# Prognostic relevance of circulating tumor cells in peripheral blood of breast cancer patients before and after adjuvant chemotherapy
# The German SUCCESS-Trial


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in Collaboration with

# Financial Disclosures

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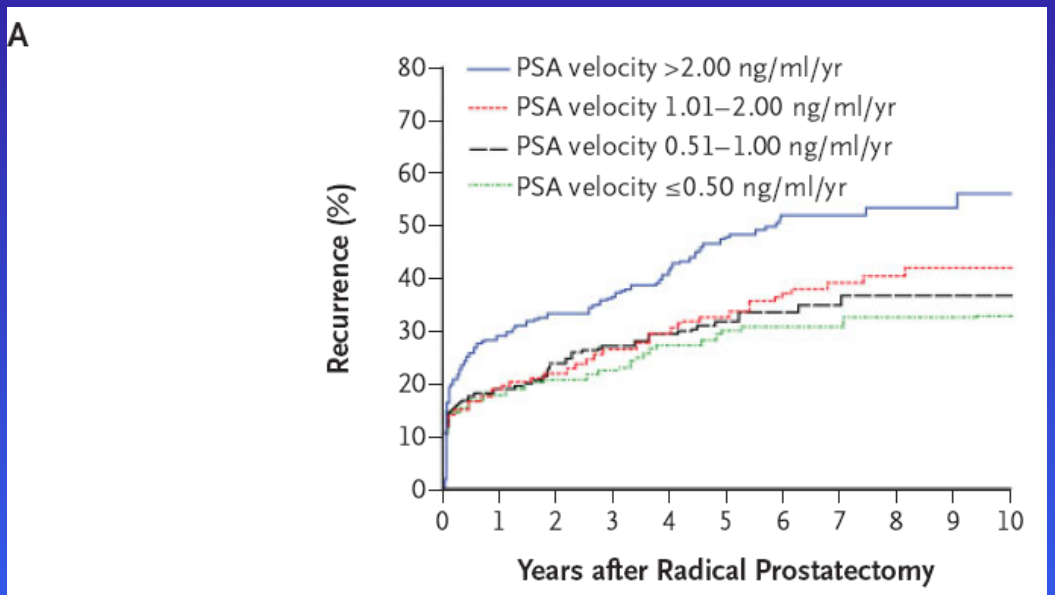
Honoraria:

Sanofi-Aventis

# Active Surveillance in Prostate Cancer




| No. at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PSA velocity >2.00 ng/ml/yr | 247 | 173 | 155 | 132 | 104 | 81 | 60 | 45 | 31 | 19 | 13 |
| PSA velocity 1.01–2.00 ng/ml/yr | 280 | 218 | 191 | 167 | 133 | 101 | 84 | 56 | 36 | 19 | 15 |
| PSA velocity 0.51–1.00 ng/ml/yr | 287 | 226 | 193 | 158 | 120 | 92 | 64 | 36 | 23 | 14 | 9 |
| PSA velocity ≤0.50 ng/ml/yr | 249 | 190 | 156 | 128 | 103 | 84 | 58 | 43 | 24 | 13 | 5 |

**Table 2.** Active Surveillance: Suggested Algorithm for Eligibility and Follow-Up

| Algorithm |
|---|
| Eligibility |
| PSA ≤ 10 |
| Gleason score ≤6 |
| T1c to T2a |
| For men with > 15-year life expectancy, < 3 cores involved, < 50% of any one core |
| Follow-up schedule |
| PSA, DRE every 3 months × 2 years, then every 6 months assuming PSA is stable |
| 10-12 core biopsies at 1 year, and then every 3 years until age 80 years |
| Optional: TRUS on alternate visits |
| Intervention |
| For PSA doubling time < 3 years (in most cases, based on at least eight determinations; about 20% of patients) |
| For grade progression to Gleason score ≥ 7 (4+3) approximately 5% of patients |

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D'Amico, NEJM 2004; 351: 125-135
Klotz, JCO 2005; 23: 8165-8169

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# Adjuvant Treatment: Why Therapeutic Monitoring?

Previously:
5 a Tam

TAM

Up-Front:
5 a AI

AI

Switch:
2-3a Tam, 2-3 a AI

TAM | AI

Extended:
5 a Tam, 5 a AI

TAM | AI

*Which strategy works best for the individual patient?*

Other examples:
length of ovarian ablation, chemotherapy, targeted treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# A Pooled Analysis of Bone Marrow Micrometastasis in Breast Cancer

Stephan Braun, M.D., Florian D. Vogl, M.D., Bjørn Naume, M.D., Wolfgang Janni, M.D., Michael P. Osborne, M.D., R. Charles Coombes, M.D., Günter Schlimok, M.D., Ingo J. Diel, M.D., Bernd Gerber, M.D., Gerhard Gebauer, M.D., Jean-Yves Pierga, M.D., Christian Marth, M.D., Daniel Oruzio, M.D., Gro Wiedswang, M.D., Erich-Franz Solomayer, M.D., Günther Kundt, M.D., Barbara Strobl, M.D., Tanja Fehm, M.D., George Y.C. Wong, Ph.D., Judith Bliss, M.Sc., Anne Vincent-Salomon, M.D., and Klaus Pantel, M.D.*

## ABSTRACT

BACKGROUND

We assessed the prognostic significance of the presence of micrometastasis in the bone marrow at the time of diagnosis of breast cancer by means of a pooled analysis.

