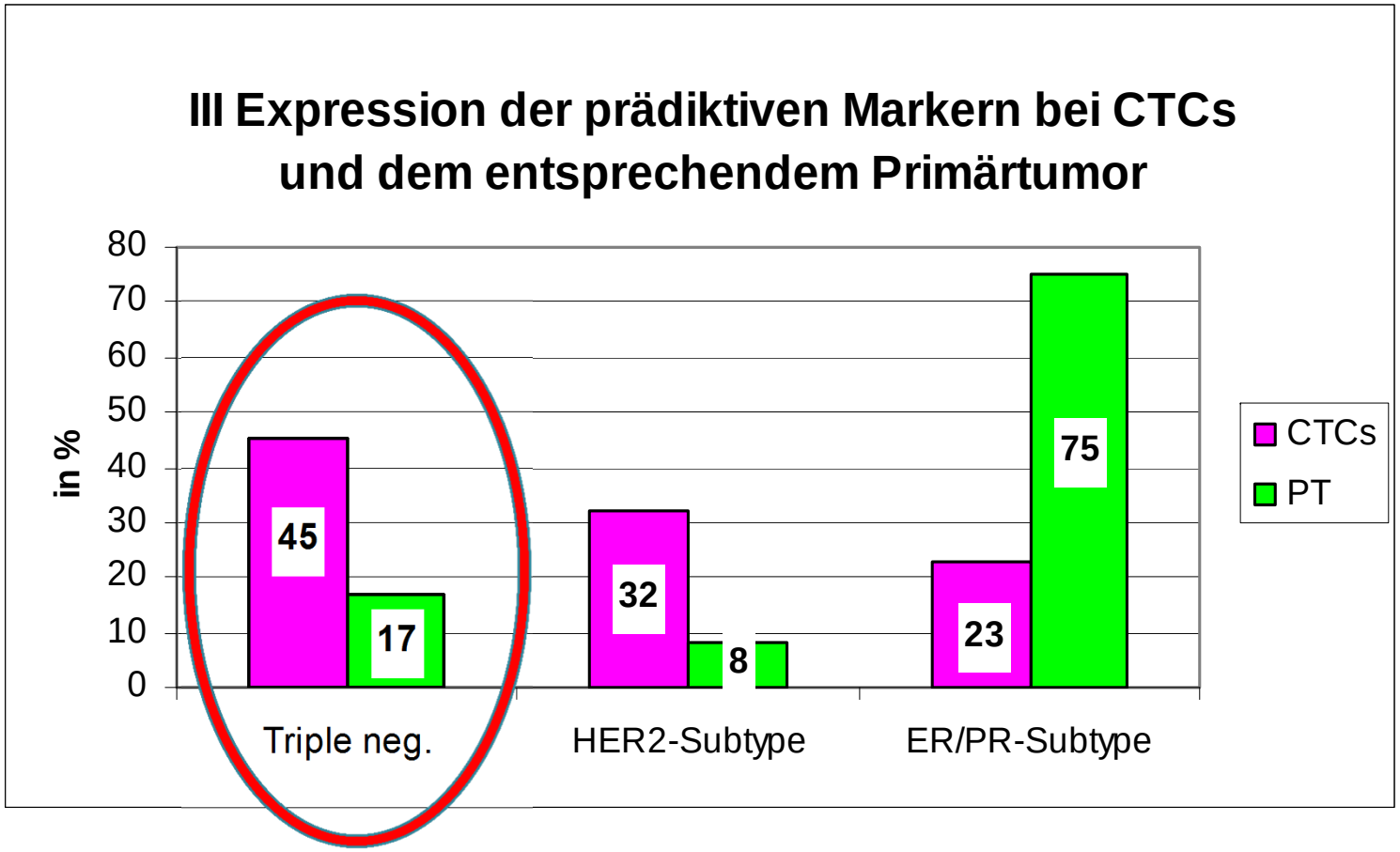
Fehm T, Kasimir-Bauer S et al, Breast Cancer Res, 11(4) pR59, 2009

Expression von prädiktiven Markern in CTC und Primärtumor in der metastasierten Situation



Aktas et al, Gynecol Oncol 2011

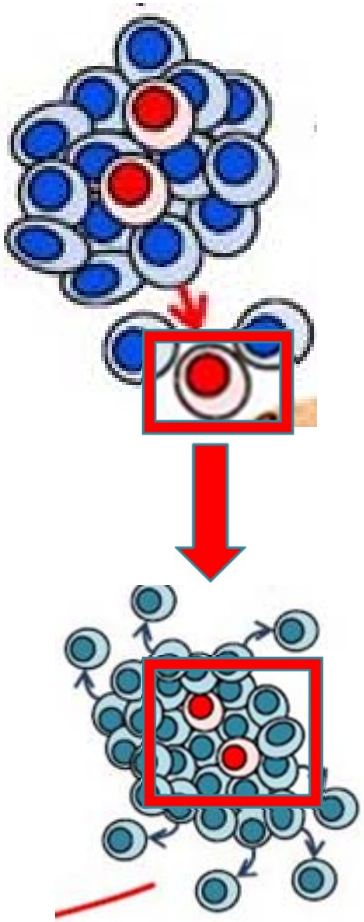
Expression von prädiktiven Markern in CTC und Primärtumor in der metastasierten Situation



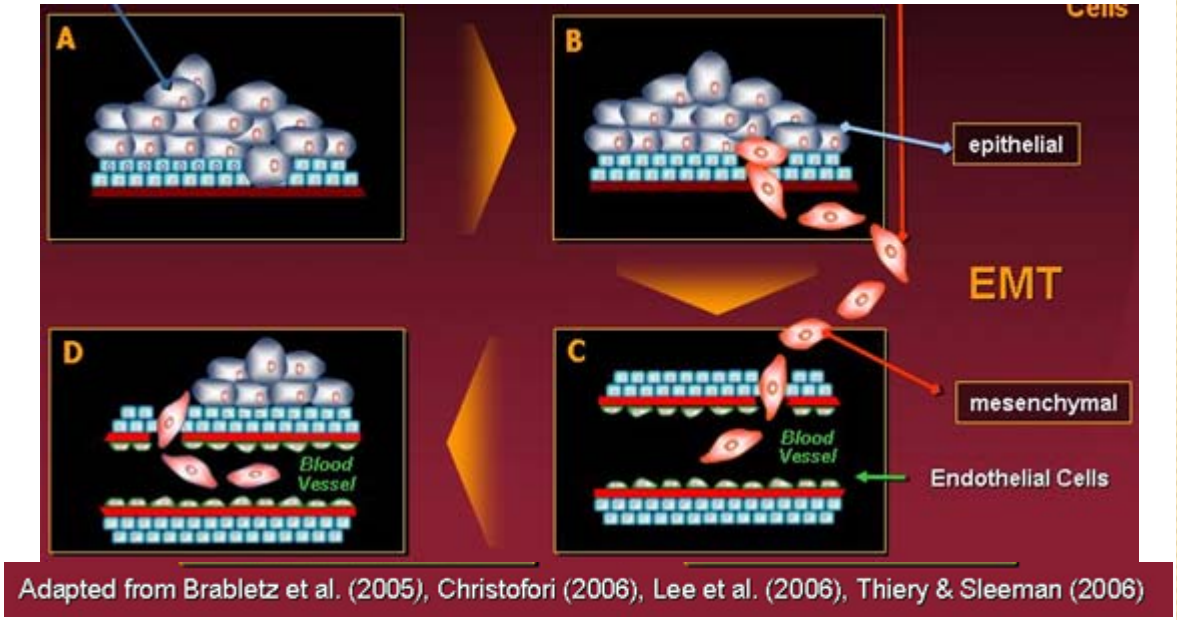
Aktas et al, Gynecol Oncol 2011

Warum sind Tumorzellen meist triple negativ?

