Disclosure Information

Financial support for the SUCCESS A study was provided by

- AstraZeneca
- Chugai
- Janssen Diagnostics (formerly Veridex)
- Lilly
- Novartis
- Sanofi-Aventis

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**Background: Circulating tumor cells**

- Circulating tumor cells (CTCs) detectable in early and metastatic breast cancer
- Prognostic relevance in the primary¹ as well as metastatic² setting established
- CTC dynamics as early treatment monitoring tool in metastatic breast cancer³
- Lack of data regarding prognostic role of CTCs assessed during long-term follow-up care

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**SUCCESS A – study design**

- 5-FU 500 mg/m², Epirubicin 100 mg/m², Cyclophosphamide 500 mg/m² q3w
- Docetaxel 100 mg/m² q2w
- Docetaxel 75 mg/m², Gemcitabine 1,000 mg/m² q3w, q8w
- Zoledronate 4 mg q 2 vs 5a (q3m x 4 vs q3m x 24)
- Tamoxifen 20 mg qd p.o. x 2a (plus Goserelin 3.6 mg depot x 2a in premenopausal pts)
- Anastrozole 1 mg qd p.o. x 3a in postmenopausal pts (Tam in premenopausal pts)

**First randomization:**
3 cycles FEC100 followed by 3 cycles docetaxel vs. 3 cycles FEC100 followed by 3 cycles docetaxel plus gemcitabine

**Second randomization:**
2 years vs. 5 years of zoledronate

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Methods: CTC assessment

CellSearch System® (Janssen Diagnostics, LLC), FDA-cleared for enumeration of CTCs:

- Immunomagnetic enrichment with an anti-EpCam-antibody (epithelial cell adhesion molecules antibodies)
- Cells labelled with anti-cytokeratin (CK-PE), DAPI and anti-CD45 antibodies
- Imaging with CellTracks Analyzer
- Definition of CTC positivity: at least 1 CTC in 21 ml of peripheral blood

Methods: Statistical analysis

- Univariate (Kaplan-Meier, Log-rank test) and multivariate (Cox regression) survival analysis
- Survival time measured beginning with the date of follow-up CTC assessment two years after adjuvant chemotherapy
- Overall survival (OS) and disease-free survival (DFS) defined according to STEEP criteria (Hudis et al. 2007, J Clin Oncol 25: 2127-2132)
**Patient characteristics**

- **3754** patients with high-risk early breast cancer (defined as pN1-3, or pT2-4, or G3, or hormone receptor negative, or age ≤ 35) randomized for SUCCESS A
- Data from **1087** patients with CTC determination both before and two years after chemotherapy **available for analysis**
- No significant differences with regard to patient and tumor characteristics between the 1087 patients included and the remaining 2667 patients (all p > 0.05)

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**Patient characteristics**

<table>
<thead>
<tr>
<th>Age at screening (years)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53</td>
<td>21 - 76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Menopausal status</th>
<th>pT1</th>
<th>pT2</th>
<th>pT3</th>
<th>unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal</td>
<td>462 (42.9%)</td>
<td>625 (57.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>600 (42.3%)</td>
<td>556 (35.9%)</td>
<td>51 (4.7%)</td>
<td>3 (0.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>pT1</th>
<th>pT2</th>
<th>pT3</th>
<th>unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>58 (5.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>528 (48.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>501 (46.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological type</th>
<th>ductal</th>
<th>lobular</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>881 (81.2%)</td>
<td>132 (12.3%)</td>
<td>74 (6.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormone receptor status</th>
<th>negative</th>
<th>positive</th>
<th>unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 (27.6%)</td>
<td>787 (72.4%)</td>
<td>15 (1.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>negative</th>
<th>positive</th>
<th>unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>793 (73.0%)</td>
<td>279 (25.7%)</td>
<td>15 (1.5%)</td>
</tr>
</tbody>
</table>
Patient characteristics

- Median time interval from the date of randomization to the date of the CTC determination during follow-up: 28.4 months
- Median follow-up duration (as measured from the date of CTC determination): 37 months

Results I: Prevalence of CTCs after two years

198 (18.2%) of the 1087 patients with at least one CTC in the blood two years after adjuvant chemotherapy (median 1 CTC, range 1 – 99 CTCs)
Results II: Associations of CTC presence after two years with patient characteristics, tumor characteristics and treatments

**No association** between the presence of CTCs two years after adjuvant chemotherapy and

- **Patient characteristics** (age, menopausal state)
- **Tumor characteristics** (tumor size, nodal stage, histological grading, histological type, hormone receptor status, HER2 status)
- **Treatments** (type of surgery, chemotherapy treatment arm, radiotherapy, endocrine therapy, HER2-targeted therapy)

(all $p > 0.10$)

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Results III: Prognostic value of CTCs assessed two years after adjuvant chemotherapy

- **Disease-free survival**
  - $p < 0.001$
  - no CTCs ($n = 889, 65$ events)
  - CTCs ($n = 198, 36$ events)

- **Overall survival**
  - $p < 0.001$
  - no CTCs ($n = 889, 22$ events)
  - CTCs ($n = 198, 21$ events)

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Results IV: Prognostic value of CTCs assessed two years after adjuvant chemotherapy

Multivariate Cox regression adjusted for age, menopausal status, tumor size, nodal stage, tumor grade, histological type, hormone receptor status, HER2 status, and presence of CTCs before chemotherapy

- DFS: Hazard ratio 2.28; 95% CI 1.48 – 3.50; p < 0.001
- OS: Hazard ratio 3.82; 95% CI 1.99 – 7.31; p < 0.001

The presence of CTCs assessed during follow-up two years after adjuvant chemotherapy is a significant independent prognostic factor for poor OS and DFS.