From the Department of Obstetrics and Gynecology, Innsbruck Medical University, Innsbruck, Austria (S.B., C.M.); Department of Obstetrics and Gynecology, General Hospital, Merano, Italy (F.D.V.); Department of Oncology, Norwegian Radium Hospital, Oslo (B.N.); Department of Obstetrics and Gynecology, Ludwig-Maximilians University, Munich, Germany (W.J., B.S.); Department of Surgery, New York Presbyterian Hospi-

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Braun S. et al, NEJM 2005, 353:793-802

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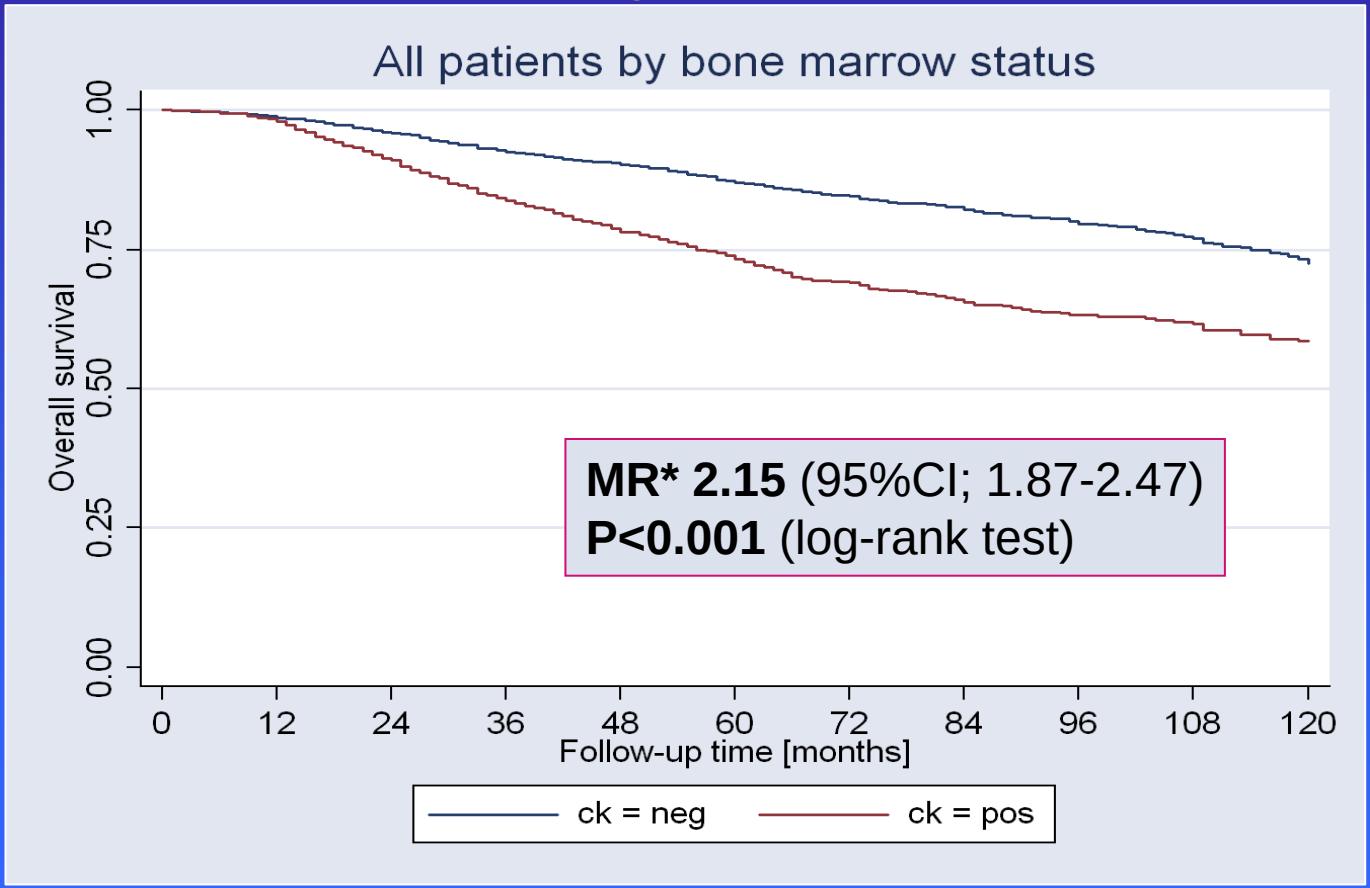
# Pooled Analysis of Bone Marrow Aspirations at Primary Diagnosis in 9 Centers (n=4.703)