Primärtumor

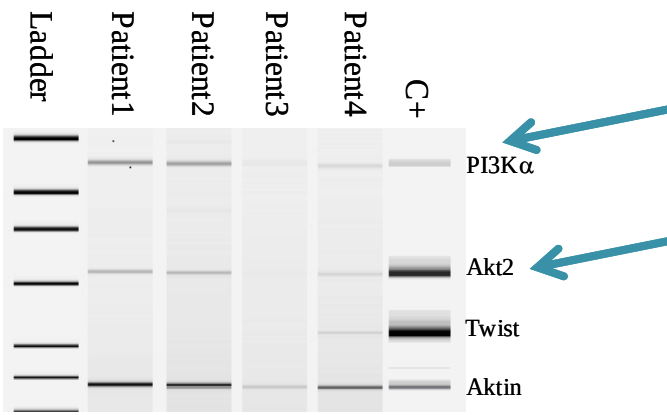


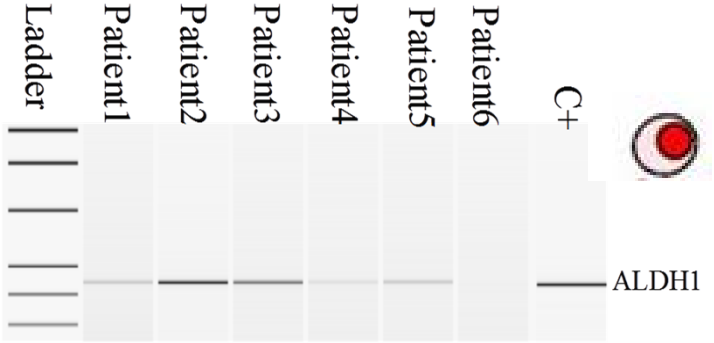
Metastase

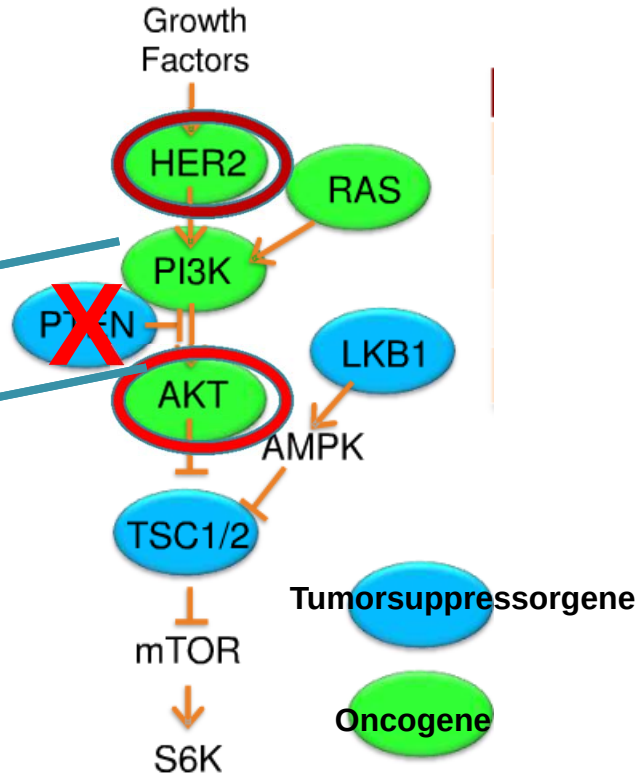


- Brustkrebsstammzellen sind Hormonrezeptor negativ *(Dontu et al. 2004, Asselin-Labat et al. 2006)*
- CTC / DTC überleben für lange Zeit
- CTC / DTC resistent gegenüber Chemotherapie
- CTC im Blut von met. Mammakarzinompatientinnen haben Stammzellcharakter (*Aktas et al., Breast Cancer Res. 2009*)