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Results V: Subgroups – CTC status before and two years after adjuvant chemotherapy

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Results VI: Subgroups – Biological subtypes

Definition of biological subtypes as used in this study

- **Luminal A like**: hormone receptor positive
  - HER2 negative
  - tumor grade G1, G2

- **Luminal B like**: hormone receptor positive
  - HER2 negative
  - tumor grade G3

- **HER2 type**: HER2 positive

- **Triple negative**: hormone receptor negative
  - HER2 negative

**No statistically significant interactions** between presence of CTCs two years after adjuvant chemotherapy and biological subtype for OS or DFS (both p > 0.05)

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<table>
<thead>
<tr>
<th>Biological subtype</th>
<th>Recurrences/women</th>
<th>CTC-CTC-positive</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>22/237 (6.2%)</td>
<td>14/237 (18.5%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Luminal B</td>
<td>15/137 (10.9%)</td>
<td>5/137 (24.2%)</td>
<td>0.012</td>
</tr>
<tr>
<td>HER2-type</td>
<td>15/230 (6.5%)</td>
<td>3/49 (6.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Triple negative</td>
<td>11/233 (4.7%)</td>
<td>10/98 (20.4%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Hormone-receptor status (HRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-negative</td>
<td>17/242 (7.0%)</td>
<td>12/242 (20.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>PR-positive</td>
<td>48/547 (8.8%)</td>
<td>20/547 (17.7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>HER2 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-negative</td>
<td>43/647 (6.7%)</td>
<td>32/647 (21.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HER2-positive</td>
<td>15/230 (6.5%)</td>
<td>3/49 (6.1%)</td>
<td>0.339</td>
</tr>
<tr>
<td>Total</td>
<td>65/885 (7.3%)</td>
<td>36/885 (19.2%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Disease-free survival**

- one or more CTCs better
- no CTCs better

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Results VI: Subgroups – Biological subtypes

<table>
<thead>
<tr>
<th>Biological subtype</th>
<th>Deaths/women CTC-negative</th>
<th>Deaths/women CTC-positive</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>6/257 (2.3%)</td>
<td>9/74 (12.2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Luminal B</td>
<td>6/137 (4.4%)</td>
<td>5/55 (9.1%)</td>
<td>0.022</td>
</tr>
<tr>
<td>HER2 type</td>
<td>5/230 (2.2%)</td>
<td>1/48 (2.1%)</td>
<td>0.660</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>4/455 (0.9%)</td>
<td>5/96 (12.8%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Hormone-receptor status (HRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-negative</td>
<td>7/242 (2.9%)</td>
<td>6/56 (10.3%)</td>
<td>0.018</td>
</tr>
<tr>
<td>ER-positive</td>
<td>25/864 (2.9%)</td>
<td>26/240 (10.7%)</td>
<td></td>
</tr>
<tr>
<td>HER2-positive</td>
<td>16/647 (2.5%)</td>
<td>19/246 (7.8%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ER-negative</td>
<td>5/230 (2.2%)</td>
<td>1/48 (2.1%)</td>
<td>0.660</td>
</tr>
<tr>
<td>Total</td>
<td>22/889 (2.5%)</td>
<td>21/238 (9.5%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Overall survival

Summary

- 198 (18.2%) of 1087 patients with at least one CTC in the blood two years after adjuvant chemotherapy
- Presence of CTCs two years after adjuvant chemotherapy is a significant independent prognostic factor for poor OS and DFS
- Patients with CTCs both before and two years after adjuvant chemotherapy had worst survival outcome
- The prognostic value of the presence of CTCs two years after chemotherapy was not evident for patients with HER2-positive tumors (but no significant interaction between presence of CTCs two years after adjuvant chemotherapy and biological subtype)
Conclusion

- The presence of CTCs as assessed during routine breast cancer follow-up care two years after adjuvant chemotherapy was associated with poor survival.

- Monitoring of minimal residual disease, such as CTC testing, during breast cancer follow-up might be used as a surveillance marker to identify patients at high risk for relapse who could benefit from tailored intensified follow-up care and/or secondary treatment intervention.

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Acknowledgements

We would like to thank all patients (n = 3754) and study centers (n = 250) for participating in this study and are grateful for financial support by AstraZeneca, Chugai, Janssen Diagnostics, Lilly, Novartis, and Sanofi-Aventis.

In cooperation with

Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie e.V.
Berufsverband niedergelassener Gynäkologischer Onkologen in Deutschland e.V.

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