## Overall Survival by Bone Marrow Status

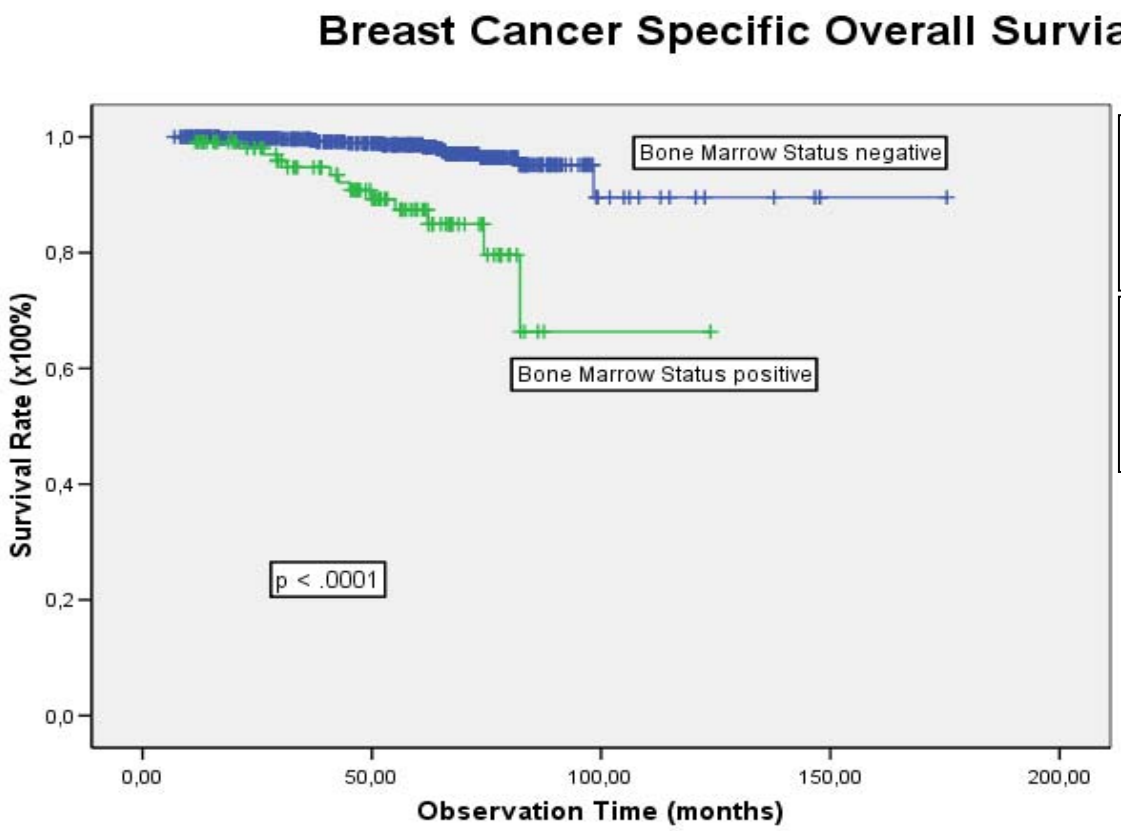



Median follow-up 62 months

Braun S. et al, NEJM 2005, 353:793-802

# Pooled Analysis of Bone Marrow Aspirations during Recurrence-free Follow-up (n=726)

## Overall Survival by Bone Marrow Status




Mean DFS **165.6** mos (156.8 – 174.5 95%CI)

Mean DFS **103.3** mos (91.0 – 115.7 95% CI)

Janni et al, SABCS 2006

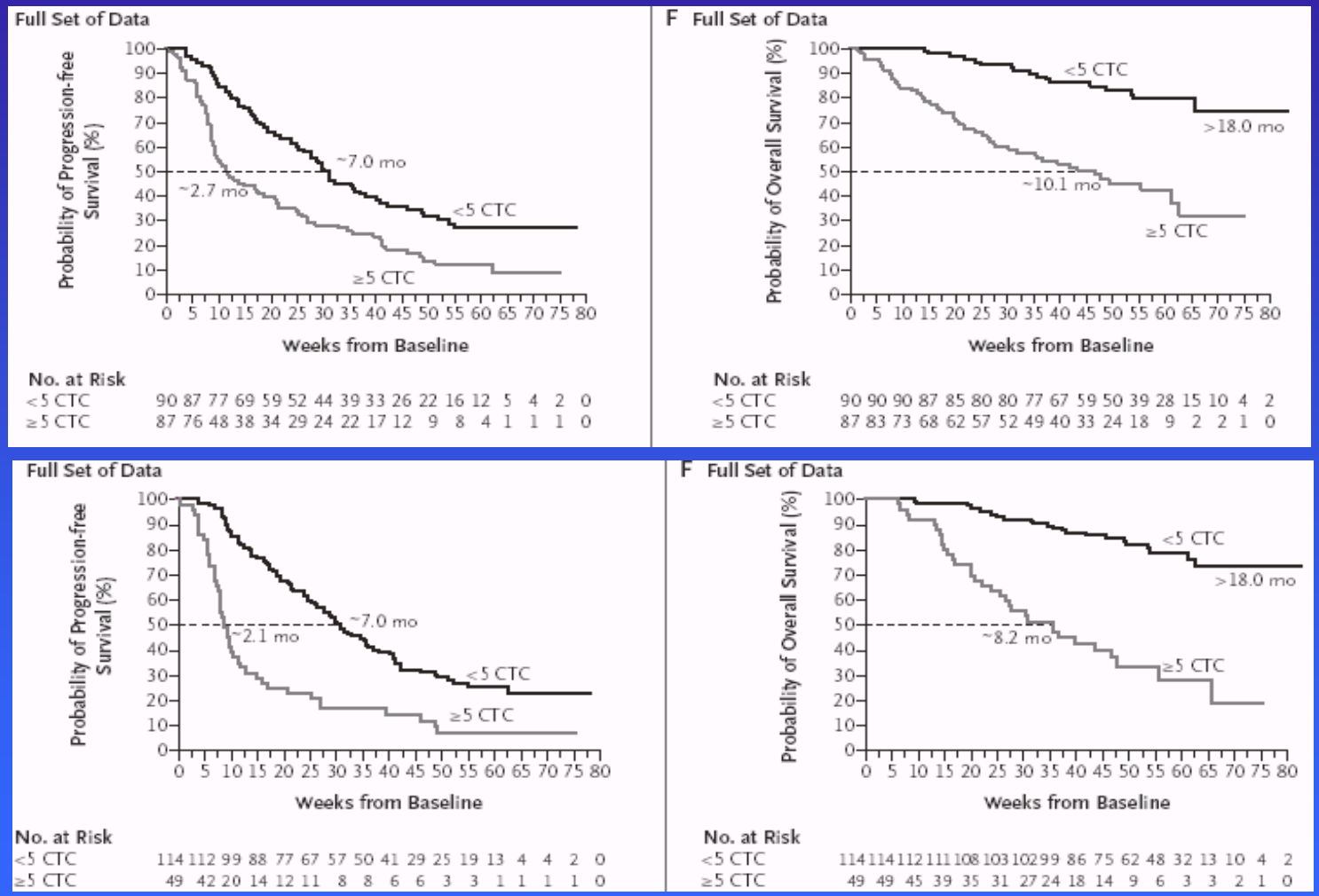
# Circulating Tumor Cells (CTCs) in Blood: A Perfect Marker for Risk Assessment and Treatment Monitoring?