Der PI3K / Akt Pathway



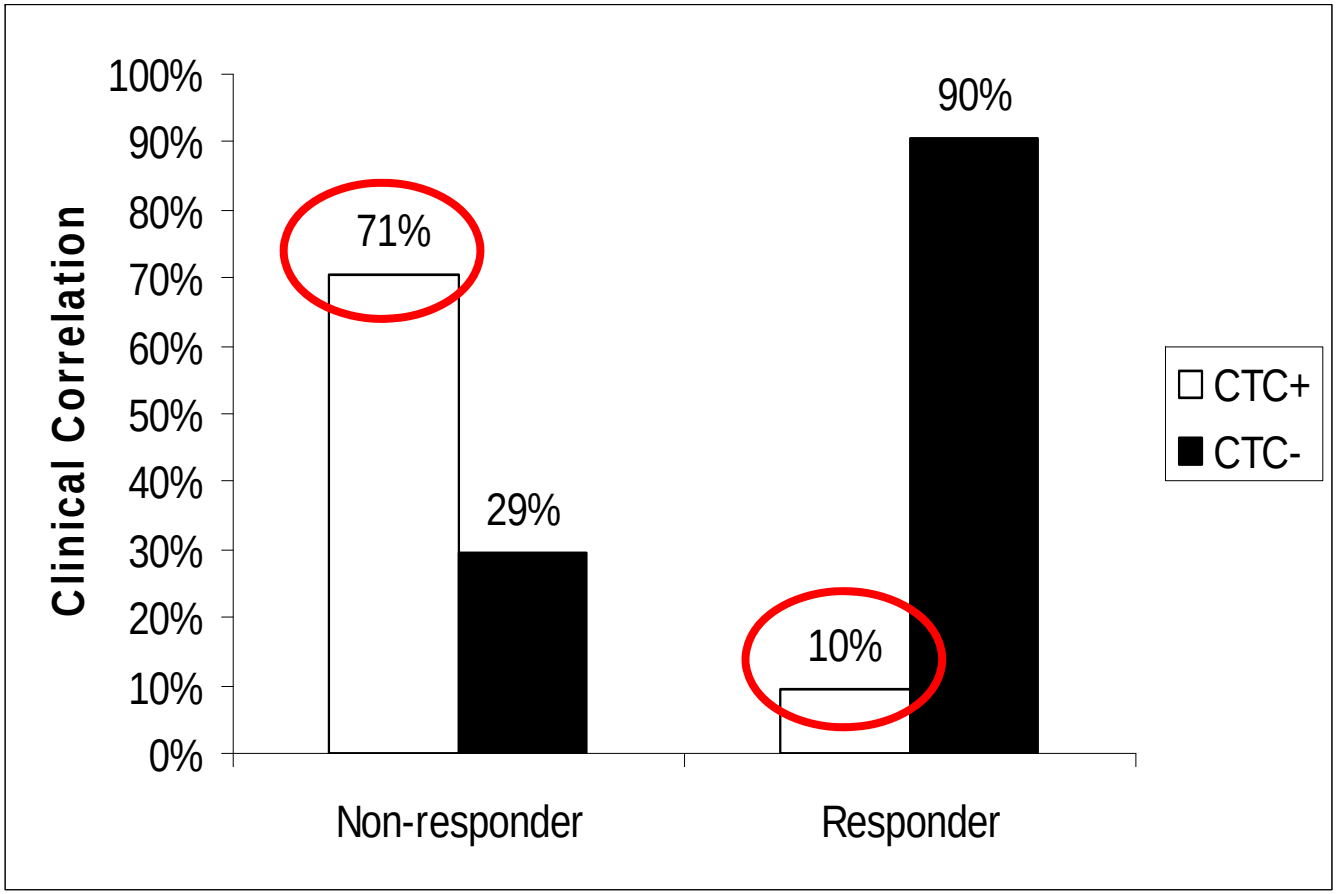




Proliferation
Inhibition der Apoptose

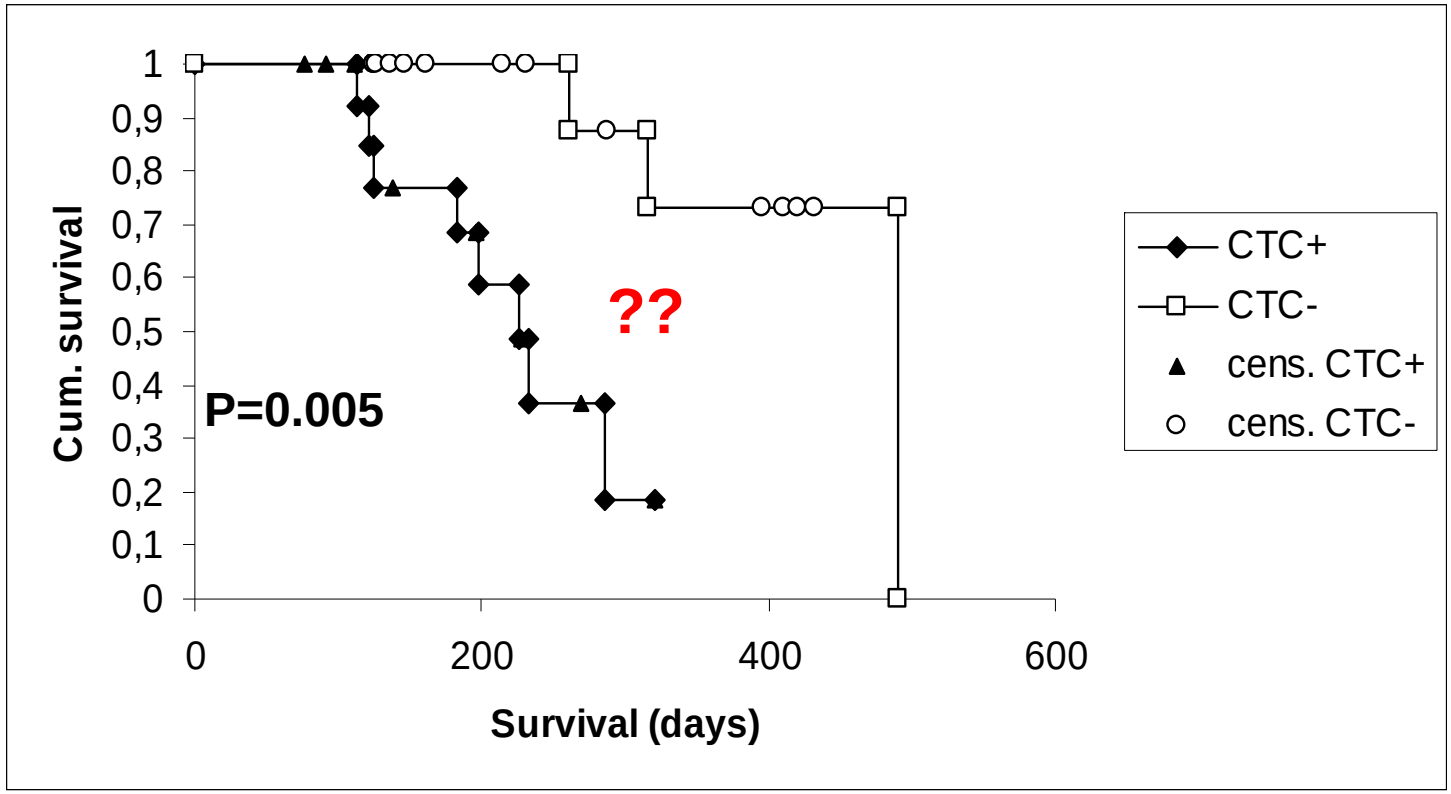
Trastuzumab Resistenz

CTC-Nachweis und Therapieansprechen



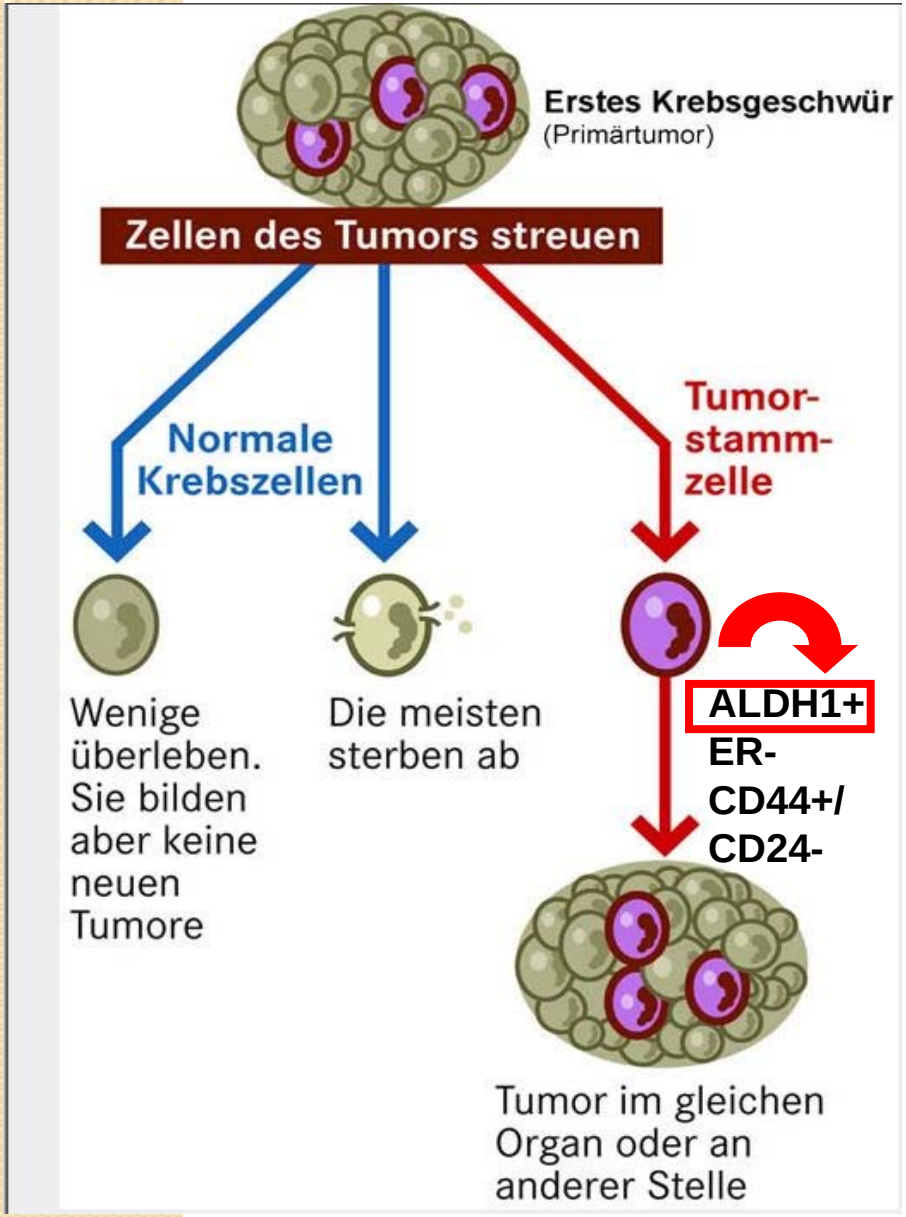
Tewes M, Aktas B et al., Breast Cancer Res Treat, 115(3) p581-90, 2008

