Prognostic relevance of circulating tumor cells in peripheral blood of breast cancer patients before and after adjuvant chemotherapy

The German SUCCESS-Trial


in Collaboration with
Financial Disclosures

Research Support:
Astra Zeneca, Chugai, Lilly, Novartis, Sanofi-Aventis, Veridex

Honoraria:
Sanofi-Aventis
Active Surveillance in Prostate Cancer

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

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

D’Amico, NEJM 2004; 351: 125-135
Klotz, JCO 2005; 23: 8165-8169
Adjuvant Treatment: Why Therapeutic Monitoring?

Previously:
- 5 a Tam

Up-Front:
- 5 a AI

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

Extended:
- 5 a Tam, 5 a AI

Which strategy works best for the individual patient?

Other examples:
- length of ovarian ablation, chemotherapy, targeted treatment
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 Fehrm, 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-
Pooled Analysis of Bone Marrow Aspirations at Primary Diagnosis in 9 Centers (n=4,703)

Overall Survival by Bone Marrow Status

Overall survival by bone marrow status:

MR* 2.15 (95% CI; 1.87-2.47)
P<0.001 (log-rank test)

Median follow-up 62 months

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

Overall Survival by Bone Marrow Status

Breast Cancer Specific Overall Survival

Mean DFS 165.6 mos (156.8 – 174.5 95%CI)
Mean DFS 103.3 mos (91.0 – 115.7 95% CI)

p < .0001
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

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

- 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

Endocrine Treatment:
Translationale Research Project (München, Erlangen, Hamburg)
Evaluation of CTCs before and after Chemotherapy

- Docetaxel 100 mg/m² q3w
- 5- FU 500 mg/m², Epirubicin 100 mg/m², Cyclophosphamide 500 mg/m² q3w
- Docetaxel 75 mg/m², Gemcitabine 1000mg/m² D1,8 q3w
Study Centers in Germany

251 active study centers
End of recruitment on 10th March 2007 with 3754 randomized patients
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)

<table>
<thead>
<tr>
<th></th>
<th>CTC+</th>
<th>CTC-</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>143 (9.5)</td>
<td>1357 (90.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor size§</strong></td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>pT1</td>
<td>43 (3.0)</td>
<td>544 (37.8)</td>
<td></td>
</tr>
<tr>
<td>pT2 - 4</td>
<td>83 (5.8)</td>
<td>768 (53.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Lymph node status</strong></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>pN0</td>
<td>30 (2.0)</td>
<td>456 (30.4)</td>
<td></td>
</tr>
<tr>
<td>pN1 - 3</td>
<td>112 (7.5)</td>
<td>901 (60.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Histopathological grading</strong></td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>G1</td>
<td>4 (0.3)</td>
<td>60 (4.0)</td>
<td></td>
</tr>
<tr>
<td>G2 - 3</td>
<td>139 (9.2)</td>
<td>1297 (86.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Hormonal status</strong></td>
<td></td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Positive</td>
<td>108 (7.2)</td>
<td>967 (64.6)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>35 (2.2)</td>
<td>390 (26.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Her2/neu-Status</strong></td>
<td></td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>Positive</td>
<td>36 (2.5)</td>
<td>339 (24.0)</td>
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<tr>
<td>Negative</td>
<td>104 (7.4)</td>
<td>933 (66.1)</td>
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§ Tumor size missing in 62 cases  
** Lymph node status missing in 1 case  
* Her2/neu-Status missing in 88 cases
3 of 74 individuals without malignant disease showed > 1 CTC
### CTCs before and after Chemotherapy (n=1500)

<table>
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<tr>
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<td><strong>CTC -</strong></td>
<td>1357 (90.5%)</td>
<td>1370 (91.3%)</td>
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<tr>
<td><strong>CTC +</strong></td>
<td>143 (9.5%)</td>
<td>130 (8.7%)</td>
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**Note:** The data represents the counts and percentage of CTCs before and after chemotherapy, with 1500 cases in total.
CTCs before and after Chemotherapy (n=1500)

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1242 (82.8%) 115 (7.7%) 15 (1.0%)
CTCs before and after Chemotherapy (n=1500)

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CTC - CTC +
1370 (91.3%) 130 (8.7%)
Disease-free Survival

CTCs before chemotherapy

CTCs after chemotherapy

p = .89

p = .04
Overall Survival

CTCs before chemotherapy

CTCs after chemotherapy

p = .71

p = .03
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.
Perspectives

CTCs in peripheral blood might be useful ...

• as independent prognostic marker?
• as tool to monitor treatment efficacy?
• for tumourbiological phenotyping of disease recurrence?
• to develop more individualized treatment strategies?
Study Design

**Endocrine Treatment:**

- Premenopausal:

- Postmenopausal:

  MRD-Surveillance in peripheral blood
Acknowledgements

3754 breast cancer patients participating in the SUCCESS trial:

All 251 participating study centers throughout Germany:

Universitätsfrauenklinik Heidelberg
Universitätsfrauenklinik Erlangen
Herrnreetstiftung Krankenhaus, Hannover
Onk.Praxis Dr. R. Lorenz / N. Hecker, Braunschweig
Onk. Praxis Prof. Tesch, Frankfurt
Onk.Praxis Dr. Forstbauer / Dr. Ziske, Troisdorf
Luisenkrankenhaus GmbH & Co. KG, Düsseldorf
Städ. Klinikum Karlsruhe
Onk. Praxis Drs. Siehl / Söling, Kassel
Städtisches Klinikum Rosenheim
Klinikum Hannover Nordstadt
Onk.Praxis Dr. Heinrich, Fürstenwalde
SRH Wald-Klinikum Gera gGmbH
St. Antonius-Hospital, Eschweiler
I. Universitätsfrauenklinik LMU, München

Diakoniekrankenhaus Schwäbisch-Hall
DRK - Kliniken & Dr. G. Schramm, Berlin
Onk.Praxis Dr. Schlag, Würzburg
Stadtklinik Baden Baden
Onk.Praxis Dr. Fett, Wuppertal
Klinikum Meiningen GmbH
Krankenhaus Böblingen
Onk.Praxis Dr. Müller, Leer
Universitätsklinikum Lübeck
Onk. Praxis Dr. Göhler / Dipl. med. Dörfel, Dresden
Klinikum Bremerhaven Reinekeheide
Universitätsklinikum des Saarlands, Homburg/Saar
Klinikum der Friedrich-Schiller-Universität Jena
Hochwald Krankenhaus, Bad Nauheim
Onk.Praxis Dr. Glados, Coesfeld
Zentralklinikum gGmbH Südhüringen, Suhl
We also thank...

**Collaborations:**
Prof. Dr. M.-W. Beckmann  
Prof. Dr. K. Pantel  
Prof. Dr. W. Lichtenegger  
Dr. D. Chatsiproios  
Prof. Dr. A. Schneeweiss  
Prof. Dr. A. Schneider

**Laboratory:**
S. Hofmann  
I. Plonner  
V. Rengel  
B. Zill  
S. Machek  
J. Rösch  
E. Zombirt

**Success Study Office:**
E.-M. Genss
J. Jückstock
P. Hepp
S. Dondl
S. Kambylis
S. Reinhard

**Unrestricted grants by:**
AstraZeneca  
Chugai  
Lilly  
Novartis  
Sanofi-Aventis  
Tosoh  
Veridex