- Easy and non-invasive accessability
- Broad availability
- Possibility of repeated measurements
- Availability throughout all time-points of the disease

**However:**

**Lack of data in the primary setting!**

# CTCs as Prognostic Marker in Metastatic Breast Cancer




SUCCESS Cristofanilli et al, NEJM 2004;351:781-91

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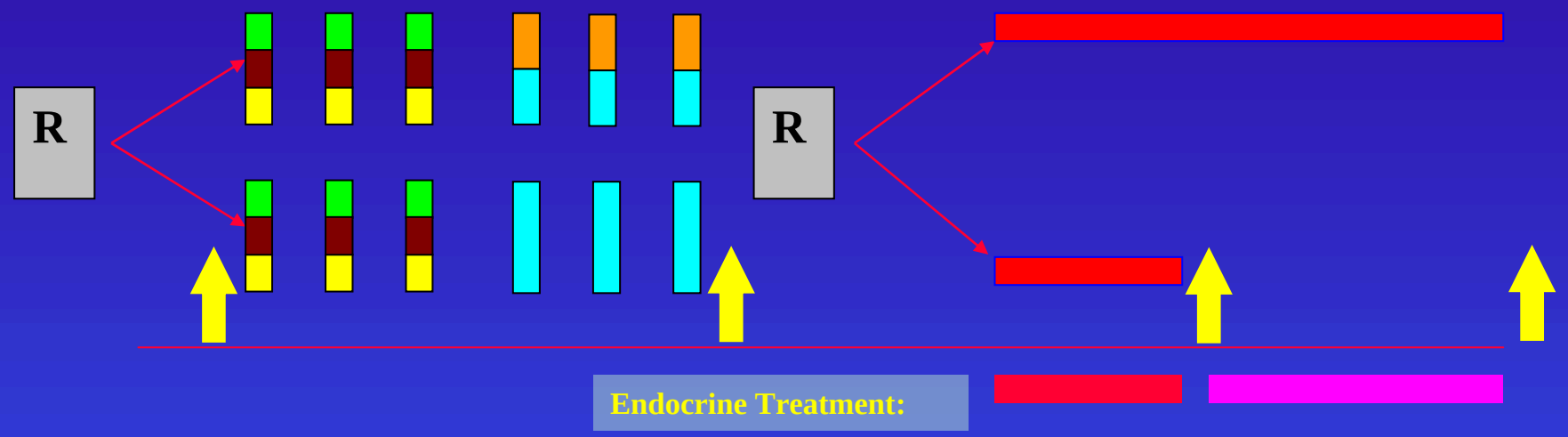
# SUCCESS-Study Design

**(Simultaneous Study of Docetaxel-Gemcitabine Combination adjuvant treatment, as well as Extended Bisphosphonate and Surveillance-Trial )**
**An initiative of the ADEBAR-Study Group**




**Translationale Research Project (München, Erlangen, Hamburg)**

- 2x2 factorial design
- High risk N0 and N+ patients
- n=3.658 patients
- Sampling of 60 ml peripheral blood at 4 different time points during treatment

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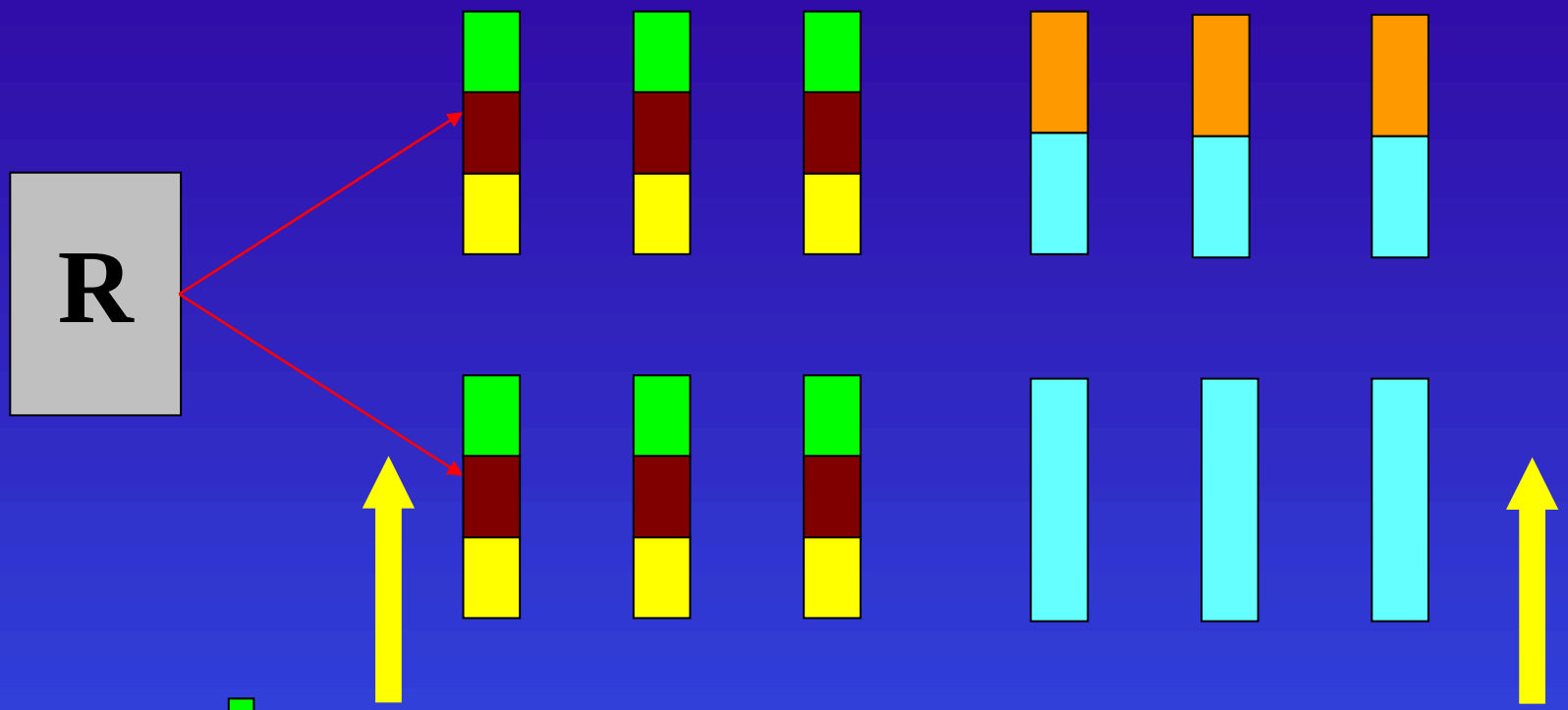
LMU
Friedrich-Alexander-Universität Erlangen-Nürnberg
Universitätsklinikum Hamburg-Eppendorf