CTC-Nachweis und OS

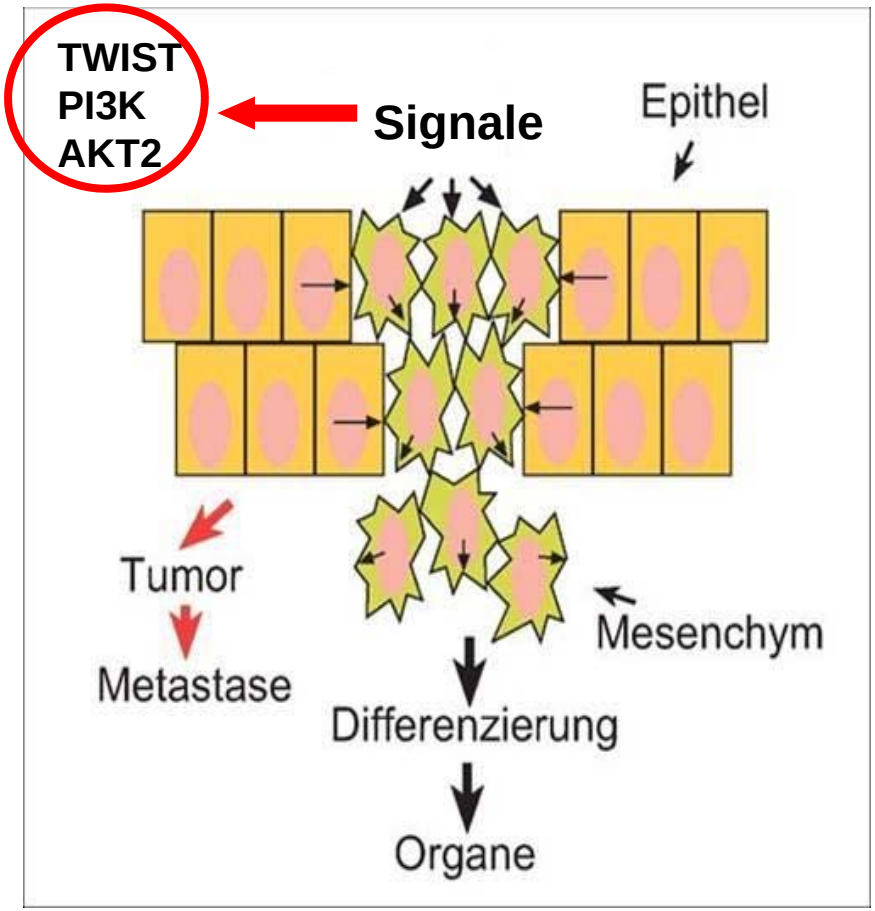


Tewes M, Aktas B et al., Breast Cancer Res Treat, 115(3) p581-90, 2008

Tumorstammzellen



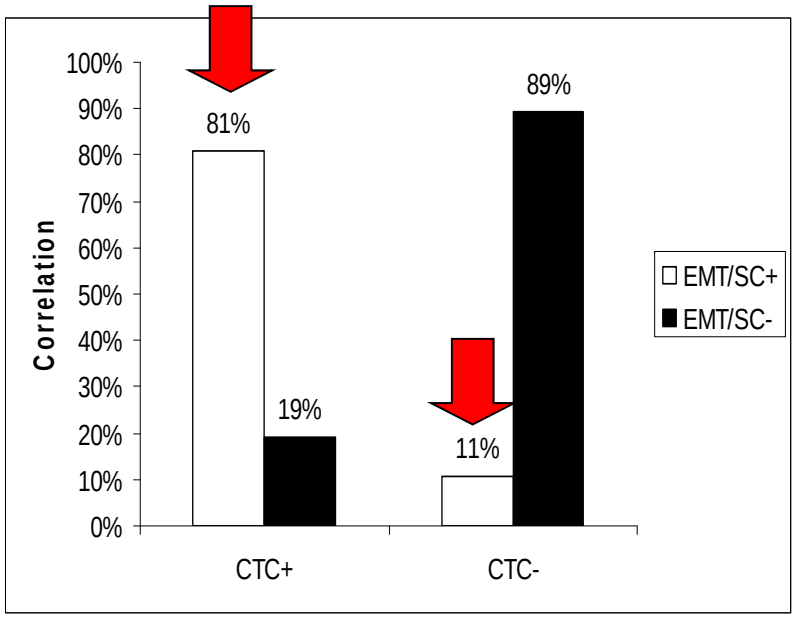
EMT



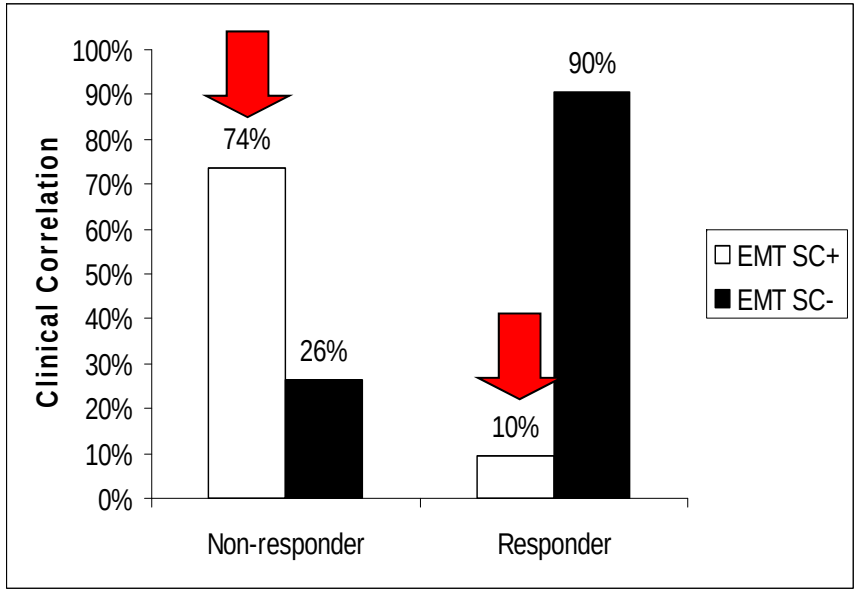
Modifiziert nach B.G. Herrmann, MPI, Berlin

CTC und Stammzellmarker

Korrelation zwischen CTC und ALDH1-/EMT-Markern



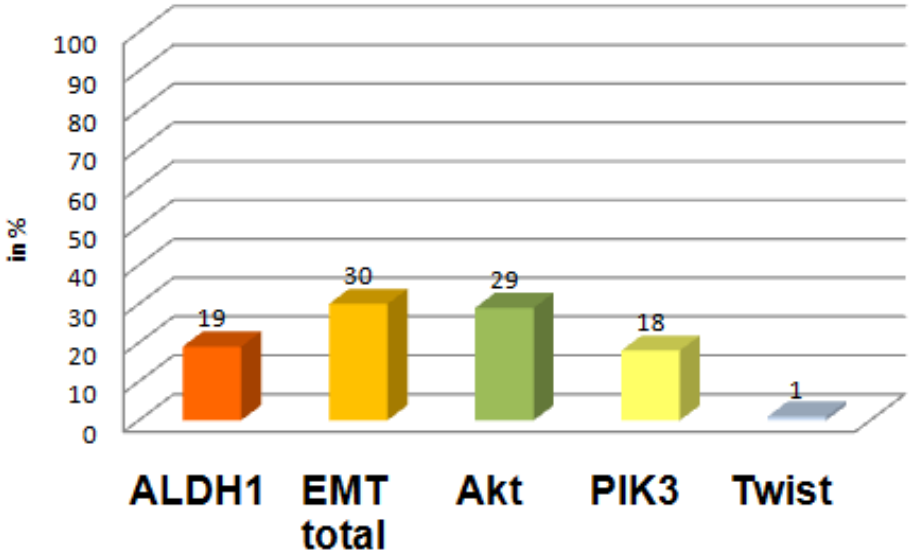
Korrelation zwischen ALDH1/EMT-Markern und Therapieansprechen

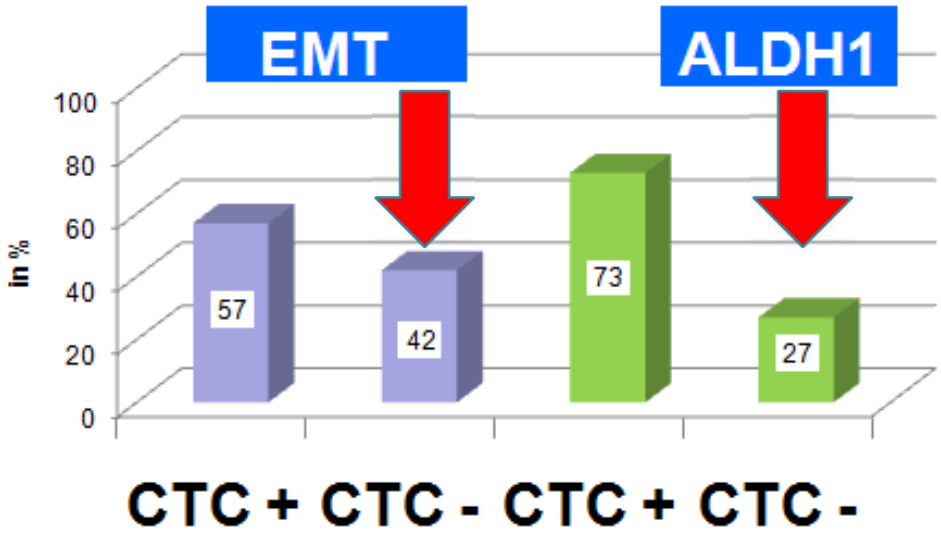


Aktas et al., Breast Cancer Res, 9;11(4):R46, 2009.