# Evaluation of CTCs before and after Chemotherapy




5- FU 500 mg/m², Epirubicin 100 mg/m², Cyclophosphamide 500 mg/m² q3w

Docetaxel 100 mg/m² q3w

Docetaxel 75 mg/m², Gemcitabine 1000mg/m² D1,8 q3w

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# Study Centers in Germany


251 active study centers

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# Patient Recruitment within the SUCCESS-Study


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# Detection of CTCs by CellsSearchSystem

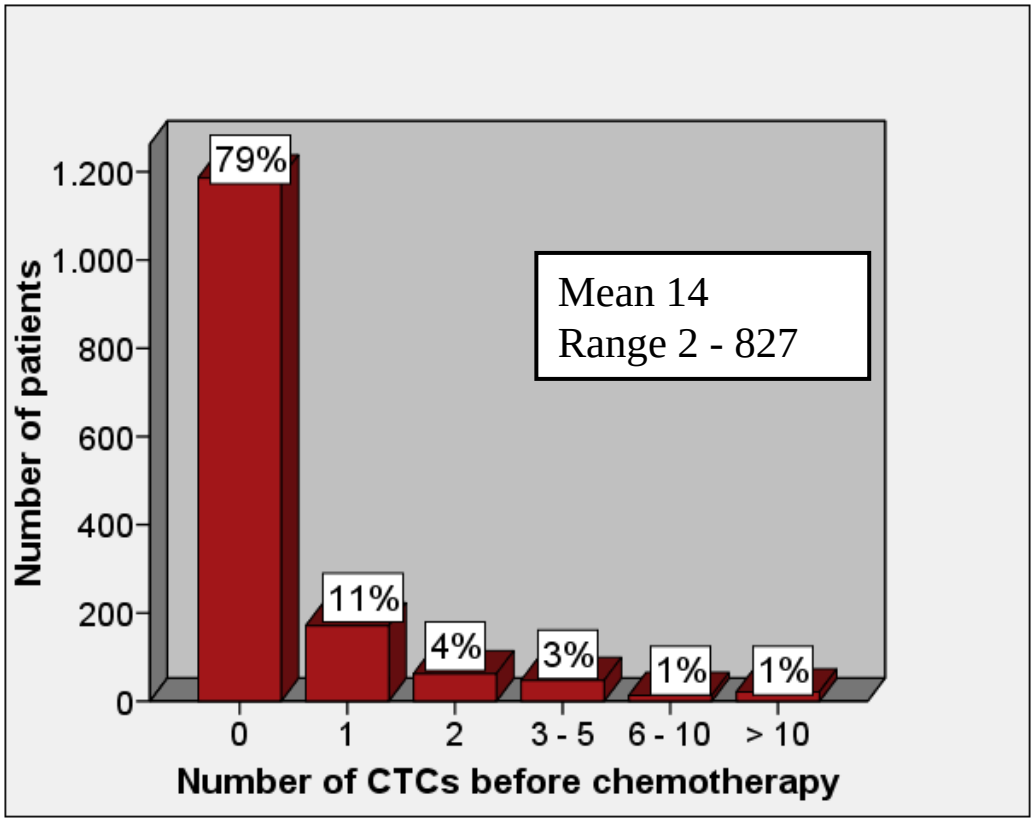
- Analysis of 23 ml of peripheral blood
- Immunomagnetic enrichment using Anti-Epcam-Antibodies
- Immunocytochemical fluorescence staining for CD45 (Leukocytes) and Cytokeratine 8,18,19 (epithelial cell marker)
- Automated preparation and analysis by CellSearchSystem and CellSpotterAnalyzer (Veridex)

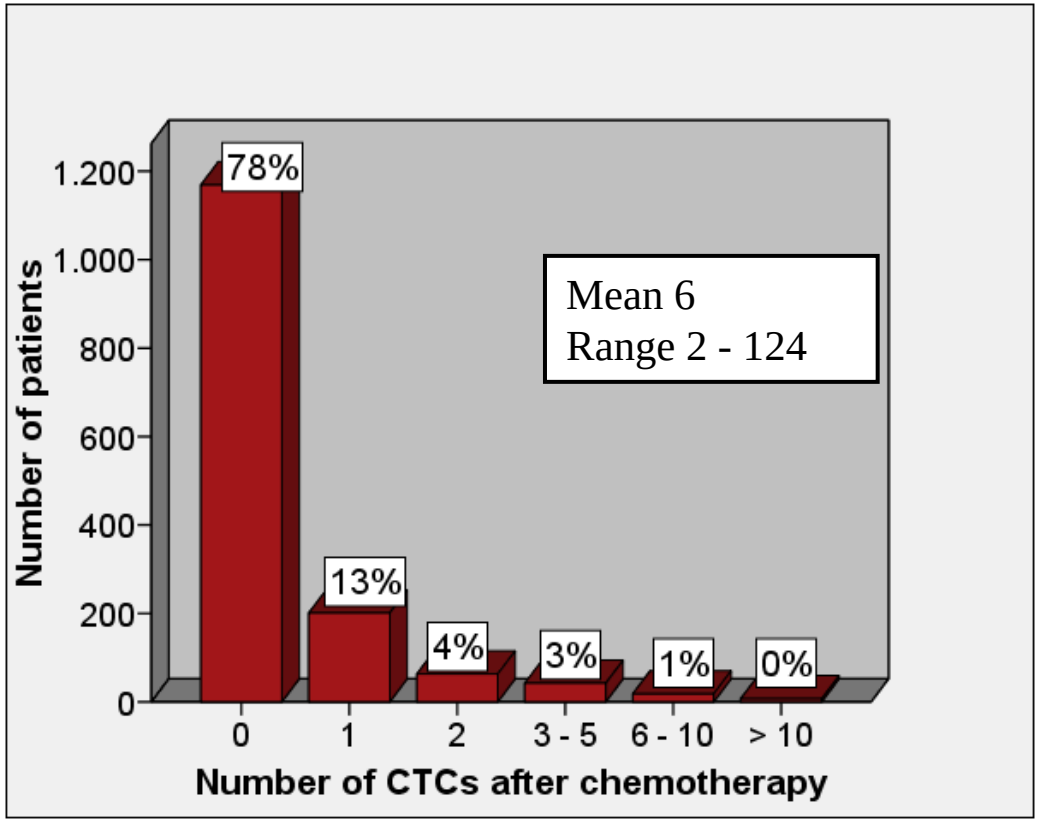
# Tumor Characteristics at Primary Diagnosis (n=1500)

| | CTC+ n (%) | | CTC- n (%) | | p-value |
|---|---|---|---|---|---|
| **Number of patients** | 143 | (9.5) | 1357 | (90.5) | |
| **Tumor size§** | | | | | **0.32** |
| pT1 | 43 | (3.0) | 544 | (37.8) | |
| pT2 - 4 | 83 | (5.8) | 768 | (53.4) | |
| **Lymph node status**** | | | | | **0.003** |
| pN0 | 30 | (2.0) | 456 | (30.4) | |
| pN1 - 3 | 112 | (7.5) | 901 | (60.1) | |
| **Histopathological grading** | | | | | **0.36** |
| G1 | 4 | (0.3) | 60 | (4.0) | |
| G2 - 3 | 139 | (9.2) | 1297 | (86.5) | |
| **Hormonal status** | | | | | **0.28** |
| Positive | 108 | (7.2) | 967 | (64.6) | |
| Negative | 35 | (2.2) | 390 | (26.0) | |
| **Her2/neu-Status*** | | | | | **0.82** |
| Positive | 36 | (2.5) | 339 | (24.0) | |
| Negative | 104 | (7.4) | 933 | (66.1) | |

§ Tumor size missing in 62 cases
** Lymph node status missing in 1 case
* Her2/neu-Status missing in 88 cases

# Number of CTCs before and after Chemotherapy




3 of 74 individuals without malignant disease showed > 1CTC

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# CTCs before and after Chemotherapy (n=1500)

| | | After Chemotherapy | |
|---|---|---|---|
| | | CTC - | CTC + |
| | | 1370 (91.3%) | 130 (8.7%) |
| **Before Chemotherapy** | | | |
| CTC - | 1357 (90.5%) | 1242 (82.8%) | 115 (7.7%) |
| CTC + | 143 (9.5%) | 128 (8.5%) | 15 (1.0%) |

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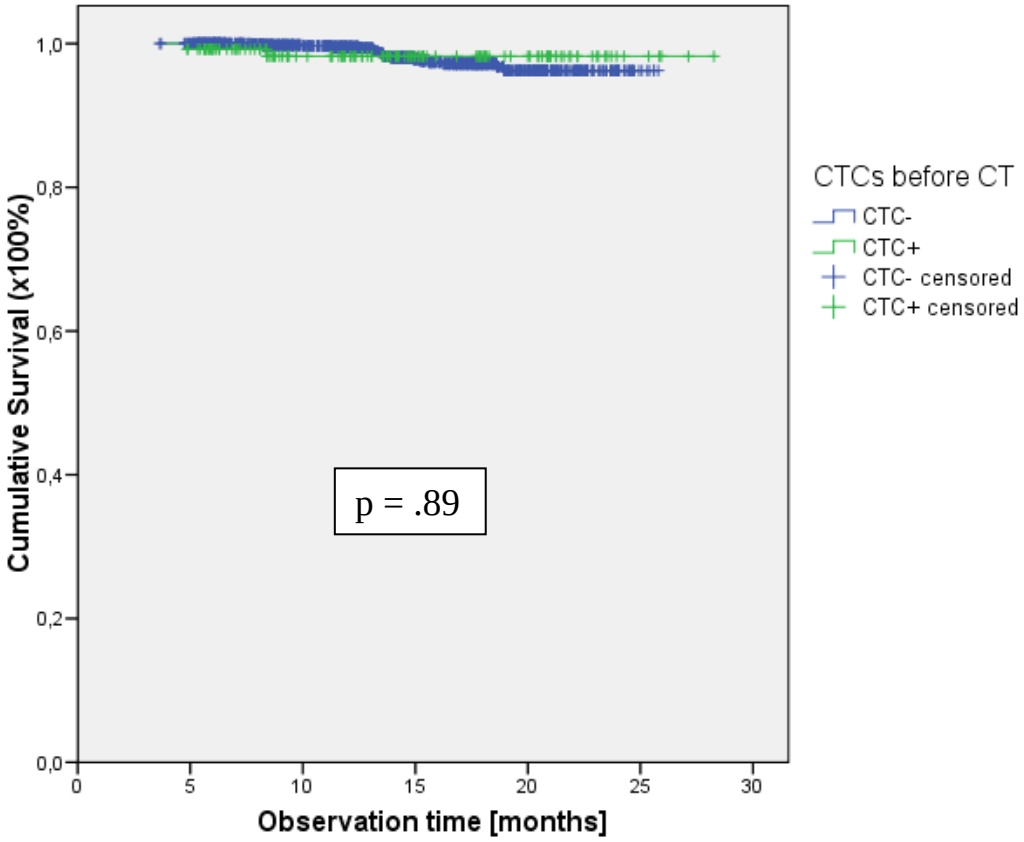
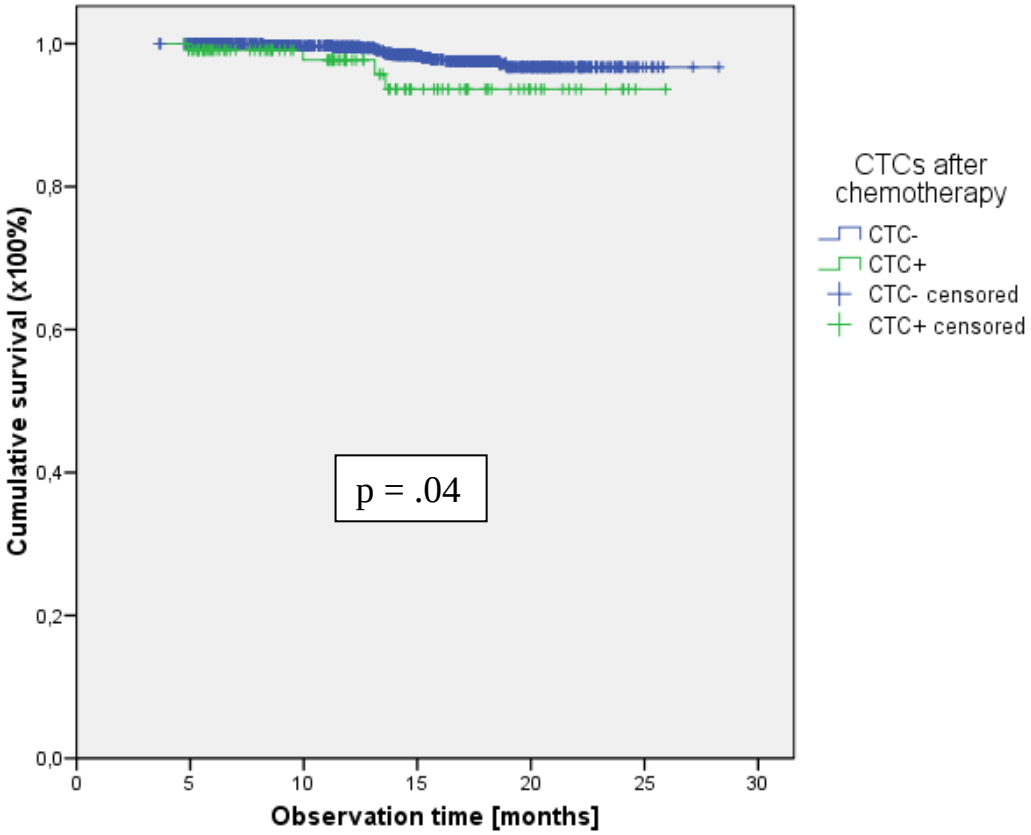
# Disease-free Survival