Nachweis von CTC im Blut von 347 Patientinnen mit primärem Mammakarzinom

Factor	n
Tumor size	
pT1	237
PT2-4	109
Nodal status	
No	239
N1	106
Grading	
I	68
II	201
III	73
ER status	
Pos	284
Neg	57
PR status	
Pos	270
Neg	57
HER2	
Pos	41
Neg	296

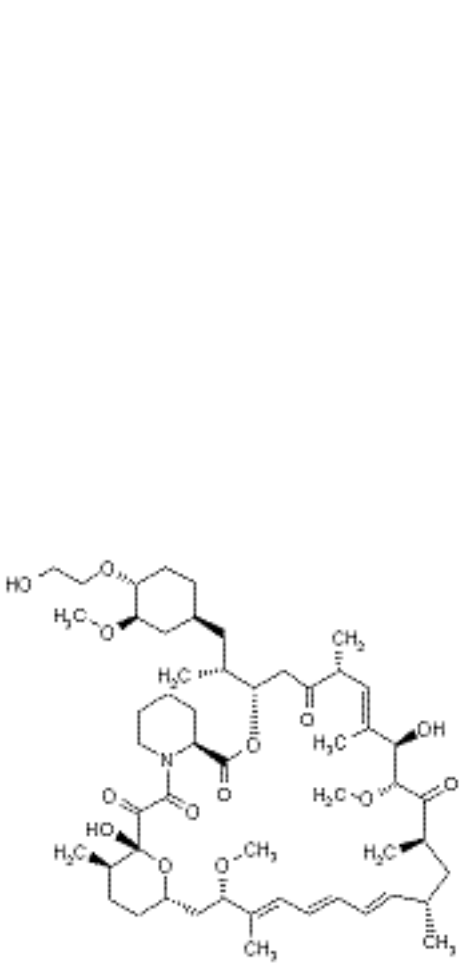




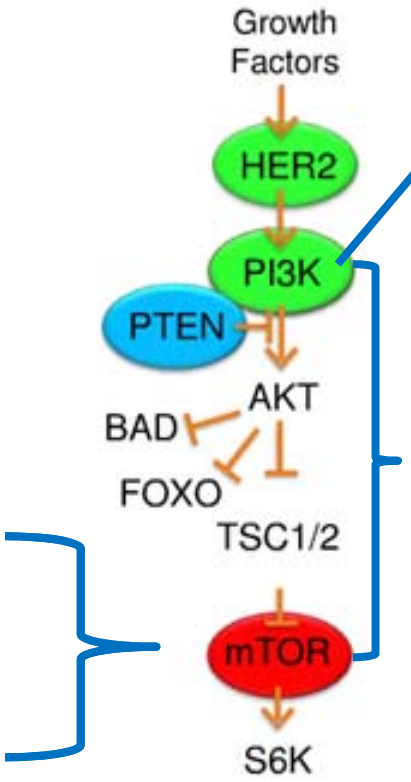
CTC-pos. 23%

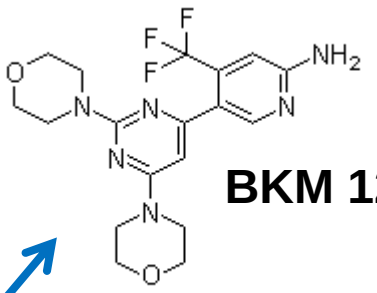
Fehm, Kasimir-Bauer et al., P3-02-09, SABCS 2010

Therapeutische Optionen

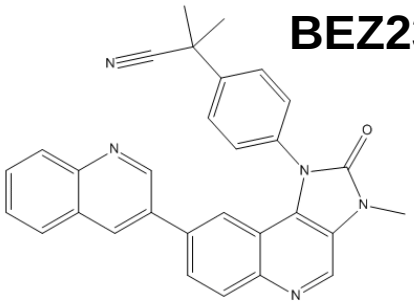


RAD001 (Everolimus)





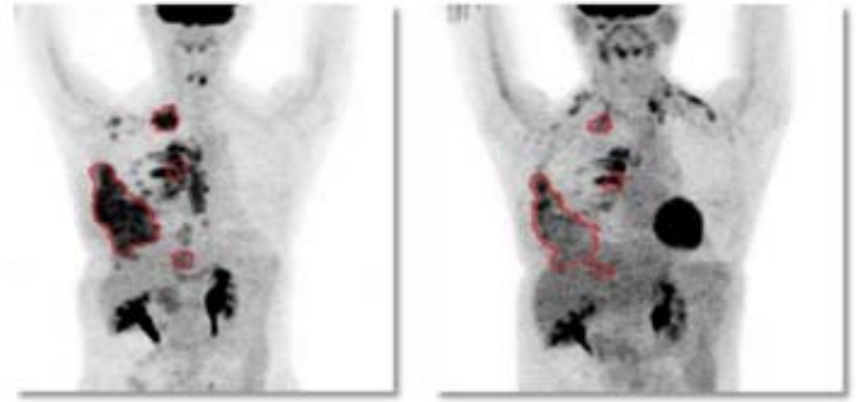
BKM 120



BEZ235

BKM 120 – PI3K Inhibitor

HER2+-Mammakarzinom

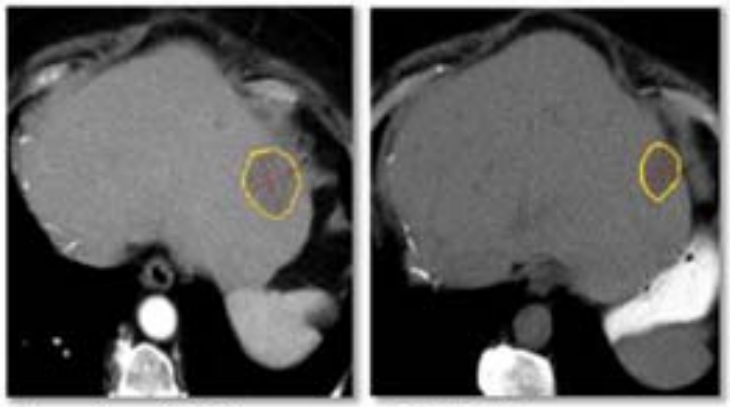


PET-CT: Studienstart **PET-CT:** Tag 28

Partielle Remissionen und Tumorreduktion (RECIST)