**CTCs before chemotherapy**

**CTCs after chemotherapy**

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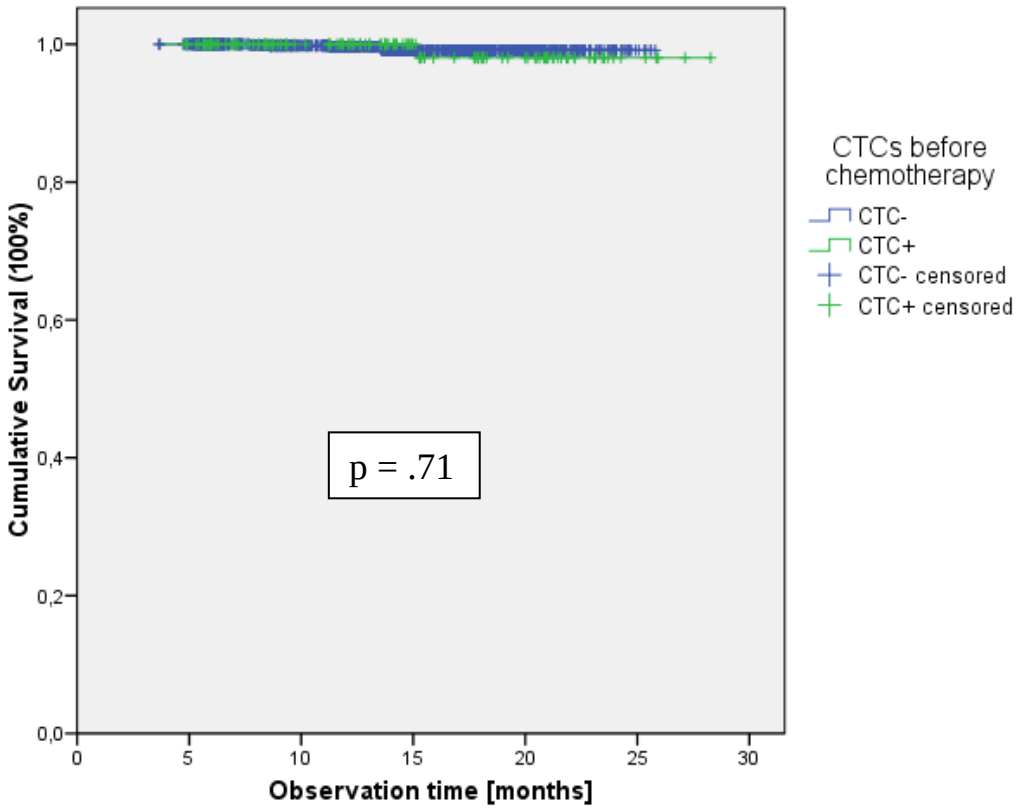
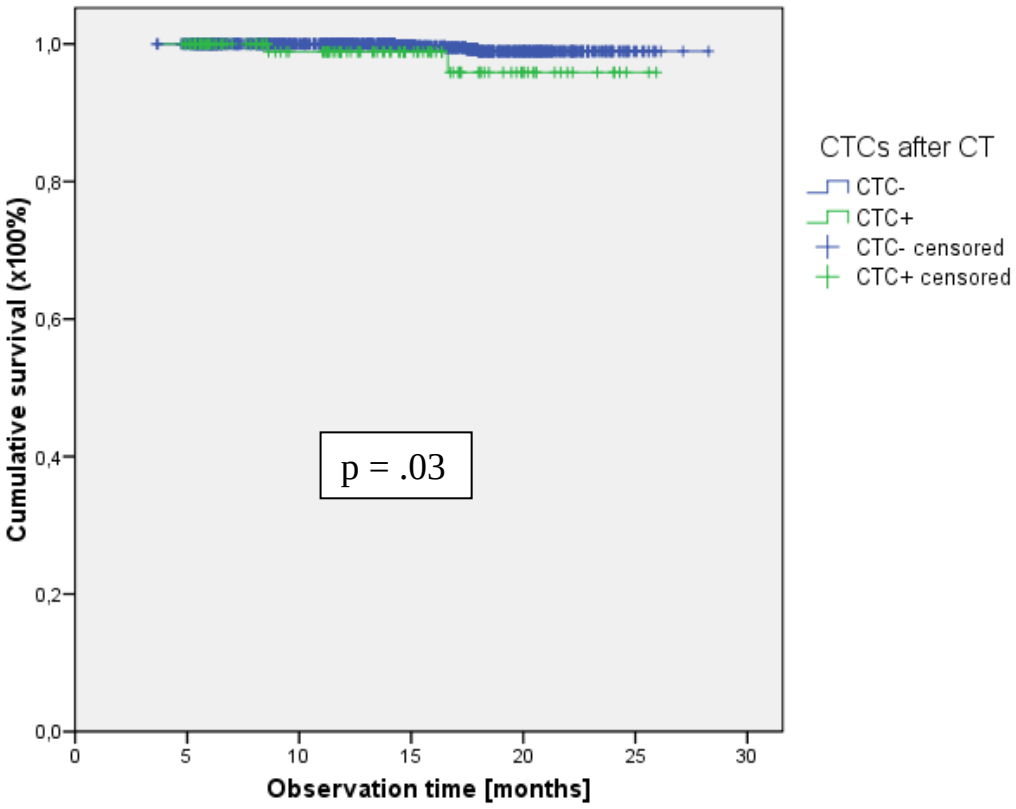
# Overall Survival