Vielzahl von Patientinnen mit klinischem „Benefit“

BEZ235- ein dualer PI3K/mTOR Inhibitor

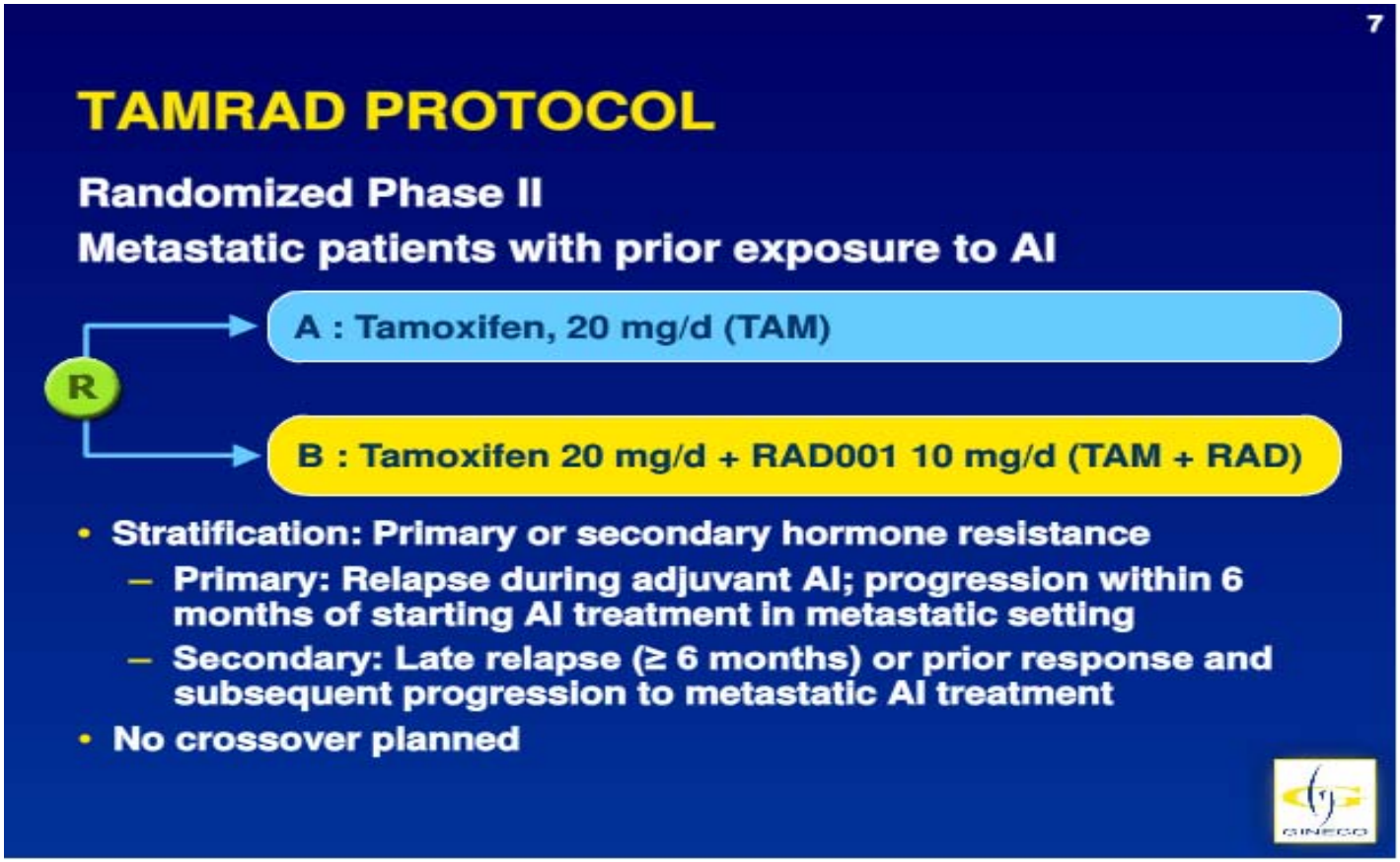


PR in Patientin mit 13 Vortherapien

Signifikante Anzahl an metabolischen CRs (PET-CT)
Signifikante Anzahl von patientinnen > 4 Mo unter Therapie
2 Patientinnen > 1 Jahr in der Studie (beide PI3K Mutationen)

Baselga et al., SABCS 2010

RAD001 (Everolimus) – mTOR Inhibitor



N=111 Patientinnen

TAM: n=57 Patientinnen

TAM+RAD001: n=54 Patientinnen

Bachelot et al., #S1-6, SABCS, 2010

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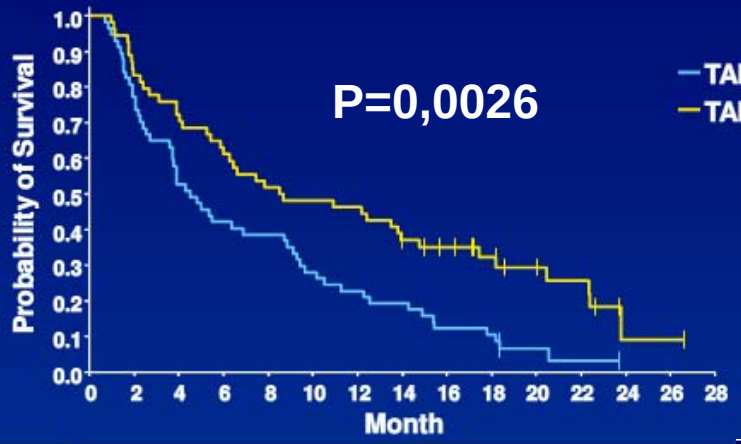
Time to Progression

TAM: 4.5 mo.
TAM + RAD: 8.6 mo.

Hazard Ratio (HR) = 0.53; 95% CI (0.35-0.81)
Exploratory log-rank: *P* = 0.0026



Patients at risk														
TAM + RAD: n =	54	45	39	34	28	26	25	19	16	12	9	7	1	1	0
TAM : n =	57	44	30	24	22	16	13	11	7	6	2	1	0	0	0

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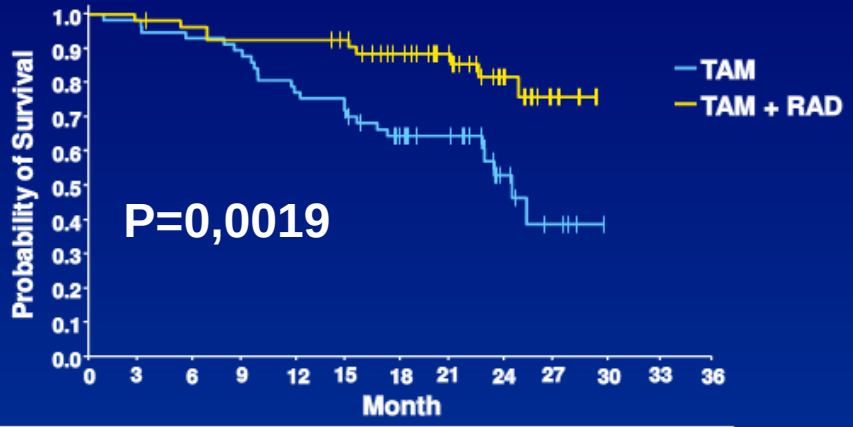
Overall Survival (as of October 2010)

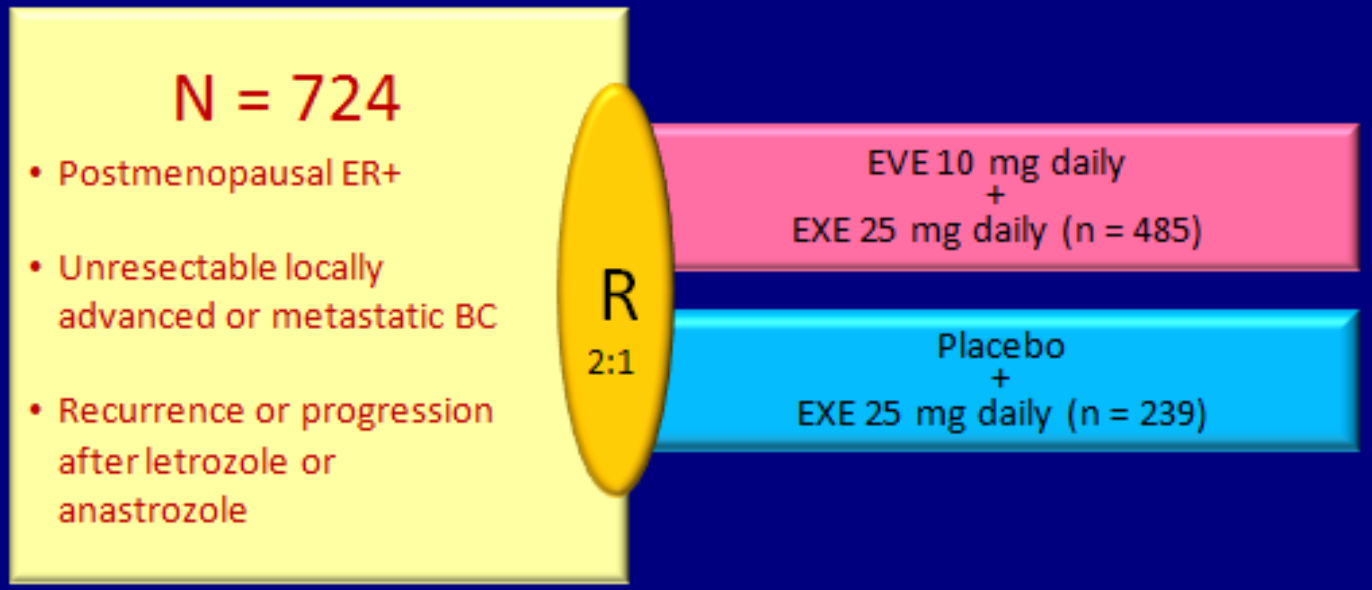
HR = 0.32; 95% CI (0.15-0.68)
Exploratory log-rank: *P* = 0.0019



Patients at risk											
TAM + RAD: n =	54	53	51	49	49	45	38	26	14	6	0
TAM : n =	57	55	53	50	44	38	30	22	9	4	0

Bachelot et al., #S1-6, SABCS, 2010

BOLERO-2 (Ph III): Everolimus in Advanced BC



Stratification: Sensitivity to prior hormone therapy and presence of visceral metastases

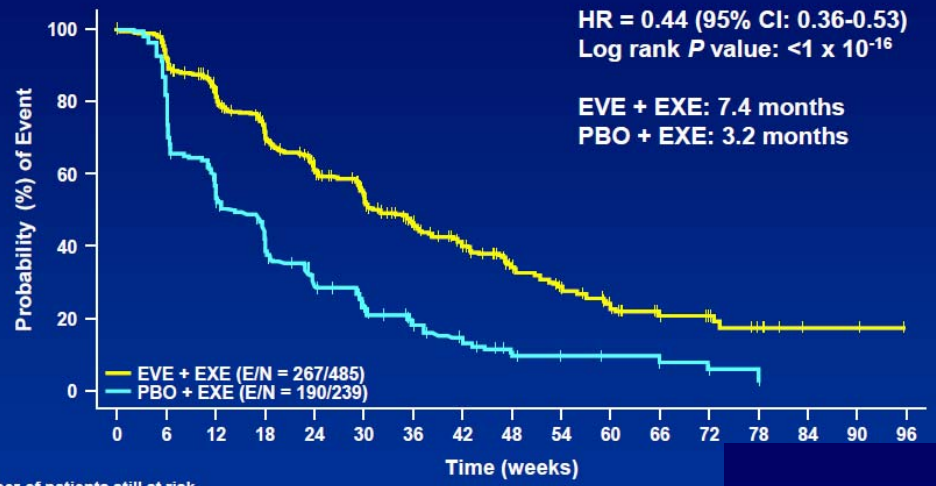
Endpoints

- **Primary**: PFS (local assessment)
- **Secondary**: OS, ORR, QOL, safety, bone markers, PK

BC = breast cancer; ER+ = estrogen receptor-positive; EVE = everolimus; EXE = exemestane; ORR, overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; QOL = quality of life

Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12-month f/up): PFS Local

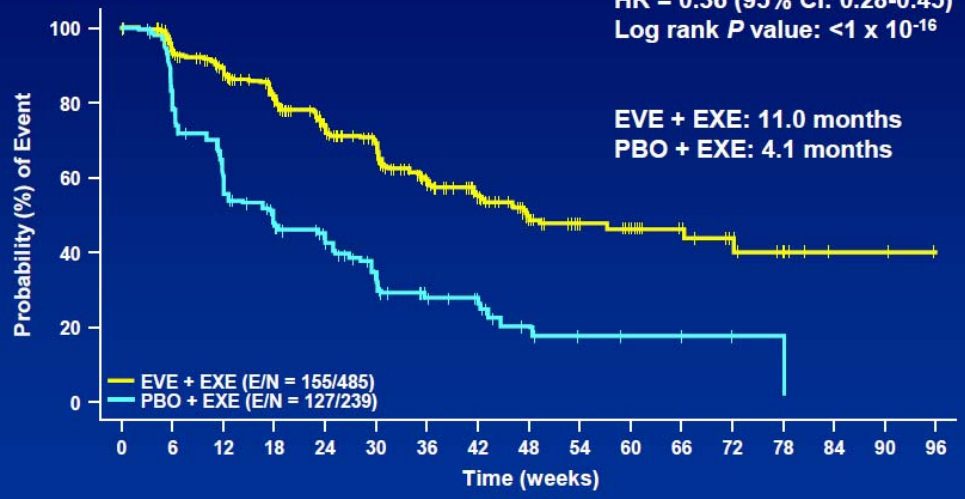


Number of patients still at risk

Everolimus	485	436	365	303	246	188	136	96	64	45	34	21	13
Placebo	239	190	131	95	63	45	29	19	12	8	6	6	4

CI = confidence interval; EVE = everolimus; EXE = exemestane; HR = hazard ratio; PBO = placebo; PFS = progression-free s
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12 mo f/up): PFS Central



Number of patients still at risk

Everolimus	485	422	351	284	224	176	119	86	57	38	32	22	12	7	2	2	0
Placebo	239	179	112	74	56	36	23	18	8	5	4	4	3	1	0	0	0

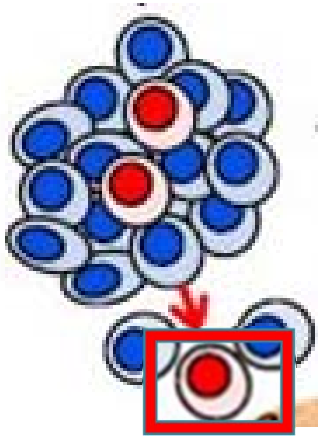
CI = confidence interval; EVE = everolimus; EXE = exemestane; HR = hazard ratio; PBO = placebo; PFS = progression-free survival.
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

15

Hortobagyi et al., #S3-7, SABCS, 2011

Fazit CTC

Prognostische Bedeutung	Ja!
Therapeutische Optionen	Ja!



?

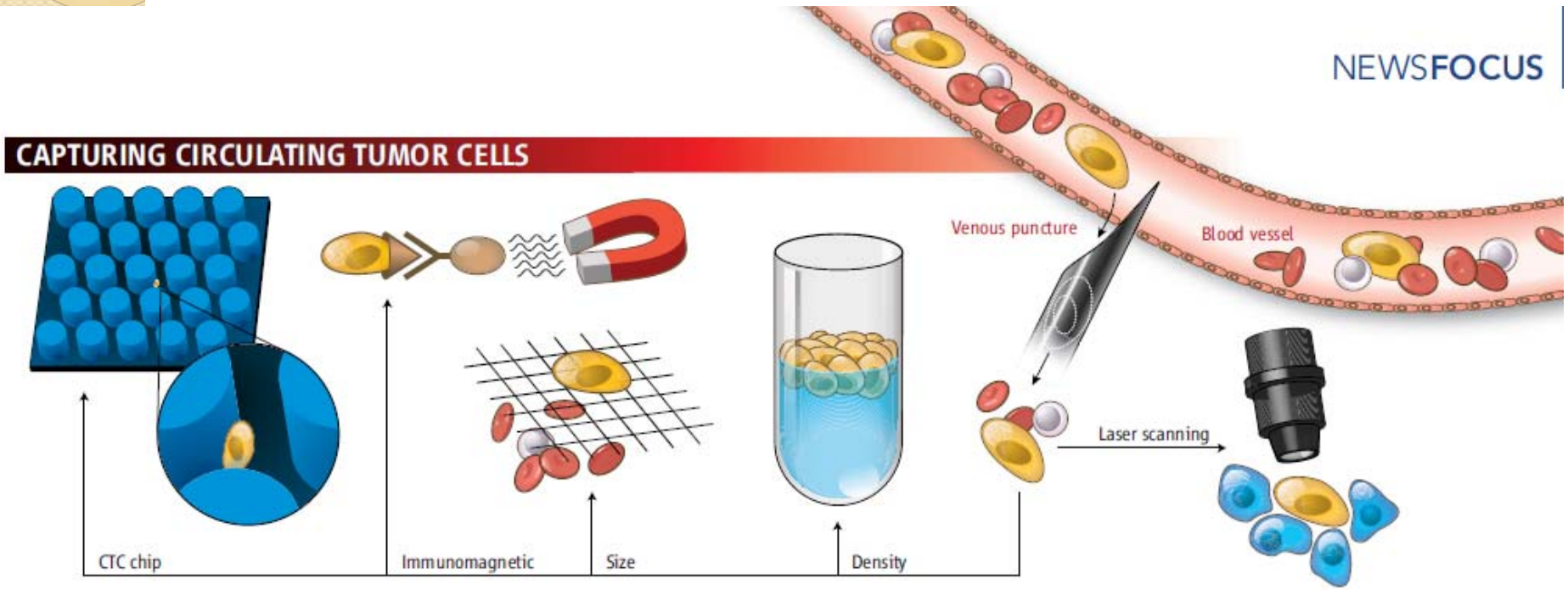
Tumorstammzellen

Circulating Tumor Cells: Not All Detected Cells Are Bad and Not All Bad Cells Are Detected

Max S. Wicha and Daniel F. Hayes, *The University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*