**CTCs before chemotherapy**

**CTCs after chemotherapy**

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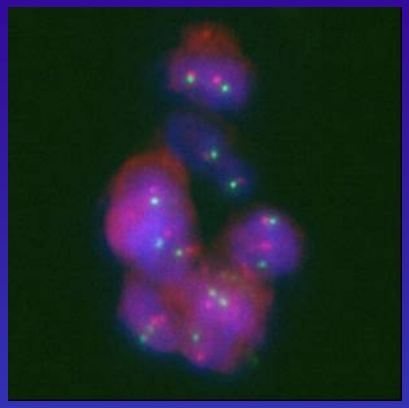

2008 ASCO Merit Award Recipient

# Conclusions

- Detection of CTCs with the CellSearchSystem is a standardized and easily applicable approach.
- In a considerable number of patients, persistent CTCs can be detected after completion of cytostatic treatment.
- Preliminary results  indicate prognostic relevance of persisting CTCs after chemotherapy.

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# Perspectives

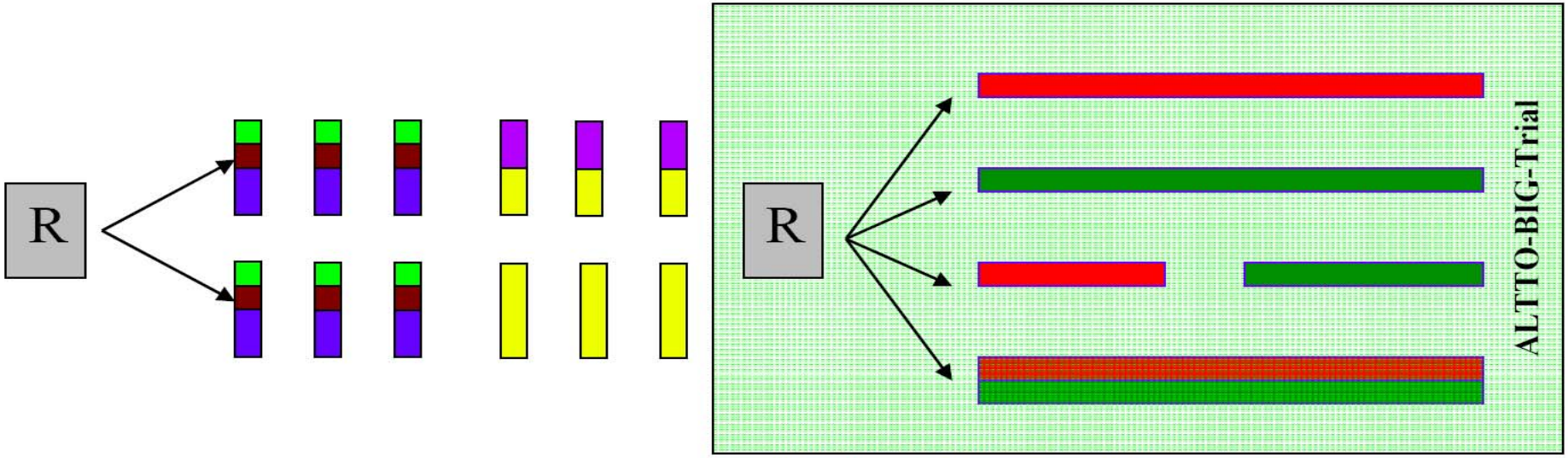
***CTCs in peripheral blood might be useful ...***

- as independent prognostic marker?
- as tool to monitor treatment efficacy?
- for tumorbiological phenotyping of disease recurrence?
- to develop more individualized treatment strategies?

ALTTo
Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial

# Study Design

SUCCESS B




***Endocrine Treatment:***

Premenopausal:

Postmemenopausal:

MRD-Surveillance in peripheral blood

# Acknowledgements

## 3754 breast cancer patients participating in the SUCCESS trial

## All 251 participating study centers throughout Germany:

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Klinikum Hannover Nordstadt
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I. Universitätsfrauenklinik LMU, München
Klinikum Chemnitz gGmbH

Diakoniekrankenhaus Schwäbisch-Hall
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Klinikum Bremerhaven Reinkenheide
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Zentralklinikum gGmbH Südthüringen, Suhl

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