See accompanying articles on pages 1547 and 1556

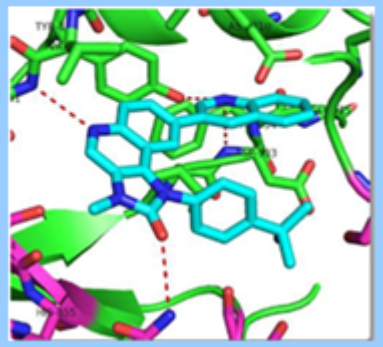
J Clin Oncol (Apr 20); 2011



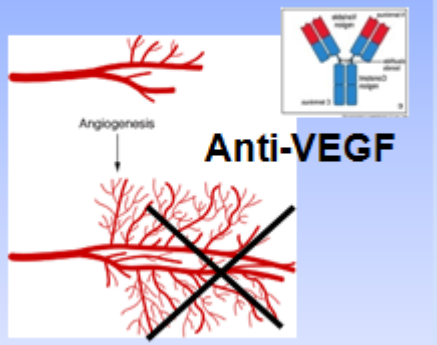
Science, New Focus, February 2010

Zusammenfassung

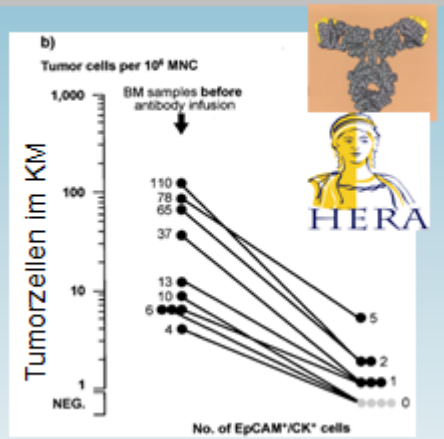
PI3K / mTOR Inhibitoren



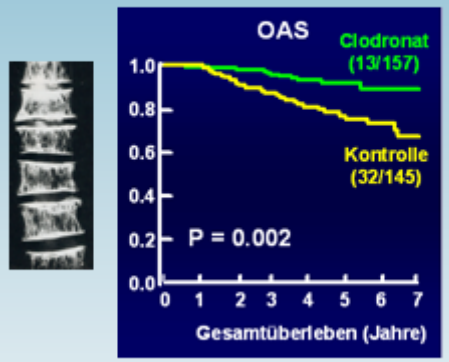
Antiangiogenese?

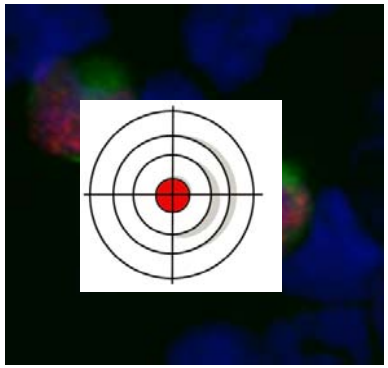


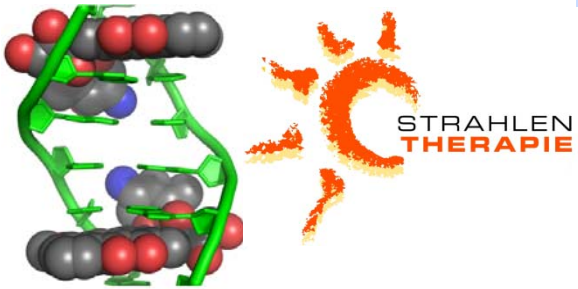
Antikörpertherapie



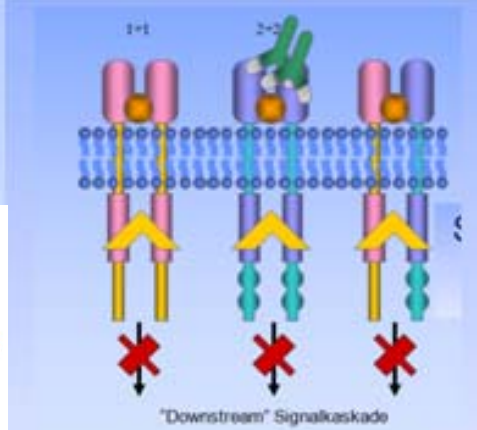
Bisphosphonate



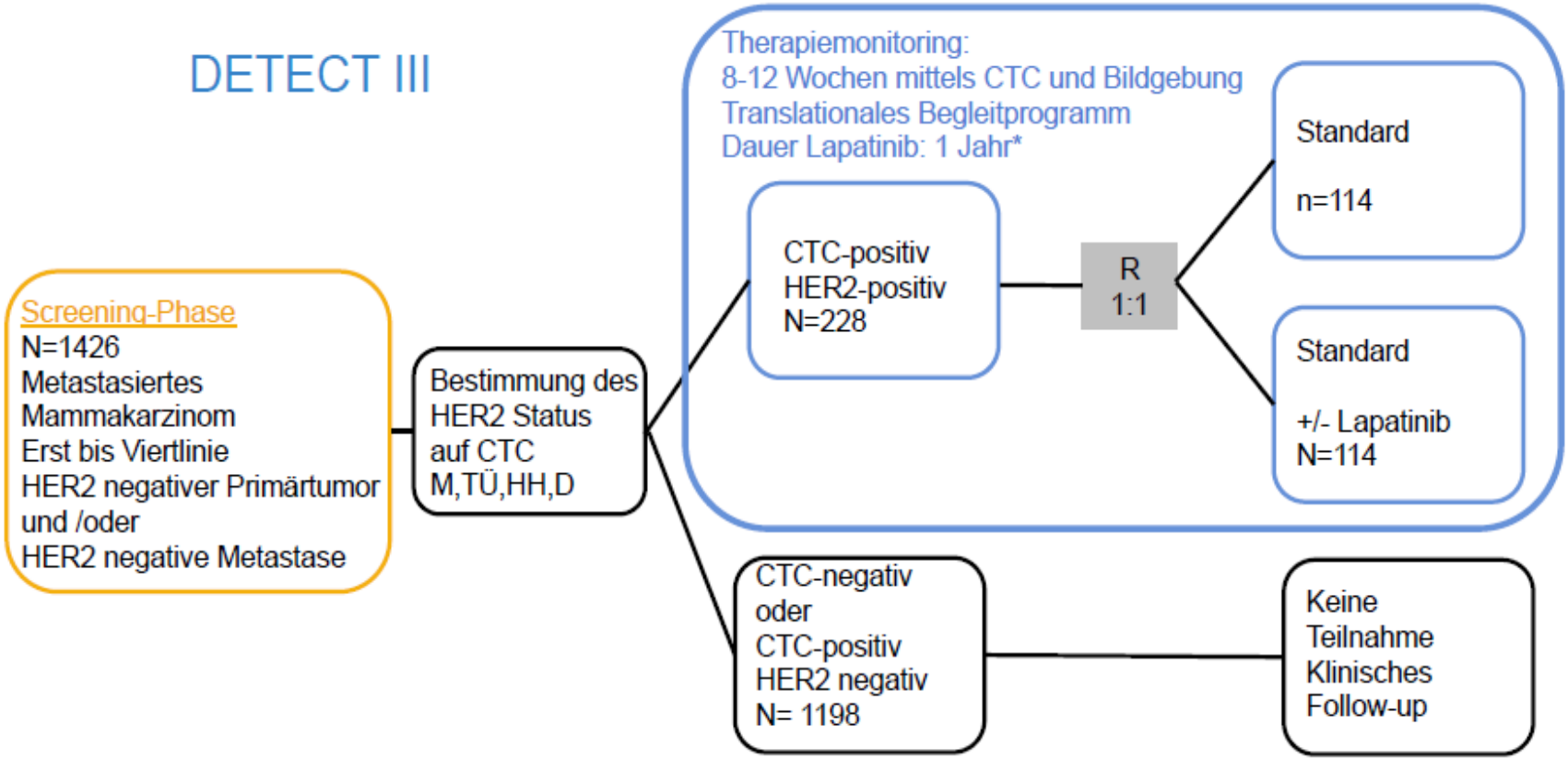




Kleine Moleküle?



Ausblick


DETECT III
Therapiemonitoring:
8-12 Wochen mittels CTC und Bildgebung
Translationales Begleitprogramm
Dauer Lapatinib: 1 Jahr*
Screening-Phase
N=1426
Metastasiertes Mammakarzinom
Erst bis Viertlinie
HER2 negativer Primärtumor
und /oder
HER2 negative Metastase
Bestimmung des HER2 Status auf CTC
M,TÜ,HH,D
CTC-positiv
HER2-positiv
N=228
R
1:1
Standard
n=114
Standard
+/- Lapatinib
N=114
CTC-negativ
oder
CTC-positiv
HER2 negativ
N= 1198
Keine Teilnahme
Klinisches Follow-up